PART X

PEDIATRICS

Section 1: Prevention

Section 2: Diagnostic

Section 3: Treatment

Prevention

Authors: Muhammad Amin Chinoy, Ambreen Rakhshinda, Sher Wali Khan

QUESTION 1: Are pediatric patients on oral or intravenous steroids at an increased risk of developing septic arthritis?

RECOMMENDATION: Unknown. There is no definitive link between the use of oral or intravenous steroids and development of septic arthritis in pediatric patients.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 86%, Disagree: 5%, Abstain: 9% (Super Majority, Strong Consensus)

RATIONALE

Septic arthritis is an infection of joints that spreads through systemic or local bacterial, viral or fungal infection. The overall prevalence of septic arthritis is relatively higher among children who are less than 4 years old. The incidence of septic arthritis has been reported to be 10 cases per 100,000 population and as high as 20 to 70 cases per 100,000 in patients with rheumatoid arthritis in the USA. The disease usually spreads through hematogenous system mainly due to intravenous drug use or prolonged use of a catheter and low immunity. The most common predisposing conditions that can develop into septic arthritis are rheumatoid arthritis, gout or osteoarthritis. In children, the hip is most commonly affected joint by septic arthritis as compared to the knee in adults accounting for 50% cases.

Computerized research of databases (PubMed, Medline Ovid and Google Scholar) was used for the literature review from 1950 to 2018. The shortage of literature could not directly link IV or oral steroid therapy as a risk factor for children to develop septic arthritis as an adverse reaction. Many randomized clinical trials were, however, found to be in favor of the prolonged use of IV and oral corticosteroid to avoid complications in pediatric patients suffering from septic arthritis and no further complications were observed that lead to the worsening of this disease [1–3]. There is still a debate whether immunosuppressive drugs, such as corticosteroids and cytotoxic agents, increase the risk for septic arthritis [4]. The potential association between administration of steroids and septic arthritis may be explained by the fact that steroids reduce the body's immunity and ability to fight infection [4]. One of the indirect causes of septic arthritis was found to be iatrogenic in 41.8% of adults, and the number of iatrogenic infections in Iceland increased from 2.8 cases/year in 1990–1994 to 9.0 cases/year in 1998–2002 ($p<0.01$) [5]. These iatrogenic infections can be linked to the use of unsterile intra-articular injections, possible use of contaminated needles or a break in the sterility during arthroscopic procedures [6,7].

The study conducted in the USA reported 32 cases of septic arthritis due to fungus-contaminated methylprednisolone vials [8]. However, these studies lacked proper evidence as these were descriptive in nature. These studies also did not fulfill our inclusion and exclusion criteria as it does not show a direct relationship of septic arthritis with steroid therapy rather than being an iatrogenic infection.

A case report published in 1957 reported septic arthritis as a reaction to steroid therapy in a woman who was 34 years old; she had been receiving corticotrophin, cortisone, hydrocortisone and prednisolone at various times in a year for the treatment of lupus erythematosus. A similar presentation was found in a man 54 years old suffering from exfoliative dermatitis and was getting treated with the same medicine. The steroid therapy resulted in septic arthritis of one knee and both hands including disfigurement of his fingers. Unfortunately, this study could not hold much evidence as it had a weak study design and the lowest number of reported cases. It also included adult patients so it cannot be generalized to children [9].

REFERENCES

[1] Harel L, Prais D, Bar-On E, Livni G, Hoffer V, Uziel Y, et al. Dexamethasone therapy for septic arthritis in children: results of a randomized double-blind placebo-controlled study. J Pediatr Orthop. 2011;31:211–215. doi:10.1097/BPO.0b013e3182092869.

[2] Odio CM, Ramirez T, Arias G, Abdelnour A, Hidalgo I, Herrera ML, et al. Double blind, randomized, placebo-controlled study of dexamethasone therapy for hematogenous septic arthritis in children. Pediatr Infect Dis J. 2003;22:883–888. doi:10.1097/01.inf.0000091293.32187.7b.

[3] Farrow L. A systematic review and meta-analysis regarding the use of corticosteroids in septic arthritis. BMC Musculoskelet Disord. 2015;16:241. doi:10.1186/s12891-015-0702-3.

[4] Lavy CBD. Septic arthritis in Western and sub-Saharan African children - a review. Int Orthop. 2007;31:137–144. doi:10.1007/s00264-006-0169-9.

[5] Geirsson AJ, Statkevicius S, Víkingsson A. Septic arthritis in Iceland 1990-2002: increasing incidence due to iatrogenic infections. Ann Rheum Dis. 2008;67:638–643. doi:10.1136/ard.2007.077131.

[6] Albert C, Brocq O, Gerard D, Roux C, Euller-Ziegler L. Septic knee arthritis after intra-articular hyaluronate injection. Two case reports. Joint Bone Spine. 2006;73:205–207. doi:10.1016/j.jbspin.2005.03.005.

[7] Sharff KA, Richards EP, Townes JM. Clinical management of septic arthritis. Curr Rheumatol Rep. 2013;15:332. doi:10.1007/s11926-013-0332-4.

[8] Chiller TM, Roy M, Nguyen D, Guh A, et al. Clinical findings for fungal infections caused by methylprednisolone injections. N Engl J Med. 2013;369:1610-1619.

[9] Mills LC, Boylston BF, Greene JA, Moyer JH. Septic arthritis as a complication of orally given steroid therapy. J Am Med Assoc. 1957;164:1310–1314.

Diagnostic

Authors: Ali Parsa, Mahzad Javid

QUESTION 1: What are the essential tests that need to be done in pediatric patients with joint infections?

RECOMMENDATION: Essential laboratory tests include serum C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cell (WBC) count, blood cultures, synovial fluid analysis and culture of tissue and/or synovial fluid. Further molecular testing and leucocyte esterase (LE) testing may have a role and warrant further research. Imaging studies include ultrasound in the hip joint. Symptoms lasting over a week warrant investigation with plain radiography. Magnetic resonance imaging (MRI) and bone scanning may have value in confirmation of the diagnosis in some patients.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 88%, Disagree: 6%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

Diagnostic evaluation of children with suspected joint infection or osteomyelitis should include CRP, WBC count and ESR [1]. CRP is valuable as a negative predictive tool since CRP < 1.0 mg/dL helps rule out the diagnosis of septic arthritis (SA) with an accuracy of 87% [2].

Synovial fluid aspiration should be performed. Samples should be transported in a heparinized syringe or pediatric culture bottles to prevent the clotting and enumeration of leukocytes [3]. Cell count and differential, gram stain and culture of the obtained synovial fluid are important steps in diagnostic work up of pediatric patients with SA [4,5].

A wide range of organisms can cause SA in pediatric patients. Thus, culture samples should be sent for both aerobic and anaerobic cultures. If an infection with unusual organisms is suspected, then a specialized culture medium may need to be used. For example, SA caused by *Kingella kingae* may require the use of cell lysis culture bottles for isolation of the organism [3]. If there is clinical suspicion for infection by *Neissena gonorrhoeae;* rectal, oropharyngeal, urogenital cultures and urine deoxyribonucleic acid (DNA) analysis are indicated [6,7].

In infants and young children, subperiosteal needle aspiration can be performed if point tenderness exists [3]. Although a WBC count > 50,000-60,000/mm^3 is typically expected, a synovial fluid leukocyte density of 5,000-8,000 cells/mm^3 has been found in cases of pediatric SA [8].

Conventional radiographs of the affected joint should also be taken in pediatric patients as imaging may show signs of osteomyelitis [9–11]. Plain radiographs are typically normal [12]. Ultrasound evaluation of the affected joint has been reported to be useful in the diagnostic work-up of SA, especially of the hip [12]. In one study, normal hip ultrasound was found to have a negative predictive value of 100% for SA [13]. In some circumstances additional imaging may be needed. MRI is the cross-sectional imaging modality of choice in pediatric patients with more than 90% sensitivity for diagnosis of SA. Sub-periosteal or soft tissue collections of pus that may require surgical drainage can be better and earlier detected on the MRI images. In the setting of acute osteomyelitis, decreased signal on T1-weighted images and increased signal on T2-weighted images is a pertinent finding [3]. MRI with and without gadolinium contrast should be ordered to identify the presence of osteoarticular infection and assess the perfusion status of the joint [14].

Radionucleotide scanning is widely used to diagnose osteomyelitis early when plain radiographs appear normal. Technetium-99m (99mTc) scintigraphy is the most common used type of radionucleotide imaging. Browne et al. reported that bone scans fail to detect about half of the cases of methicillin-resistant *Staphylococcus aureus* (MRSA) osteomyelitis [9]. Indium 111–labeled leukocyte scans are another option for diagnosis of osteomyelitis [15]. At present, there is no evidence that supports superiority of radionucleotide scanning over MRI.

Molecular analyses of the synovial fluid using polymerase chain reaction (PCR) or next generation sequencing (NGS) may provide a useful adjunct to conventional culture for the identification of the infective organisms. These assays may be effective in the detection of atypical bacteria, such as mycobacterium, anaerobic pathogens and facilitate pathogen identification in culture-negative disease [7].

The use of serum or synovial molecular markers in the diagnosis of SA has been explored. Procalcitonin is an emerging biomarker for the diagnosis of SA with a high specificity for detecting joint infections, but studies have only been conducted in adults [16–19]. Another biomarker that has been explored in the setting of pediatric SA is LE. LE has been in clinical use for over 30 years, mostly as a point-of-care test for the diagnosis of urinary tract infection. The first application of this test in orthopaedic patient population was explored by Parvizi et al. [20]. In the latter study, investigators reported over 80% sensitivity and 100% specificity with the use of LE dipstick testing for diagnosis of periprosthetic joint infection (PJI). A recent study demonstrated that LE is a valuable test for diagnosis of native SA, but evidence for its efficacy in the pediatric age group is sparse [21].

Finally, the role of interleukin-6 (IL-6), a cytokine that is released by fibroblasts, has also been explored in the pediatric patient population. IL-6 is an acute-phase reactant that is thought to play a role in increasing CRP production by the liver [22]. IL-6 may be detected earlier than CRP in bone and joint infections, however, its associated cost and limited availability in the clinical setting have prevented it from becoming a mainstay in diagnosis of orthopaedic infections [22,23].

In conclusion, it appears that conventional serum tests, namely CRP and ESR, plain radiographs and synovial fluid analysis are the most important tests in work-up of a pediatric patient with suspected SA and/or osteomyelitis. Molecular biomarkers or techniques involving DNA sequencing may play a role in facilitating

diagnosis, as they have demonstrated superior sensitivity over conventional cultures.

REFERENCES

[1] Kocher MS, Zurakowski D, Kasser JR. Differentiating between septic arthritis and transient synovitis of the hip in children: an evidence-based clinical prediction algorithm. J Bone Joint Surg Am. 1999;81:1662–1670.
[2] Levine MJ, McGuire KJ, McGowan KL, Flynn JM. Assessment of the test characteristics of C-reactive protein for septic arthritis in children. J Pediatr Orthop. 2003;23:373–377.
[3] Brewster D. Feigin & Cherry's Textbook of Pediatric Infectious Diseases. J Paediatr Child Health. 2011;47:319–320. doi:10.1111/j.1440-1754.2011.02088.x.
[4] Nelson JD. The bacterial etiology and antibiotic management of septic arthritis in infants and children. Pediatrics. 1972;50:437–440.
[5] Barton LL, Dunkle LM, Habib FH. Septic arthritis in childhood. A 13-year review. Am J Dis Child. 1960 1987;141:898–900.
[6] Moumile K, Merckx J, Glorion C, Berche P, Ferroni A. Osteoarticular infections caused by Kingella kingae in children: contribution of polymerase chain reaction to the microbiologic diagnosis. Pediatr Infect Dis J. 2003;22:837–839.
[7] Verdier I, Gayet-Ageron A, Ploton C, Taylor P, Benito Y, Freydiere A-M, et al. Contribution of a broad range polymerase chain reaction to the diagnosis of osteoarticular infections caused by Kingella kingae: description of twenty-four recent pediatric diagnoses. Pediatr Infect Dis J. 2005;24:692–696.
[8] Ropes MW. Examination of synovial fluid. Bull Rheum Dis. 1957;7:S 21–22.
[9] Browne LP, Mason EO, Kaplan SL, Cassady CI, Krishnamurthy R, Guillerman RP. Optimal imaging strategy for community-acquired Staphylococcus aureus musculoskeletal infections in children. Pediatr Radiol. 2008;38:841–847. doi:10.1007/s00247-008-0888-8.
[10] Chung T. Magnetic resonance imaging in acute osteomyelitis in children. Pediatr Infect Dis J. 2002;21:869–870. doi:10.1097/01.inf.0000028181.95121.aa.
[11] Harcke HT. Role of imaging in musculoskeletal infections in children. J Pediatr Orthop. 1995;15:141–143.
[12] Jaramillo D, Treves ST, Kasser JR, Harper M, Sundel R, Laor T. Osteomyelitis and septic arthritis in children: appropriate use of imaging to guide treatment. AJR Am J Roentgenol. 1995;165:399–403. doi:10.2214/ajr.165.2.7618566.
[13] Zawin JK, Hoffer FA, Rand FF, Teele RL. Joint effusion in children with an irritable hip: US diagnosis and aspiration. Radiology. 1993;187:459–463. doi:10.1148/radiology.187.2.8475290.
[14] Montgomery NI, Epps HR. Pediatric Septic Arthritis. Orthop Clin North Am. 2017;48:209–216. doi:10.1016/j.ocl.2016.12.008.
[15] Schauwecker DS. Osteomyelitis: diagnosis with In-111-labeled leukocytes. Radiology. 1989;171:141–146. doi:10.1148/radiology.171.1.2928518.
[16] Butbul-Aviel Y, Koren A, Halevy R, Sakran W. Procalcitonin as a diagnostic aid in osteomyelitis and septic arthritis. Pediatr Emerg Care. 2005;21:828–832.
[17] Maharajan K, Patro DK, Menon J, Hariharan AP, Parija SC, Poduval M, et al. Serum Procalcitonin is a sensitive and specific marker in the diagnosis of septic arthritis and acute osteomyelitis. J Orthop Surg. 2013;8:19. doi:10.1186/1749-799X-8-19.
[18] Fottner A, Birkenmaier C, von Schulze Pellengahr C, Wegener B, Jansson V. Can serum procalcitonin help to differentiate between septic and nonseptic arthritis? Arthroscopy. 2008;24:229–233. doi:10.1016/j.arthro.2007.07.029.
[19] Faesch S, Cojocaru B, Hennequin C, Pannier S, Glorion C, Lacour B, et al. Can procalcitonin measurement help the diagnosis of osteomyelitis and septic arthritis? A prospective trial. Ital J Pediatr. 2009;35:33. doi:10.1186/1824-7288-35-33.
[20] Parvizi J, Jacovides C, Antoci V, Ghanem E. Diagnosis of periprosthetic joint infection: the utility of a simple yet unappreciated enzyme. J Bone Joint Surg Am. 2011;93:2242–2248. doi:10.2106/JBJS.J.01413.
[21] Kelly EG, Cashman JP. Leucocyte esterase in the rapid diagnosis of paediatric septic arthritis. Med Hypotheses. 2013;80:191–193. doi:10.1016/j.mehy.2012.11.026.
[22] Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. N Engl J Med. 1999;340:448–454. doi:10.1056/NEJM199902113400607.
[23] Buck C, Bundschu J, Gallati H, Bartmann P, Pohlandt F. Interleukin-6: a sensitive parameter for the early diagnosis of neonatal bacterial infection. Pediatrics. 1994;93:54–58.

Authors: Ali Parsa, Mohammad Hammad

QUESTION 2: Are there conditions where the erythrocyte sedimentation rate (ESR) and other blood tests are unreliable for diagnosis of pediatric musculoskeletal infections?

RECOMMENDATION: Yes. Serum tests including ESR, C-reactive protein (CRP) and absolute white blood cell (WBC) count might be unreliable for diagnosis of pediatric musculoskeletal infections in neonates, patients with rheumatological disease, post-trauma, post-surgery, patients with Lyme arthritis and those receiving intravenous immunoglobulin (IVIG) administration.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 88%, Disagree: 3%, Abstain: 9% (Super Majority, Strong Consensus)

RATIONALE

Various serology tests including WBC count, ESR and CRP are traditionally used to diagnose septic arthritis (SA)/osteomyelitis (OM) in children. Their diagnostic value is less than synovial fluid analysis and cultures that usually are utilized to prove the infection. ESR and CRP are almost always elevated in any inflammatory process (trauma, rheumatologic disease) with low specificity for infection [1,2].

Leukocytosis is not a typical feature in children with SA [3]. It has been shown that studies including more SA rather than OM have a lower rate of leukocytosis [4]. Results of an evidence-based study showed that overall diagnostic accuracy of peripheral WBC count for SA is not acceptable regardless of selected cutoff point [1].

The challenging age group in children is neonates and young infants in whom the infection is caused by organisms, such as coagulase-negative Staphylococci [4]. Owing to the non-characteristic features of osteoarticular infection, Sankaran et al. in a prospective study reported that fever, poor feeding and irritability are seen in less than 30% of infants with SA. Beside the paucity of sign and symptoms in this study, neutrophil count was found to be normal in 70% [5].

CRP is more sensitive than ESR for diagnosis of infection; its level rising as soon as six hours after disease initiation. Different studies have shown its usefulness in the diagnosis of SA [6,7], resolution of infection in neonates [8] and its ability to differentiate transient synovitis of the hip from SA [9]. Levine et al. reported that ESR and CRP are better as negative predictors for SA, particularly when the CRP level is less than 1mg/dL with an accuracy of less than 85% [8].

Lyme arthritis in children may be associated with clinical findings similar to SA. CRP and ESR levels are reported to be increased in 64% to 100% of patients with Lyme arthritis, respectively [10,11]. CRP and ESR were not found to be useful tests to differentiate Lyme disease and SA [12]. Administration of IVIG in children can also result in increased levels of ESR, interfering with diagnosis of SA/OM and rendering the test ineffective in monitoring response to treatment [13].

Even though CRP and WBC counts of synovial samples are believed to be useful tests for diagnosis of SA and distinguishing it from juvenile inflammatory arthritis (JIA), a recent report demonstrates that these tests might not be sufficiently specific as there is significant overlap in the value of these tests in both conditions [14].

In addition, the levels of CRP and ESR may be elevated following trauma and after surgical procedures [15], rendering these tests less useful in post-trauma and postoperative periods.

REFERENCES

[1] Carpenter CR, Schuur JD, Everett WW, Pines JM. Evidence-based diagnostics: adult septic arthritis. Acad Emerg Med. 2011;18:781–796. doi:10.1111/j.1553-2712.2011.01121.x.

[2] Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. N Engl J Med. 1999;340:448–454. doi:10.1056/NEJM199902113400607.

[3] Kliegman R, Nelson WE, editors. Nelson Textbook of Pediatrics. 19th ed. Philadelphia, PA: Elsevier/Saunders; 2011.

[4] Rønnestad A, Abrahamsen TG, Gaustad P, Finne PH. C-reactive protein (CRP) response patterns in neonatal septicaemia. APMIS. 1999;107:593–600.

[5] Sankaran G, Zacharia B, Roy A, Purayil SP. Current clinical and bacteriological profile of septic arthritis in young infants: a prospective study from a tertiary referral centre. Eur J Orthop Surg Traumatol. 2018;28:573–578. doi:10.1007/s00590-018-2142-x.

[6] Kallio MJ, Unkila-Kallio L, Aalto K, Peltola H. Serum C-reactive protein, erythrocyte sedimentation rate and white blood cell count in septic arthritis of children. Pediatr Infect Dis J. 1997;16:411–413.

[7] Peltola H, Vahvanen V, Aalto K. Fever, C-reactive protein, and erythrocyte sedimentation rate in monitoring recovery from septic arthritis: a preliminary study. J Pediatr Orthop. 1984;4:170–174.

[8] Levine MJ, McGuire KJ, McGowan KL, Flynn JM. Assessment of the test characteristics of C-reactive protein for septic arthritis in children. J Pediatr Orthop. 2003;23:373–377.

[9] Eich GF, Superti-Furga A, Umbricht FS, Willi UV. The painful hip: evaluation of criteria for clinical decision-making. Eur J Pediatr. 1999;158:923–928.

[10] Willis AA, Widmann RF, Flynn JM, Green DW, Onel KB. Lyme arthritis presenting as acute septic arthritis in children. J Pediatr Orthop. 2003;23:114–118.

[11] Keane B, Top J, Burbridge M. Septic arthritis versus lyme arthritis: a case of diagnostic difficulty. Hosp Pediatr. 2018;8:170–172. doi:10.1542/hpeds.2017-0142.

[12] Baldwin KD, Brusalis CM, Nduaguba AM, Sankar WN. Predictive factors for differentiating between septic arthritis and lyme disease of the knee in children. J Bone Joint Surg Am. 2016;98:721–728. doi:10.2106/JBJS.14.01331.

[13] Salehzadeh F, Noshin A, Jahangiri S. IVIG Effects on erythrocyte sedimentation rate in children. Int J Pediatr. 2014;2014:981465. doi:10.1155/2014/981465.

[14] Aupiais C, Basmaci R, Ilharreborde B, Blachier A, Desmarest M, Job-Deslandre C, et al. Arthritis in children: comparison of clinical and biological characteristics of septic arthritis and juvenile idiopathic arthritis. Arch Dis Child. 2017;102:316–322. doi:10.1136/archdischild-2016-310594.

[15] Kallio P, Michelsson JE, Lalla M, Holm T. C-reactive protein in tibial fractures. Natural response to the injury and operative treatment. J Bone Joint Surg Br. 1990;72:615–617.

Authors: Muhammad Amin Chinoy, Syed Ahmed Hussain, Sher Wali Khan

QUESTION 3: For pediatric patients with suspected septic arthritis (SA), does the clinical criteria override inconclusive laboratory tests?

RECOMMENDATION: For pediatric patients with suspected SA, the clinical criteria override inconclusive laboratory tests.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 91%, Disagree: 2%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

It is well known that there are no standard tests that can accurately diagnose SA in children [1–7]. Thus, it is not uncommon to face a situation where the diagnosis of SA is strongly suspected, but laboratory tests remain inconclusive [3,4]. Among all the existing diagnostic tests for septic arthritis, isolation of infective organisms from the synovial joint is considered as the gold standard for this condition [3,5,6]. However, the latter can hardly be considered a gold standard as the probability of isolating an infective microorganism from the synovial fluid of patients with SA ranges from 22%-82% [7]. Culture results are affected by numerous factors including antibiotic administration and the virulence of the infective organism.

To improve the yield of a culture, it is recommended that antibiotic treatment is initiated after joint aspiration has been performed. In case of negative culture, laboratory tests, clinical symptoms and radiological signs are important for the diagnosis of SA [1,7]. As no single diagnostic test for SA in children exists [8], it is recommended that the diagnosis of SA should rest on the opinion of experienced clinicians and override the laboratory tests [1,3,4]. A systematic review revealed that, despite the use of laboratory investigations, the gold standard for the diagnosis of SA is the level of clinical suspicion of a physician experienced in the management of pediatric patients with musculoskeletal infections [3,4,8].

Although analysis of the synovial fluid can be useful in the diagnosis of SA in children, aspiration of the joint may require administration of general anesthesia and is complicated. The decision to perform aspiration should rest with the clinician and be determined based on the degree of suspicion for SA. Diagnosis of SA should rely on less invasive tests as much as possible [5].

Despite the extensive literature investigating the clinical and laboratory features of septic arthritis, the number of studies that exist on the significance of clinical features and laboratory tests for diagnosis of SA in children is limited.

Among the eight published studies, one is a systematic review, two are retrospective studies, two are review articles, one is a community-based epidemiological study and two are case series [1–8]. Based on the evaluation of the available literature, we are unable to determine the most effective diagnostic protocol for SA in children. Among the reviewed studies, one proposes that not all children can be classified as having or not having SA on the basis of historical, clinical, laboratory or radiologic findings [8]. The latter raises the need for additional tests, such as joint aspiration.

Another study endorses the same principle recommending that any patient without clear-cut evidence for SA, or lack thereof, needs an examination of the joint fluid for diagnosis [1]. Another study reported that the diagnosis is rarely established by the history and physical examination, and the clinician is led to rely on ancillary tests, specifically the white blood cell (WBC) count from peripheral blood and other serological markers for inflammation, such as the erythrocyte sedimentation rate [4]. A retrospective study examined the incidence, etiology and clinical features of septic arthritis in children less than 24 months and concluded that the diagnosis of SA in children needed to be made based on a high index of suspicion and could not be excluded based on lack of fever and normal laboratory tests [2].

Based on our understanding of the literature, and in the absence of an absolute test, it appears that the diagnosis of SA in children needs to be made using a combination of clinical findings, laboratory tests and appropriate imaging. For patients with equivocal findings, clinical suspicion should override laboratory findings, because missing SA in a child, especially when caused by a virulent organism, can have serious consequences.

REFERENCES

[1] Molteni RA. The differential diagnosis of benign and septic joint disease in children. Clinical, radiologic, laboratory, and joint fluid analysis, based on 37 children with septic arthritis and 97 with benign aseptic arthritis. Clin Pediatr (Phila). 1978;17:19–23. doi:10.1177/000992287801700104.

[2] Yagupsky P, Bar-Ziv Y, Howard CB, Dagan R. Epidemiology, etiology, and clinical features of septic arthritis in children younger than 24 months. Arch Pediatr Adolesc Med. 1995;149:537–540.

[3] Mathews CJ, Weston VC, Jones A, Field M, Coakley G. Bacterial septic arthritis in adults. Lancet Lond Engl. 2010;375:846–855. doi:10.1016/S0140-6736(09)61595-6.

[4] Li SF, Cassidy C, Chang C, Gharib S, Torres J. Diagnostic utility of laboratory tests in septic arthritis. Emerg Med J EMJ. 2007;24:75–77. doi:10.1136/emj.2006.037929.

[5] Kunnamo I, Kallio P, Pelkonen P, Hovi T. Clinical signs and laboratory tests in the differential diagnosis of arthritis in children. Am J Dis Child. 1960 1987;141:34–40.

[6] Al Saadi MM, Al Zamil FA, Bokhary NA, Al Shamsan LA, Al Alola SA, Al Eissa YS. Acute septic arthritis in children. Pediatr Int. 2009;51:377–380. doi:10.1111/j.1442-200X.2008.02791.x.

[7] Rutz E, Spoerri M. Septic arthritis of the paediatric hip - A review of current diagnostic approaches and therapeutic concepts. Acta Orthop Belg. 2013;79:123–134.

[8] Kang S-N, Sanghera T, Mangwani J, Paterson JMH, Ramachandran M. The management of septic arthritis in children: systematic review of the English language literature. J Bone Joint Surg Br. 2009;91-B:1127–1133. doi:10.1302/0301-620X.91B9.22530.

Authors: Ali Parsa, Mohammad Hammad

QUESTION 4: Is there a role for arthrocentesis (joint puncture) of an infected joint in a pediatric patient?

RECOMMENDATION: Yes. Arthrocentesis of an infected joint is effective for decompression of the joint. However, some children need arthrotomy.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 83%, Disagree: 11%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

Arthrocentesis (joint puncture) is one of the most valuable procedures for the diagnosis and treatment of joint diseases [1]. In children with septic arthritis (SA), arthrocentesis can be very useful for both diagnosis and as means of treatment [2,3]. It is safe and simple, but approaching the joint correctly, especially of the hip, is not possible for all physicians in emergency departments [4].

In a child with acutely swollen, red, painful joint and fever, if C-reactive protein (CRP) > 20mg/dL or erythrocyte sedimentation rate (ESR) > 20mm/h, then arthrocentesis may be indicated to confirm the diagnosis [5]. Arthrocentesis is also used as the treatment of SA in combination with antibiotic therapy. Ultrasound-guided aspiration of the hip evacuates pus, reduces damage to the articular surfaces, differentiates joint sepsis from other arthritides and helps direct antibiotic treatment [6,7]. Furthermore, there is a concern about the adverse effect of emergent open arthrotomy in severely inflamed joints, and it is debatable whether early decompressive arthrotomy is always useful [8–11].

In a retrospective study, hip arthrocentesis was found to avert the need for invasive surgery in more than 80 % of children (ranging from 3 months to 15 years of age) in a cohort of 261 culture-positive patients with SA. Outcome was comparable between arthrotomy and non-arthrotomy group. The study found that in the case of adjacent osteomyelitis, arthrotomy was more useful [12]. The results are supported by another study by Journeau et al. that reported favorable outcome in about 90% of the patients with hip arthrocentesis. They identified CRP > 100 mg/L, polymorphonuclear cell > 15,000, and ESR > 25 mm/hr as predictive of the need for arthrotomy [13].

In a prospective randomized trial, 201 consecutive children with the diagnosis of SA, arthrocentesis and arthrotomy were compared, and the patients were followed for one year. There were no differences regarding clinical outcome in any of the groups; hospital stay was lower in arthrocentesis group [8]. Smith et al. in a randomized control trial reported similar results for outcome of arthrotomy vs. arthrocentesis in 61 children with SA of the shoulder [10]. The findings of the latter study are also reflected in another study by Pääkkönen et al. involving nine children with SA affecting the shoulder [14].

Existing evidence for knee joint is different. Arthroscopic irrigation and decompression has been found to be successful in the majority of patients. The procedure can be performed through a single portal and without the need for a repeat procedure. In a retrospective study, around 40% of children older than three years who underwent a knee arthrocentesis required further arthrotomy to eradicate the infection and high initial CRP levels were identified as a predictor of aspiration failure [15].

REFERENCES

[1] Punzi L, Oliviero F. Arthrocentesis and synovial fluid analysis in clinical practice: value of sonography in difficult cases. Ann N Y Acad Sci. 2009;1154:152–158. doi:10.1111/j.1749-6632.2009.04389.x.

[2] Shmerling RH, Delbanco TL, Tosteson AN, Trentham DE. Synovial fluid tests. What should be ordered? JAMA. 1990;264:1009–1014.
[3] Baker DG, Schumacher HR. Acute monoarthritis. N Engl J Med. 1993;329:1013–1020. doi:10.1056/NEJM199309303291407.
[4] Courtney P, Doherty M. Joint aspiration and injection. Best Pract Res Clin Rheumatol. 2005;19:345–369. doi:10.1016/j.berh.2005.01.009.
[5] Pääkkönen M. Septic arthritis in children: diagnosis and treatment. Pediatr Health Med Ther. 2017;8:65–68. doi:10.2147/PHMT.S115429.
[6] Freeman K, Dewitz A, Baker WE. Ultrasound-guided hip arthrocentesis in the ED. Am J Emerg Med. 2007;25:80–86. doi:10.1016/j.ajem.2006.08.002.
[7] Tsung JW, Blaivas M. Emergency department diagnosis of pediatric hip effusion and guided arthrocentesis using point-of-care ultrasound. J Emerg Med. 2008;35:393–399. doi:10.1016/j.jemermed.2007.10.054.
[8] Lavy CBD, Thyoka M, Mannion S, Pitani A. Aspiration or lavage in septic arthritis? A long-term prospective study of 150 patients. Orthop Proc. 2003;85-B:109–109. doi:10.1302/0301-620X.85BSUPP_II.0850109a.
[9] Griffet J, El Hayek T. [Percutaneous drainage of septic hip arthritis in children]. Rev Chir Orthop Reparatrice Appar Mot. 1996;82:251–254.
[10] Smith SP, Thyoka M, Lavy CBD, Pitani A. Septic arthritis of the shoulder in children in Malawi. A randomised, prospective study of aspiration versus arthrotomy and washout. J Bone Joint Surg Br. 2002;84:1167–1172.
[11] Givon U, Liberman B, Schindler A, Blankstein A, Ganel A. Treatment of septic arthritis of the hip joint by repeated ultrasound-guided aspirations. J Pediatr Orthop. 2004;24:266–270.
[12] Pääkkönen M, Kallio MJT, Peltola H, Kallio PE. Pediatric septic hip with or without arthrotomy: retrospective analysis of 62 consecutive nonneonatal culture-positive cases. J Pediatr Orthop. Part B 2010;19:264–269. doi:10.1097/BPB.0b013e32833822be.
[13] Journeau P, Wein F, Popkov D, Philippe R, Haumont T, Lascombes P. Hip septic arthritis in children: assessment of treatment using needle aspiration/irrigation. Orthop Traumatol Surg Res OTSR. 2011;97:308–313. doi:10.1016/j.otsr.2011.01.009.
[14] Pääkkönen M, Peltola H, Kallio M, Kallio P. [Pediatric septic shoulder arthritis. Is routine arthrotomy still necessary?]. Duodecim. 2011;127:716–719.
[15] Tornero E, De Bergua-Domingo JM, Domenech P, Soldado F, Torner F, Castellanos J, et al. Knee arthritis in children: when can be safely treated with needle joint aspiration? A large children's tertiary hospital study. J Pediatr Orthop. 2018;Publish Ahead of Print. doi:10.1097/BPO.0000000000000883.

Authors: Muhammad Amin Chinoy, Sher Wali Khan

QUESTION 5: Is there a role for percutaneous bone sampling (biopsy) for microbiological diagnosis of septic arthritis/osteomyelitis (OM)? If so, when should this be performed?

RECOMMENDATION: Yes. Percutaneous bone sampling (biopsy) is very safe and cost-effective and can be obtained from any site under the guidance of fluoroscopy or computed tomography (CT). It has a low sensitivity for microbiological diagnosis of OM that can be enhanced by the addition of histopathological examination. Literature suggests that bone sampling should be performed before initiating empirical antibiotic therapy.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 88%, Disagree: 7%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

OM is described as inflammation of the bone marrow and adjoining bone and is usually related with cortical and trabecular destruction. It can be caused by bacteria, fungi and a variety of other organisms [1]. Prompt identification and treatment of OM is necessary since undiagnosed cases can result in chronic pain, amputation and death. Even though clinical symptoms, inflammatory serological markers and imaging, such as magnetic resonance imaging (MRI), play an essential role in reaching a diagnosis of OM, the most important aspect of diagnosis relies on isolation of the infective organism from the infection site [2–4]. Pathogen identification and determination of its antibiotic susceptibility are paramount for successful treatment with antimicrobial therapy. Blood cultures may also be positive in a small number of patients with OM, which can guide antimicrobial therapy, so definite diagnosis and suitable therapy depend on tissue samples collected through bone biopsy [4].

Although surgical biopsy is also an option for confirming the diagnosis, percutaneous biopsy with fluoroscopic or computed tomography (CT) guidance has been proven to be a more reasonable, faster and more cost-effective modality with fewer complications [5,6]. The first percutaneous vertebral bone biopsy was performed by Ball in 1934. The use of image guidance was first seen with radiography in 1949, fluoroscopy in 1969, CT in 1981, MRI in 1986 and CT fluoroscopy in 1996 [6].

Literature review from the 1990's and early 2000's stated the accuracy of a percutaneous biopsy of vertebral lesions guided with CT or fluoroscopy ranged from 88% to 100% [6]. The recent and most comprehensive retrospective review done by Sehn and Gilula reported that 63 of 113 cases were positive when samples were tested histologically (55.7%) and only 28 of the 92 cases were positive when samples were investigated microbiologically (30.4%). Culture and/or pathology review was positive in 73 (64.6%) of the 113 cases. Pathology review along with culture of biopsy specimen supported a diagnosis of OM in 64.6% of investigated cases. However, the age of the participants ranged from 1 to 92 years [7]. This is in contrast to the study done in the 1990s and early 2000s [6].

Ballah et al. reported that there were 26 biopsies performed, 21 out of 26 biopsies were diagnostic (81%); 2/26 (8%) were false-negative extracting nonlesional tissue, 2/26 (8%) were nondiagnostic and 1/26 (4%) were technically unsuccessful. The diagnoses were as follows: 12/26 biopsies (46%) were OM; 3/26 (11%) biopsies were Langerhans cell histiocytosis; 3/26 biopsies (11%) were normal bone; 2/26 (8%) biopsies were malignant tumors and 1/26 (4%) biopsies were osteoblastoma. Of 12 children with OM only 3 had a positive culture; 9/12 (75%) children had a negative culture. They did not report any p-value or confidence interval. They concluded that percutaneous CT guided vertebral bone biopsy is safe in children with a high degree of diagnostic accuracy [8].

A systematic review and meta-analysis of 7 studies (later excluded 2 studies) indicated that image-guided percutaneous needle aspiration biopsy has a high specificity (99.9%) and, therefore, is quite effective when positive. However, it has low sensitivity (52.2%) and can miss a substantial proportion of patients. Image-guided spinal biopsy had a diagnostic odds ratio (DOR) of 45.50 (95% confidence interval [CI], 13.66–151.56), a likelihood ratio of positive test (LRP) of 16.76 (95% CI, 5.51–50.95), a likelihood ratio of negative test (LRN) of 0.39 (95% CI, 0.24–0.64), a sensitivity of 52.2% (95% CI, 45.8–58.5) and a specificity of 99.9% (95% CI, 94.5–100). The results of this study strengthen

the importance of image-guided percutaneous spinal biopsy [9].

Wu et al. observed that out of 41 (age range 3 to 82 years) histologically positive cases of OM, 14 (34%) cases were positive at culture. The proportion of positive culture results in confirmed cases of OM on the basis of histology was low. Patients who were on antimicrobial therapy in a 24 hour period of the biopsy, 24% had a positive culture, and the patients who were not on antibiotics had a 42% culture positivity rate. Larger prospective studies are required to investigate this finding further. They also advised or requested physicians to hold antibiotics for at least 24 hours before the biopsy [10].

Rankine et al. performed a retrospective study on 20 patients who had percutaneous spinal biopsies, with 8 out of 20 patients (40%) on antibiotics before the biopsy. An organism was isolated in 8 out of 20 cases (40%). Out of 8 patients on antibiotics, an organism was isolated in only 2 cases (25%). The result of the biopsy helped to modify the treatment in 7 of the 20 patients (35%). They also suggested that spinal biopsy should be done before starting antibiotic and a sample should be sent for both microbiology and histopathology [11].

Ng et al. reviewed the histopathological, cytological and microbiological results of patients who underwent bone and para-osseous biopsies between July 1977 and March 1996. The 502 biopsies were taken from 477 patients (age range for male patients was 5-86 years and for female patients was 2-86 years). Tumors were reported in 40% of the biopsies and infection in 16%. The latter study confirms the importance of bone biopsy in confirming diagnosis of infection and also detecting the presence of neoplasm, a differential diagnosis that needs to be born in mind when encountering pediatric patients suspected of infection. A bone biopsy can be taken from any site under the guidance of fluoroscopy or CT [12].

In conclusion, our extensive search of the literature has revealed one study evaluating the role of bone biopsy in children with the remainder of the studies being performed in an adult population. Based on the available evidence, we recommend that percutaneous bone biopsy under fluoroscopic or CT guidance is a reasonable, fast and cost-effective modality for diagnosis of OM and differentiating infection from neoplasm. It carries low complication rate but the ability of this test to isolate the infective organism in OM remains low. The above studies suggest that percutaneous bone biopsy shows high specificity but low sensitivity in microbiological diagnosis of OM but the combining results of microbiological examination with histological evaluation of the samples enhances the sensitivity. Literature also suggests that bone biopsy should be performed before initiating empirical antibiotic therapy in order to increase its yield for isolation of the infective organism.

REFERENCES

[1] Stedman TL, Dirckx JH, editors. Stedman's Concise Medical Dictionary for the Health Professions. Ill. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2001.

[2] Sammak B, Abd El Bagi M, Al Shahed M, Hamilton D, Al Nabulsi J, Youssef B, et al. Osteomyelitis: a review of currently used imaging techniques. Eur Radiol. 1999;9:894–900.

[3] Termaat MF, Raijmakers PGHM, Scholten HJ, Bakker FC, Patka P, Haarman HJTM. The accuracy of diagnostic imaging for the assessment of chronic osteomyelitis: a systematic review and meta-analysis. J Bone Joint Surg Am. 2005;87:2464–2471. doi:10.2106/JBJS.D.02691.

[4] White LM, Schweitzer ME, Deely DM, Gannon F. Study of osteomyelitis: utility of combined histologic and microbiologic evaluation of percutaneous biopsy samples. Radiology. 1995;197:840–842. doi:10.1148/radiology.197.3.7480765.

[5] Kim BJ, Lee JW, Kim SJ, Lee GY, Kang HS. Diagnostic yield of fluoroscopy-guided biopsy for infectious spondylitis. AJNR Am J Neuroradiol. 2013;34:233–238. doi:10.3174/ajnr.A3120.

[6] Tehranzadeh J, Tao C, Browning CA. Percutaneous needle biopsy of the spine. Acta Radiol Stockh Swed. 1987 2007;48:860–868. doi:10.1080/02841850701459783.

[7] Sehn JK, Gilula LA. Percutaneous needle biopsy in diagnosis and identification of causative organisms in cases of suspected vertebral osteomyelitis. Eur J Radiol. 2012;81:940–946. doi:10.1016/j.ejrad.2011.01.125.

[8] Ballah D, Nijs E, Keller MS, Zhu X, Krishnamurthy G, Cahill AM. Percutaneous CT-guided vertebral bone biopsy in children. Pediatr Radiol. 2013;43:582–588. doi:10.1007/s00247-012-2542-8.

[9] Pupaibool J, Vasoo S, Erwin PJ, Murad MH, Berbari EF. The utility of image-guided percutaneous needle aspiration biopsy for the diagnosis of spontaneous vertebral osteomyelitis: a systematic review and meta-analysis. Spine J. 2015;15:122–131. doi:10.1016/j.spinee.2014.07.003.

[10] 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;188:1529–1534. doi:10.2214/AJR.06.1286.

[11] Rankine JJ, Barron DA, Robinson P, Millner PA, Dickson RA. Therapeutic impact of percutaneous spinal biopsy in spinal infection. Postgrad Med J. 2004;80:607–609. doi:10.1136/pgmj.2003.017863.

[12] Ng CS, Salisbury JR, Darby AJ, Gishen P. Radiologically guided bone biopsy: results of 502 biopsies. Cardiovasc Intervent Radiol. 1998;21:122–128.

Authors: Ali Parsa, Irene Kalbian, Karan Goswami

QUESTION 6: Is there any role for polymerase chain reaction (PCR) or molecular testing in pediatric musculoskeletal infection (PMSI)?

RECOMMENDATION: PCR may be a useful diagnostic adjunct with the potential to expedite a preliminary diagnosis of PMSI in comparison to the use of microbiological culture alone. Furthermore, PCR can enable pathogen identification in cases where the organism is indolent, fastidious or difficult to culture. However, data remains sparse and further research is needed to standardize molecular techniques, minimize contamination and explore emerging molecular methods that are primer-independent.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 93%, Disagree: 2%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

The diagnosis of musculoskeletal infection is typically based on pertinent clinical findings, synovial fluid analysis and a positive gram stain or culture confirming the microbial identity of a pathogen [1]. Although culture results are used to identify the infecting organism and determine antimicrobial sensitivity, culture is often limited by sampling methodology, processing issues, early antibiotic administration, and/or the presence of hard to culture organisms [2–4]. PCR and other molecular techniques have been investigated to a limited

degree as diagnostic tools and are showing promise for improving PMSI diagnosis.

Evidence for the diagnostic use of PCR in PMSI is sparse. In a prospective study exploring the utility of PCR, Verdier et al. enrolled 171 pediatric patients with osteoarticular infection (OAI). From this cohort, 64 culture-positive specimens were identified, of which 9 cases were positive for *Kingella kingae*. When the 107 culture-negative specimens were tested with PCR, 15 additional cases of *Kingella kingae* were detected [5]. Similarly, Chometon et al. conducted a study of 131 patients with acute pediatric OAI in a single hospital and found that pathogen identification improved from 45% by culture alone to 66% with both culture and PCR testing [6].

Ferroni et al. performed a prospective study with 197 acute pediatric OAI cases in a single hospital and found that the use of PCR in addition to culture and histology increased bacterial diagnosis by 54%.

There is additional evidence for the utility of PCR aiding diagnosis of musculoskeletal infection from studies examining adult cases. However, the reported sensitivity of PCR varies widely in the literature from 43.8% to 92.5% and specificity ranges from 92.9% to 100% [7–9]. Despite this variation, investigators consistently conclude that the rapid availability of the results (<1 day) make PCR an adjunctive tool for guiding early treatment prior to the availability of culture results [7,8], especially in the setting of a negative culture [9]. It should be noted that these studies used different standards to compare to PCR performance; Bonilla et al. and Fenollar et al. used culture results as their gold standard, while Fihman et al. used clinician diagnostic judgment based on predetermined factors [7,9]. This significant inconsistency renders the results difficult to compare and interpret across studies.

PCR has also shown promise as a valuable tool for diagnosing tuberculosis affecting the bones and joints [10–12]. *Mycobacterium tuberculosis* is a particularly difficult organism to culture because false-negative results are relatively common. Therefore, a rapid, reliable diagnostic test is still needed. A study of 24 samples (21 patients) showed that PCR had 100% sensitivity and 87.5% specificity for identifying tuberculous disease affecting the bones and joints. However, two false-positive results were seen in patients who had previously been diagnosed with tuberculosis [10].

An infected joint can rapidly progress into a medical emergency. Rapid molecular diagnostic tools could play a crucial role in identifying and treating the infection promptly [13]. PCR is a sensitive, rapid and widely-available molecular methodology that can detect microbial pathogens in clinical samples. However, in order to obtain reliable and consistent results it is necessary to standardize PCR preparation protocols and take care to avoid contamination [1,13].

Further research is needed to investigate the role that PCR and other molecular methods can play in identifying a pathogen.

REFERENCES

[1] Mathews CJ, Coakley G. Septic arthritis: current diagnostic and therapeutic algorithm. Curr Opin Rheumatol. 2008;20(4):457–462.
[2] Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. N Engl J Med. 2004;351(16):1645–1654.
[3] Widmer AF. New developments in diagnosis and treatment of infection in orthopedic implants. Clin Infect Dis. 2001;33:S94–106. doi:10.1086/321863.
[4] Cai HY, Caswell JL, Prescott JF. Nonculture molecular techniques for diagnosis of bacterial disease in animals: a diagnostic laboratory perspective. Vet Pathol. 2014;51:341–350. doi:10.1177/0300985813511132.
[5] Verdier I, Gayet-Ageron A, Ploton C, Taylor P, Benito Y, Freydiere A-M, et al. Contribution of a broad range polymerase chain reaction to the diagnosis of osteoarticular infections caused by Kingella kingae: description of twenty-four recent pediatric diagnoses. Pediatr Infect Dis J. 2005;24:692–696.
[6] Chometon S, Benito Y, Chaker M, Boisset S, Ploton C, Bérard J, et al. Specific real-time polymerase chain reaction places Kingella kingae as the most common cause of osteoarticular infections in young children: Pediatr Infect Dis J. 2007;26:377–381. doi:10.1097/01.inf.0000259954.88139.f4.
[7] Bonilla H, Kepley R, Pawlak J, Belian B, Raynor A, Saravolatz LD. Rapid diagnosis of septic arthritis using 16S rDNA PCR: a comparison of 3 methods. Diagn Microbiol Infect Dis. 2011;69:390–395. doi:10.1016/j.diagmicrobio.2010.11.010.
[8] Fihman V, Hannouche D, Bousson V, Bardin T, Lioté F, Raskine L, et al. Improved diagnosis specificity in bone and joint infections using molecular techniques. J Infect. 2007;55:510–517. doi:10.1016/j.jinf.2007.09.001.
[9] Fenollar F, Roux V, Stein A, Drancourt M, Raoult D. Analysis of 525 samples to determine the usefulness of PCR amplification and sequencing of the 16S rRNA gene for diagnosis of bone and joint infections. J Clin Microbiol. 2006;44:1018–1028. doi:10.1128/JCM.44.3.1018-1028.2006.
[10] Titov AG, Vyshnevskaya EB, Mazurenko SI, Santavirta S, Konttinen YT. Use of polymerase chain reaction to diagnose tuberculous arthritis from joint tissues and synovial fluid. Arch Pathol Lab Med. 2004;128:205–209. doi:10.1043/1543-2165(2004)128<205:UOPCRT>2.0.CO;2.
[11] Verettas D, Kazakos C, Tilkeridis C, Dermon A, Petrou H, Galanis V. Polymerase chain reaction for the detection of Mycobacterium tuberculosis in synovial fluid, tissue samples, bone marrow aspirate and peripheral blood 2003;69:4.
[12] Fujimoto N, Gemba K, Yao A, Ozaki S, Ono K, Wada S, et al. Tuberculosis diagnosed by PCR analysis of synovial fluid. J Infect Chemother. 2010;16:53–55. doi:10.1007/s10156-009-0010-7.
[13] Shirtliff ME, Mader JT. Acute septic arthritis. Clin Microbiol Rev. 2002;15:527–544. doi:10.1128/CMR.15.4.527-544.2002.

Author: Mahzad Javid

QUESTION 7: How can we differentiate between sickle cell crisis and septic arthritis/osteomyelitis (OM)?

RECOMMENDATION: A combination of clinical, laboratory and imaging studies are all needed for differentiating between sickle cell crisis and infection. A positive aspiration for infection from the joint or periosteum confirms the presence of infection while sequential ultrasounds in the absence of sub-periosteal fluid collection favor sickle cell crisis. Tri-phasic bone scan in the first 24 hours can differentiate vaso-occlusive crisis (VOC) from acute infection. Contrast-enhanced magnetic resonance imaging (MRI) is fairly accurate in differentiating infection from infarction.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 87%, Disagree: 0%, Abstain: 13% (Super Majority, Strong Consensus)

RATIONALE

Differentiating bone and joint infection from osteonecrosis (ON) in sickle cell disease (SCD) can be very challenging. Clinical presentation is an important tool in distinguishing OM from VOC in SCD: sudden, often severe pain; no or low-grade fever of less than 100 F (<38 c); inflam-

matory markers only mildly elevated; and elevated HB/HCT ratio are all indicative of crisis and ON [1–3]. Also, pain in more than one site is more likely to be a crisis and not OM [4,5].

Inusa et al. [6] in a retrospective study demonstrated that mean initial white blood cell count was 14.9 in VOC and 17.8 in OM. They reported mean C-reactive protein (CRP) as the more informative test in differentiating OM from VOC–86.4 vs. 39.8. Therefore, CRP should be included in the risk criteria for infection in an SCD patient with fever [7,8]. Radiographs in early phases of OM or VOC are usually normal, with periosteal reaction showing up in both conditions within the first 2 weeks [4,9].

Ultrasound scans alone can diagnose OM in SCD cases with 74% sensitivity and 63% specificity [10]. Ultrasound scan within the first six days shows periosteal elevation and/or fluid collection in 76% of OM, while 91% of VOC cases show no evidence of fluid collection. Repeat ultrasound is needed to confirm the diagnosis of VOC when fluid collection remains negative [6].

Combination of ultrasound and CRP was found to be a reliable, cost-effective measure in distinguishing OM from VOC [6]. Triphasic isotope bone scans and labeled WBC scans can be helpful in later stages [11–14]. Sequential radionuclide bone marrow scanning and bone scan within the first 24 hours differentiate bone infarction from acute infection [15,16].

T1-weighted MRI has low intensity in the medullary infarct and high intensity in T2-weighted images [4,11]. Contrast material enhancement on MRI may distinguish accurately between infection and infarction [17]. Un-enhanced bone marrow signal intensity on fat-saturated MRI images is not a reliable criterion for differentiation of infection from infarction according to Delgado [18].

Aspiration of pus from the subperiosteal region or joint, or positive blood culture remains the gold standard for diagnosing infection in SCD, bearing in mind that a negative blood culture does not rule out infection [8,19,20].

REFERENCES

[1] Vanderhave KL, Perkins CA, Scannell B, Brighton BK. Orthopaedic manifestations of sickle cell disease. J Am Acad Orthop Surg. 2018;26:94–101. doi:10.5435/JAAOS-D-16-00255.

[2] Berger E, Saunders N, Wang L, Friedman JN. Sickle cell disease in children: differentiating osteomyelitis from vaso-occlusive crisis. Arch Pediatr Adolesc Med. 2009;163:251–255. doi:10.1001/archpediatrics.2008.545.

[3] Worrall D, Smith-Whitley K, Wells L. Hemoglobin to hematocrit ratio: the strongest predictor of femoral head osteonecrosis in children with sickle cell disease. J Pediatr Orthop. 2016;36:139–144. doi:10.1097/BPO.0000000000000409.

[4] Munk PL, Helms CA, Holt RG. Immature bone infarcts: findings on plain radiographs and MR scans. AJR Am J Roentgenol. 1989;152:547–549. doi:10.2214/ajr.152.3.547.

[5] Sennara H, Gorry F. Orthopedic aspects of sickle cell anemia and allied hemoglobinopathies. Clin Orthop Relat Res. 1978:154–157.

[6] Inusa BPD, Oyewo A, Brokke F, Santhikumaran G, Jogeesvaran KH. Dilemma in differentiating between acute osteomyelitis and bone infarction in children with sickle cell disease: the role of ultrasound. PloS One. 2013;8:e65001. doi:10.1371/journal.pone.0065001.

[7] Morrissey BJ, Bycroft TP, Almossawi O, Wilkey OB, Daniels JG. Incidence and predictors of bacterial infection in febrile children with sickle cell disease. Hemoglobin. 2015;39:316–319. doi:10.3109/03630269.2015.1065419.

[8] Almeida A, Roberts I. Bone involvement in sickle cell disease. Br J Haematol. 2005;129:482–490. doi:10.1111/j.1365-2141.2005.05476.x.

[9] Chambers JB, Forsythe DA, Bertrand SL, Iwinski HJ, Steflik DE. Retrospective review of osteoarticular infections in a pediatric sickle cell age group. J Pediatr Orthop. 2000;20:682–685.

[10] William RR, Hussein SS, Jeans WD, Wali YA, Lamki ZA. A prospective study of soft-tissue ultrasonography in sickle cell disease patients with suspected osteomyelitis. Clin Radiol. 2000;55:307–310. doi:10.1053/crad.1999.0377.

[11] Ganguly A, Boswell W, Aniq H. Musculoskeletal manifestations of sickle cell anaemia: a pictorial review. Anemia. 2011;2011:794283. doi:10.1155/2011/794283.

[12] Ejindu VC, Hine AL, Mashayekhi M, Shorvon PJ, Misra RR. Musculoskeletal manifestations of sickle cell disease. Radiographics. 2007;27:1005–1021. doi:10.1148/rg.274065142.

[13] Palestro CJ, Love C, Tronco GG, Tomas MB, Rini JN. Combined labeled leukocyte and technetium 99m sulfur colloid bone marrow imaging for diagnosing musculoskeletal infection. Radiographics. 2006;26:859–870. doi:10.1148/rg.263055139.

[14] Umans H, Haramati N, Flusser G. The diagnostic role of gadolinium enhanced MRI in distinguishing between acute medullary bone infarct and osteomyelitis. Magn Reson Imaging. 2000;18:255–262.

[15] Skaggs DL, Kim SK, Greene NW, Harris D, Miller JH. Differentiation between bone infarction and acute osteomyelitis in children with sickle-cell disease with use of sequential radionuclide bone-marrow and bone scans. J Bone Joint Surg Am. 2001;83-A:1810–1813.

[16] Kim HC, Alavi A, Russell MO, Schwartz E. Differentiation of bone and bone marrow infarcts from osteomyelitis in sickle cell disorders. Clin Nucl Med. 1989;14:249–254.

[17] Jain R, Sawhney S, Rizvi SG. Acute bone crises in sickle cell disease: the T1 fat-saturated sequence in differentiation of acute bone infarcts from acute osteomyelitis. Clin Radiol. 2008;63:59–70. doi:10.1016/j.crad.2007.07.017.

[18] Delgado J, Bedoya MA, Green AM, Jaramillo D, Ho-Fung V. Utility of unenhanced fat-suppressed T1-weighted MRI in children with sickle cell disease – can it differentiate bone infarcts from acute osteomyelitis? Pediatr Radiol. 2015;45:1981–1987. doi:10.1007/s00247-015-3423-8.

[19] Wong AL, Sakamoto KM, Johnson EE. Differentiating osteomyelitis from bone infarction in sickle cell disease. Pediatr Emerg Care. 2001;17:60–63; quiz 64.

[20] Keeley K, Buchanan GR. Acute infarction of long bones in children with sickle cell anemia. J Pediatr. 1982;101:170–175.

Treatment

Authors: Ali Parsa, Alexander J. Shope

QUESTION 1: What are the indications for surgical intervention in cases of osteomyelitis/septic arthritis? How should treatment progress and resolution be monitored?

RECOMMENDATION: Septic arthritis is an orthopaedic emergency and needs prompt surgical treatment. Based on current evidence, there are no clear indications for the timing of surgical intervention in cases of osteomyelitis. The current literature does suggest monitoring disease progression, treatment efficacy and resolution by trending C-reactive protein (CRP) levels.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 91%, Disagree: 3%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

The treatment of musculoskeletal infections in children has long been debated. Evidence has shown that it can be appropriate to treat this condition medically. However, surgery can play a critical therapeutic role for patients not responding to medical treatment or those presenting with massive bioburden in the joint that may require evacuation.

Osteomyelitis in the pediatric population often has overlapping clinical features with other diseases, making its diagnosis challenging [1]. Not only are the clinical presentations diverse, the epidemiologic aspects of the pathology also play a critical role in its therapy. Patient age, sex, socioeconomic status and even geographical location all point to different etiologies, making treatment choices challenging [1,2]. Patients living in the United States can be at particular risk of aggressive osteomyelitis infections due to the presence of highly virulent strains of methicillin-resistant *Staphylococcus aureus* (MRSA). Ninety percent of MRSA isolates found in the U.S. are related to the USA300 strain which is positive for *pvl* and *fnbB* genes–coding for the Panton-Valentine Leucocidin toxin and fibronectin binding factor respectively [3]. Patients contracting strains such as these are at increased risk of subperiosteal abscess formation, septic thrombophlebitis, endocarditis and large muscle abscesses [3]. Another pathogen, *Kingella kingae*, has also recently emerged as an etiology of osteomyelitis and septic arthritis with a milder clinical presentation as well as lower inflammatory markers and white-blood cell (WBC) counts [4]. This further emphasizes the diversity in which these conditions can present.

Because of the multifaceted nature of osteomyelitis, care of these patients requires a coordinated, multidisciplinary approach in order to avoid potentially devastating complications of a missed osteomyelitis diagnosis [1]. As with many conditions in medicine, early diagnosis and treatment initiation are paramount. Unfortunately, there are no gold standard tests to aid in the diagnosis of septic arthritis or osteomyelitis in the pediatric patient population [5]. Additionally, the lack of clear-cut surgical indications makes treatment plans complicated [1,6–9].

Osteomyelitis was found to be concomitant with septic arthritis in about 30% of cases [1,3]. Typically, bacteria seed in the metaphyseal region of long bones where capillaries make sharp turns resulting in serpentine routes of blood flow [1,3,5]. If the infection develops in the intracapsular portion of metaphyseal bone (i.e., proximal femur, humerus, radius or lateral distal tibia) there is a higher likelihood of extension into the joint space [1,3]. Joint space involvement creates an increase in intra-articular pressure, recruitment of leukocytes and subsequent release of cytokines, which can cause cartilage damage in as little as eight hours [4,10].

Proponents for surgical intervention have argued that the operative intervention can halt the disease progression [1,6,11]. Surgery and debridement of the joint can reduce the likelihood for osteonecrosis by enhancing the vascular supply to the bone, thereby allowing for improved antibiotic delivery and penetration to the site of infection [6]. Likewise, with osteoarticular involvement, decompressing and washing out the joint helps stem permanent damage by decreasing intra-articular pressure and reducing proteolytic enzymes resulting in degradation of the cartilage and sub-chondral bone [10,11].

Despite these valid arguments, studies have not been conducted that effectively define surgical indications for osteomyelitis and septic arthritis. Indications for surgery in the literature are based on expert opinions, case series and cohort studies with none providing evidence-based clinical guidelines for surgical intervention in the case of osteomyelitis [6,7,9]. Additionally, the surgical procedures used for osteomyelitis are diverse, ranging from bone biopsy and subperiosteal abscess drainage to more involved procedures, such as the creation of a cortical window and extensive debridement [1]. Dartnell et al. conducted a systematic review of the literature and found very little evidence to support surgical intervention in pediatric patients with osteomyelitis and/or septic arthritis due to a lack of randomized controlled trials [8]. At best, current recommendations for surgery include [1,6–8,12]:

- Failure to improve in 48-72 hours despite antibiotic treatment
- Presence of frank pus on aspiration of the joint
- Identification of sequestered abscess

However, none of these recommendations come with quantitative evidence from randomized controlled studies.

Septic arthritis is considered an orthopaedic emergency and necessitates prompt treatment [13–15]. Across the current literature, it is well agreed that septic arthritis requires surgical removal of the inciting materials [5,10]. Guidelines and appropriate randomized trials to establish statistical evidence are still lacking. Moreover, numerous suggestions of the exact joint decompression technique exist (i.e., arthrotomy versus arthroscopy versus needle aspiration).

El-Sayed et al. conducted a prospective controlled study to compare hip arthrotomy versus arthroscopy in the setting of septic

hip arthritis [13]. Open arthrotomy had been considered the gold standard at the time of his study. The latter study reported no statistical differences in clinical results (according to Bennett's clinical assessment criteria), such as prolonged post-operative joint aches, joint range of motion limitations or infection recurrence [13]. Mean hospital length of stay was shorter for the arthroscopic group compared to the arthrotomy group (mean of 3.8 days versus 6.4 days, $p < 0.0001$) [13]. The results of this study suggest that hip arthroscopy is a valid alternative to hip arthrotomy for septic arthritis of the hip joint. Similar findings were reported by another study [5].

For septic arthritis of the knee, arthroscopy tends to be the operative choice [12,13]. Again, data is lacking to support these claims. Other studies have suggested that arthrotomy may be better for septic arthritis of the shoulder and the hip joint due to the tight space in these joints to allow entry of arthroscopic instruments [10,12]. Baker et al. noted that arthroscopy can be a viable alternative as well in the shoulder and ankle joints [12]. Conversely, Peltola et al. report in their prospective randomized trial that most of the included patients in their study did not require any operative procedures beyond a diagnostic aspiration [16]. Despite the debate over the technique and necessity of surgical interventions, the literature does emphasize that early diagnosis and prompt treatment are paramount when caring for suspected septic arthritis patients [5,8,10,13].

Other studies have attempted to streamline the diagnostic approach to patients with suspected septic arthritis. Kocher et al. established a clinical algorithm in order to aid in early diagnosis of pediatric septic hips [14]. Their criteria included the inability or refusal of the patient to bear weight, history of fever (defined as an oral temperature >38.5 °C), a serum WBC count greater than 12,000 cells/mm^3 and an erythrocyte sedimentation rate (ESR) greater than 40 mm/hr [14]. Later studies found greater efficacy when incorporating CRP into this algorithm [17–19]. However, this clinical algorithm has not been fully validated across all populations and further studies must be carried out before it can be applied universally [15,20].

Despite significant heterogeneity in the literature regarding surgical indications and operative techniques for osteomyelitis and septic arthritis, there is more of a consensus on the use of CRP and ESR for aiding in diagnosis and monitoring treatment response [8,17]. CRP has been proven as an effective test for diagnosis and monitoring of response to treatment [5,8,10,16]. ESR was classically associated as a laboratory marker for osteomyelitis but has now been widely replaced by CRP [10]. The short half-life of CRP allows for more precise monitoring for efficacy of treatment. Decreasing CRP levels are indicative of treatment efficacy [8,16]. Pääkkönen et al. found that even with persistent pyrexia, decreasing CRP levels could be used to justify switching antibiotics from intravenous to oral [10]. They also report that they were able to safely discontinue antibiotics after 10 days as long as CRP levels were less than 20 mg/dL [10,16]. In circumstances when the CRP levels does not decline or continues to increase, further workup or additional interventions may be necessary as this suggests a suboptimal clinical response to the current treatment [16].

REFERENCES

[1] Funk SS, Copley LAB. Acute hematogenous osteomyelitis in children: pathogenesis, diagnosis, and treatment. Orthop Clin North Am. 2017;48:199–208. doi:10.1016/j.ocl.2016.12.007.

[2] Malcius D, Trumpulyte G, Barauskas V, Kilda A. Two decades of acute hematogenous osteomyelitis in children: are there any changes? Pediatr Surg Int. 2005;21:356–359. doi:10.1007/s00383-005-1432-7.

[3] Agarwal A, Aggarwal AN. Bone and joint infections in children: septic arthritis. Indian J Pediatr. 2016;83:825–833. doi:10.1007/s12098-015-1816-1.

[4] Ceroni D, Cherkaoui A, Combescure C, François P, Kaelin A, Schrenzel J. Differentiating osteoarticular infections caused by Kingella kingae from those due to typical pathogens in young children: Pediatr Infect Dis J. 2011;30:906–909. doi:10.1097/INF.0b013e31821c3aee.

[5] Iliadis AD, Ramachandran M. Paediatric bone and joint infection. EFORT Open Rev. 2017;2:7–12. doi:10.1302/2058-5241.2.160027.

[6] Castellazzi L, Mantero M, Esposito S. Update on the management of pediatric acute osteomyelitis and septic arthritis. Int J Mol Sci. 2016;17. doi:10.3390/ijms17060855.

[7] Street M, Puna R, Huang M, Crawford H. Pediatric acute hematogenous osteomyelitis. J Pediatr Orthop. 2015;35:634–639. doi:10.1097/BPO.0000000000000332.

[8] Dartnell J, Ramachandran M, Katchburian M. Haematogenous acute and subacute paediatric osteomyelitis: a systemic review of the literature. J Bone Joint Surg Br. 2012;94(5):584-585.

[9] DeRonde KJ, Girotto JE, Nicolau DP. Management of pediatric acute hematogenous osteomyelitis, part I: antimicrobial stewardship approach and review of therapies for methicillin-susceptible Staphylococcus aureus, Streptococcus pyogenes, and Kingella kingae. Pharmacotherapy. 2018;Jun 19. doi:10.1002/phar.2160.

[10] Pääkkönen M, Peltola H. Management of a child with suspected acute septic arthritis. Arch Dis Child. 2012;97(3):287-292. doi:10.1136/archdischild-2011-300462.

[11] Ceroni D, Kampouroglou G, Anderson della Llana R, Salvo D. Osteoarticular infections in young children: what has changed over the last years? Swiss Med Wkly. 2014;144:w13971. doi:10.4414/smw.2014.13971.

[12] Baker ADL, Macnicol MF. Haematogenous osteomyelitis in children: epidemiology, classification, aetiology and treatment. Paediatr Child Health. 2008;18:75–84. doi:10.1016/j.paed.2007.11.002.

[13] El-Sayed AMM. Treatment of early septic arthritis of the hip in children: comparison of results of open arthrotomy versus arthroscopic drainage. J Child Orthop. 2008;2:229–237. doi:10.1007/s11832-008-0094-0.

[14] Kocher MS, Mandiga R, Zurakowski D, Barnewolt C, Kasser JR. Validation of a clinical prediction rule for the differentiation between septic arthritis and transient synovitis of the hip in children: J Bone Joint Surg Am. 2004;86A(8):1629–1635. doi:10.2106/00004623-200408000-00005.

[15] Uzoigwe CE. Another look: is there a flaw to current hip septic arthritis diagnostic algorithms? Clin Orthop Relat Res. 2014;472:1645–1651. doi:10.1007/s11999-013-3142-0.

[16] Peltola H, Pääkkönen M, Kallio P, Kallio MJT. Prospective, randomized trial of 10 days versus 30 days of antimicrobial treatment, including a short-term course of parenteral therapy, for childhood septic arthritis. Clin Infect Dis. 2009;48:1201–1210. doi:10.1086/597582.

[17] Caird MS, Flynn JM, Leung YL, Millman JE, D'Italia JG. Factors distinguishing septic arthritis from transient synovitis of the hip in children. J Bone Joint Surg Am. 2006:88(6):1251–1257.

[18] Jung ST, Rowe SM, Moon ES, Song EK, Yoon TR, Seo HY. Significance of laboratory and radiologic findings for differentiating between septic arthritis and transient synovitis of the hip. J Pediatr Orthop 2003;23:368–372.

[19] Singhal R, Perry DC, Khan FN, Cohen D, Stevenson HL, James LA, et al. The use of CRP within a clinical prediction algorithm for the differentiation of septic arthritis and transient synovitis in children. J Bone Joint Surg Br. 2011;93-B:1556–1561. doi:10.1302/0301-620X.93B11.26857.

[20] Sultan J, Hughes PJ. Septic arthritis or transient synovitis of the hip in children: the value of clinical prediction algorithms. J Bone Joint Surg Br. 2010;92-B:1289–1293. doi:10.1302/0301-620X.92B9.24286.

Author: Mahzad Javid

QUESTION 2: How radical should surgery be for osteomyelitis/septic arthritis?

RECOMMENDATION: In pediatric patients with osteomyelitis/septic arthritis who require surgical intervention, aggressive debridement and copious irrigation of the infected joint is required.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 89%, Disagree: 7%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

The treatment of choice for septic arthritis in children is irrigation and debridement of the septic joint to clear the joint of bacteria and destructive enzymes and also decrease the intra-articular pressure to avoid articular cartilage damage and ischemia [1,2].

Septic arthritis of the hip joint has been posited as an emergent condition in pediatric patients often requiring open arthrotomy as soon as confirmation of the disease is made with joint aspiration [1–5].

There are a few reports that show equivalent outcome for treatment of hip septic arthritis when arthroscopy versus arthrotomy was employed [6,7]. Repeated aspirations of the hip joint under ultrasound guidance was shown to be effective in 85% of children without the need for an arthrotomy [4,8–11]. The indication for surgical treatment of septic arthritis of other joints remains controversial. Drainage of any large effusion present in joints is usually advocated. In ankle, knee and shoulder joints, arthroscopic irrigation or aspiration and lavage may be appropriate [1,3].

There is no consensus for the time, type and extent of surgical procedures in patients with osteomyelitis [1]. Surgery is recommended in the presence of subperiosteal abscess, bone necrosis or direct invasion of the growth plate that may be seen in magnetic resonance imaging (MRI) images [2]. It is also indicated if a patient does not respond to antibiotic therapy, based on clinical examination, laboratory indices and imaging studies (particularly MRI) [1].

The decision to drain a subperiosteal collection seen on ultrasound cannot be based purely on the size of collection but needs to take into account the clinical findings of the patient and the response to antibiotic therapy [12–14].

During surgical intervention often a cortical window is created [1,15], but the optimal treatment for sub-periosteal abscess remains controversial in terms of whether or not a corticotomy or intramedullary drainage needs to be performed [1,16,17]. There is limited evidence to suggest that subperiosteal drainage alone is adequate management for a subperiosteal abscess [18–20].

Montgomery et al. [21] in a retrospective comparative study demonstrated that in patients with subperiosteal abscess, intramedullary drainage significantly decreased the need for repeat surgery. Another factor to consider when dealing with pediatric patients with septic arthritis is the virulence of the infective organism. In patients with methicillin-resistant *Staphylococcus aureus* (MRSA) infections, more aggressive surgical intervention is warranted, as these patients are at risk of relapse and often need repeated surgeries [15,22–24].

REFERENCES

[1] Copley LAB. Pediatric musculoskeletal infection: trends and antibiotic recommendations. J Am Acad Orthop Surg. 2009;17:618–626.

[2] Arkader A, Brusalis CM, Warner WC, Conway JH, Noonan K. Update in pediatric musculoskeletal infections: when it is, when it isn't, and what to do. Instr Course Lect. 2017;66:495–504.

[3] Faust SN, Clark J, Pallett A, Clarke NMP. Managing bone and joint infection in children. Arch Dis Child. 2012;97:545–553. doi:10.1136/archdischild-2011-301089.

[4] Rutz E, Spoerri M. Septic arthritis of the paediatric hip - A review of current diagnostic approaches and therapeutic concepts. Acta Orthop Belg. 2013;79:123–134.

[5] Samora JB, Klingele K. Septic arthritis of the neonatal hip: acute management and late reconstruction. J Am Acad Orthop Surg. 2013;21:632–641. doi:10.5435/JAAOS-21-10-632.

[6] El-Sayed AMM. Treatment of early septic arthritis of the hip in children: comparison of results of open arthrotomy versus arthroscopic drainage. J Child Orthop. 2008;2:229–237. doi:10.1007/s11832-008-0094-0.

[7] Nusem I, Jabur MKA, Playford EG. Arthroscopic treatment of septic arthritis of the hip. Arthroscopy. 2006;22(8):902.e1-3. doi:10.1016/j.arthro.2005.12.057.

[8] Givon U, Liberman B, Schindler A, Blankstein A, Ganel A. Treatment of septic arthritis of the hip joint by repeated ultrasound-guided aspirations. J Pediatr Orthop. 2004;24:266–270.

[9] Journeau P, Wein F, Popkov D, Philippe R, Haumont T, Lascombes P. Hip septic arthritis in children: assessment of treatment using needle aspiration/irrigation. Orthop Traumatol Surg Res. 2011;97:308–313. doi:10.1016/j.otsr.2011.01.009.

[10] Griffet J, Oborocianu I, Rubio A, Leroux J, Lauron J, Hayek T. Percutaneous aspiration irrigation drainage technique in the management of septic arthritis in children. J Trauma. 2011;70:377–383. doi:10.1097/TA.0b013e3182031 8f0.

[11] Weigl DM, Becker T, Mercado E, Bar-On E. Percutaneous aspiration and irrigation technique for the treatment of pediatric septic hip: effectiveness and predictive parameters. J Pediatr Orthop B. 2016;25:514–519. doi:10.1097/BPB.0000000000000345.

[12] Mah ET, LeQuesne GW, Gent RJ, Paterson DC. Ultrasonic signs of pelvic osteomyelitis in children. Pediatr Radiol. 1994;24:484–487.

[13] Howard CB, Einhorn M, Dagan R, Nyska M. Ultrasound in diagnosis and management of acute haematogenous osteomyelitis in children. J Bone Joint Surg Br. 1993;75:79–82.

[14] Dartnell J, Ramachandran M, Katchburian M. Haematogenous acute and subacute paediatric osteomyelitis. J Bone Joint Surg. 2012;94:12.

[15] Pendleton A, Kocher MS. Methicillin-resistant staphylococcus aureus bone and joint infections in children. J Am Acad Orthop Surg. 2015;23:29–37. doi:10.5435/JAAOS-23-01-29.

[16] Frank G, Mahoney HM, Eppes SC. Musculoskeletal infections in children. Pediatr Clin North Am. 2005;52:1083–1106, ix. doi:10.1016/j.pcl.2005.04.003.

[17] Pääkkönen M, Peltola H. Management of a child with suspected acute septic arthritis. Arch Dis Child. 2011; 97(3):287–292.

[18] Cole WG, Dalziel RE, Leitl S. Treatment of acute osteomyelitis in childhood. J Bone Joint Surg Br. 1982;64:218–223.

[19] McCarthy JJ, Dormans JP, Kozin SH, Pizzutillo PD. Musculoskeletal infections in children: basic treatment principles and recent advancements. Instr Course Lect. 2005;54:515–528.

[20] Labbé J-L, Peres O, Leclair O, Goulon R, Scemama P, Jourdel F, et al. Acute osteomyelitis in children: the pathogenesis revisited? Orthop Traumatol Surg Res. 2010;96:268–275. doi:10.1016/j.otsr.2009.12.012.

[21] Montgomery CO, Porter A, Sachleben B, Suva LJ, Rabenhorst B. Treatment of subperiosteal abscesses in children: is drainage of the intramedullary canal required? J Pediatr Orthop B. 2017;26:497–500. doi:10.1097/BPB.0000000000000283.

[22] Hawkshead JJ, Patel NB, Steele RW, Heinrich SD. Comparative severity of pediatric osteomyelitis attributable to methicillin-resistant versus methicillin-sensitive Staphylococcus aureus. J Pediatr Orthop. 2009;29:85–90. doi:10.1097/BPO.0b013e3181901c3a.

[23] Vander Have KL, Karmazyn B, Verma M, Caird MS, Hensinger RN, Farley FA, et al. Community-associated methicillin-resistant Staphylococcus aureus in acute musculoskeletal infection in children: a game changer: J Pediatr Orthop. 2009;29:927–931. doi:10.1097/BPO.0b013e3181bd1e0c.

[24] Dohin B, Gillet Y, Kohler R, Lina G, Vandenesch F, Vanhems P, et al. Pediatric bone and joint infections caused by Panton-Valentine leukocidin-positive Staphylococcus aureus. Pediatr Infect Dis J. 2007;26:1042–1048. doi:10.1097/INF.0b013e318133a85e.

Author: Ali Parsa

QUESTION 3: Is there a role for arthroscopic washout in children with septic arthritis?

RECOMMENDATION: Yes. Arthroscopy is a useful tool in the treatment of septic arthritis in children.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 83%, Disagree: 10%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

Early diagnosis of septic arthritis (SA) in the pediatric age group is essential in order to avoid adverse sequelae associated with delayed SA, such as osteonecrosis, chondrolysis, relapse or recurrent SA and sepsis, and is more important than the type of drainage[1–3].

For decades, the prevailing treatment of pediatric SA after early diagnosis was open arthrotomy, irrigation and debridement [2,4,5]. The optimal technique for drainage is controversial between needle aspiration, arthrotomy or arthroscopy. Arthroscopic drainage in adults with knee SA is the accepted treatment of choice, as functional outcome and success of treatment is better using this method of treatment [6,7]. Arthroscopic treatment of SA in pediatric patients is defined as a successful option for septic arthritis of the hip, knee, ankle and shoulder in children [8,9].

Despite concern about traction in septic hips during the infection process, several studies have demonstrated its safety [10–13].

Kim et al. and Chung et al. reported good results of hip arthroscopy utilization in SA [11,14,15]. In a prospective comparative study on hip SA, children treated arthroscopically had better functional outcomes (90% excellent vs. 70% in open arthrotomy group), significantly shorter hospital stays and a lower rate of scarring due to the less invasive nature [16].

A recent study with a 2.5-year follow-up supported these results [9]. In these reports, all repeated drainage was done arthroscopically, and it was safe for even very young children.

In a 7-year follow-up comparative study of arthroscopic washout vs. open arthrotomy, Johns et al. reported reduced rates of repeat drainage, earlier knee range of motion and weight-bearing in the arthroscopic arm; however, these trends did not reach a statistically significant difference [17].

In a series of 76 children with arthroscopically-treated septic arthritis, a combination of arthroscopic lavage and antibiotic therapy successfully eradicated infection in 91% patients, and open revision was only required in 4% of these cases [18].

In summary, arthroscopic washout is a useful procedure for the treatment of pediatric septic arthritis, but the evidence is weaker than in the adult literature. Limited sample size and an absence of randomized clinical trials are evident in both knee and hip SA in the pediatric setting. Thus, there is no definitive evidence to support arthroscopic washout over open arthrotomy in children.

REFERENCES

[1] Forlin E, Milani C. Sequelae of septic arthritis of the hip in children: a new classification and a review of 41 hips. J Pediatr Orthop. 2008;28:524–528. doi:10.1097/BPO.0b013e31817bb079.

[2] Shaw BA, Kasser JR. Acute septic arthritis in infancy and childhood. Clin Orthop Relat Res. 1990:212–225.

[3] Sucato DJ, Schwend RM, Gillespie R. Septic arthritis of the hip in children. J Am Acad Orthop Surg. 1997;5(5):249–260.

[4] Fabry G, Meire E. Septic arthritis of the hip in children: poor results after late and inadequate treatment. J Pediatr Orthop. 1983;3:461–466.

[5] Paterson DC. Acute suppurative arthritis in infancy and childhood. J Bone Joint Surg Br. 1970;52:474–482.

[6] Lane JG, Falahee MH, Wojtys EM, Hankin FM, Kaufer H. Pyarthrosis of the knee. Treatment considerations. Clin Orthop Relat Res. 1990:198–204.

[7] Bussière F, Beaufils P. [Role of arthroscopy in the treatment of pyogenic arthritis of the knee in adults. Report of 16 cases]. Rev Chir Orthop Reparatrice Appar Mot. 1999;85:803–810.

[8] Thompson RM, Gourineni P. Arthroscopic treatment of septic arthritis in very young children. J Pediatr Orthop. 2017;37:e53–57. doi:10.1097/BPO.0000000000000659.

[9] Sanpera I, Raluy-Collado D, Sanpera-Iglesias J. Arthroscopy for hip septic arthritis in children. Orthop Traumatol Surg Res. 2016;102:87–89. doi:10.1016/j.otsr.2015.10.008.

[10] DeAngelis NA, Busconi BD. Hip arthroscopy in the pediatric population. Clin Orthop Relat Res. 2003:60–63. doi:10.1097/01.blo.0000043044.84315.90.

[11] Kim S-J, Choi N-H, Ko S-H, Linton JA, Park H-W. Arthroscopic treatment of septic arthritis of the hip. Clin Orthop Relat Res. 2003:211–214.

[12] Ivey M, Clark R. Arthroscopic debridement of the knee for septic arthritis. Clin Orthop Relat Res. 1985:201–206.

[13] Smith MJ. Arthroscopic treatment of the septic knee. Arthroscopy. 1986;2(1):30–34.

[14] Chung WK, Slater GL, Bates EH. Treatment of septic arthritis of the hip by arthroscopic lavage. J Pediatr Orthop. 1993;13:444–446.

[15] Kim SJ, Choi NH, Kim HJ. Operative hip arthroscopy. Clin Orthop Relat Res. 1998:156–165.

[16] El-Sayed AMM. Treatment of early septic arthritis of the hip in children: comparison of results of open arthrotomy versus arthroscopic drainage. J Child Orthop. 2008;2:229–237. doi:10.1007/s11832-008-0094-0.

[17] Johns B, Loewenthal M, Ho E, Dewar D. Arthroscopic versus open treatment for acute septic arthritis of the knee in children. Pediatr Infect Dis J. 2018;37:413–418. doi:10.1097/INF.0000000000001795.

[18] Stutz G, Kuster MS, Kleinstück F, Gächter A. Arthroscopic management of septic arthritis: stages of infection and results. Knee Surg Sports Traumatol Arthrosc. 2000;8(5):270–274. doi:10.1007/s001670000129.

Authors: Craig A. Aboltins, Brennan Collins, Parham Sendi, Ali Parsa

QUESTION 4: Should the length of antibiotic usage be different for a primary septic arthritis (SA) versus osteomyelitis (OM)?

RECOMMENDATION: Although there is a tendency towards prescribing a longer course of antibiotics in pediatric patients with OM compared to primary SA, this practice is not based on conclusive evidence.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 93%, Disagree: 2%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

For decades, it has been believed that a prolonged course of antibiotic therapy (four to six weeks) is necessary to improve long-term outcomes when treating OM and SA in children [1–3]. In recent years, the efficacy of prescribing a prolonged course of antibiotics in the treatment of SA has begun to be questioned. Recent studies, including clinical trials, have demonstrated that a shorter duration (less than one week) of antibiotic therapy, in particular intravenous antibiotics, is effective in treating selective groups of pediatric patients with musculoskeletal infection while reducing length of stay, complications and healthcare costs [4–9].

Jagodzinski et al. demonstrated in a prospective study that three to five days of parenteral antibiotic therapy was sufficient for treating osteoarticular infection in children [10]. However, the Infectious Diseases Society of America (IDSA) currently recommends

a six-week course of antibiotics are administered to children with methicillin-resistant *Staphylococcus aureus* (MRSA) infection of the musculoskeletal system [11].

There is also no consensus or published studies about the optimal transition time from intravenous to oral antibiotic therapy in pediatric osteoarticular infection. There is, however, agreement in clinical practice that a transition from parenteral to oral antibiotics should occur when clinical signs and serum laboratory markers improve [12–14].

An extensive search of the literature revealed 33 retrospective observational studies related to management of pediatric musculoskeletal infections. The median length of antibiotic usage in these studies ranged from two to five weeks for SA patients and three to eight weeks for OM patients. Many of these studies had small sample sizes, short follow-up duration and heterogeneous patient populations, thus precluding meaningful comparison. In studies analyzing both SA and OM populations, a longer duration of antibiotics was consistently reported for OM patients [15–17].

There have been no high-level studies examining the appropriate length of antibiotic treatment for pediatric patients with SA vs. OM. In the absence of such concrete evidence, it remains unclear if the length of antibiotic treatment should be different for primary SA vs. OM. From the results of review of the available literature, it appears that uncomplicated cases of SA may be treated with a shorter duration of antibiotics than OM. This aligns with current guidelines from the European Society for Pediatric Infectious Diseases as well as the Australasian Society for Infectious Diseases, which both recommend an average of two to three weeks of antibiotics in SA and three to four weeks of antibiotics in OM [18,19]. Australian Therapeutic Guidelines suggest similar durations of three weeks in SA and three weeks minimum in OM [20,21]. However, length of antibiotic usage should be evaluated individually and guided by clinical response. There is a paucity of data on antibiotic duration in neonates, immunocompromised patients, patients with bone abscesses, those with chronic OM and infections caused by MRSA. The optimal length of therapy in these groups is yet to be defined. Thus, larger prospective randomized clinical trials of methodological rigor are required.

REFERENCES

[1] Kliegman RM, Nelson WE, editors. Nelson Textbook of Pediatrics, 19. ed., Philadelphia, PA: Elsevier, Saunders; 2011.
[2] Feigin RD, Cherry JD. James D. Textbook of Pediatric Infectious Diseases. 2nd ed. Philadelphia, PA: Saunders; 1987.
[3] Peltola H, Pääkkönen M. Acute osteomyelitis in children. N Engl J Med. 2014;370:352–360. doi:10.1056/NEJMra1213956.
[4] Pääkkönen M, Peltola H. Simplifying the treatment of acute bacterial bone and joint infections in children. Expert Rev Anti Infect Ther. 2011;9:1125–1131. doi:10.1586/eri.11.140.
[5] Arnold SR, Elias D, Buckingham SC, Thomas ED, Novais E, Arkader A, et al. Changing patterns of acute hematogenous osteomyelitis and septic arthritis: emergence of community-associated methicillin-resistant Staphylococcus aureus. J Pediatr Orthop. 2006;26:703–708. doi:10.1097/01.bpo.0000242431.91489.b4.
[6] Pääkkönen M, Peltola H. Treatment of acute septic arthritis. Pediatr Infect Dis J. 2013;32:684–685. doi:10.1097/INF.0b013e31828e1721.
[7] Majewski J, Del Vecchio M, Aronoff S. Route and length of therapy of acute uncomplicated hematogenous osteomyelitis: do we have the answers yet? Hosp Pediatr. 2014;4:44–47. doi:10.1542/hpeds.2013-0035.
[8] Pääkkönen M, Peltola H. Management of a child with suspected acute septic arthritis. Arch Dis Child. 2012;97:287–292. doi:10.1136/archdischild-2011-300462.
[9] Pääkkönen M, Peltola H. Antibiotic treatment for acute haematogenous osteomyelitis of childhood: moving towards shorter courses and oral administration. Int J Antimicrob Agents. 2011;38:273–280. doi:10.1016/j.ijantimicag.2011.04.007.
[10] Jagodzinski NA, Kanwar R, Graham K, Bache CE. Prospective evaluation of a shortened regimen of treatment for acute osteomyelitis and septic arthritis in children. J Pediatr Orthop. 2009;29:518–525. doi:10.1097/BPO.0b013e3181ab472d.
[11] Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. Clin Infect Dis. 2011;52:e18-55. doi:10.1093/cid/ciq146.
[12] Chou ACC, Mahadev A. The use of C-reactive protein as a guide for transitioning to oral antibiotics in pediatric osteoarticular infections. J Pediatr Orthop. 2016;36:173–177. doi:10.1097/BPO.0000000000000427.
[13] Arnold JC, Cannavino CR, Ross MK, Westley B, Miller TC, Riffenburgh RH, et al. Acute bacterial osteoarticular infections: eight-year analysis of C-reactive protein for oral step-down therapy. Pediatrics. 2012;130:e821-828. doi:10.1542/peds.2012-0220.
[14] Pääkkönen M, Kallio MJT, Peltola H, Kallio PE. Antibiotic treatment and surgery for acute hematogenous calcaneal osteomyelitis of childhood. J Foot Ankle Surg. 2015;54:840–843. doi:10.1053/j.jfas.2015.01.006.
[15] Calvo C, Núñez E, Camacho M, Clemente D, Fernández-Cooke E, Alcobendas R, et al. Epidemiology and management of acute, uncomplicated septic arthritis and osteomyelitis: Spanish multicenter study. Pediatr Infect Dis J. 2016;35:1288–1293. doi:10.1097/INF.0000000000001309.
[16] Syrogiannopoulos G, Nelson J. Duration of antimicrobial therapy for acute suppurative osteoarticular infections. The Lancet. 1988;331:37–40. doi:10.1016/S0140-6736(88)91013-6.
[17] Vinod MB, Matussek J, Curtis N, Graham HK, Carapetis JR. Duration of antibiotics in children with osteomyelitis and septic arthritis. J Paediatr Child Health. 2002;38:363–367. doi:10.1046/j.1440-1754.2002.00007.x.
[18] Saavedra-Lozano J, Falup-Pecurariu O, Faust SN, Girschick H, Hartwig N, Kaplan S, et al. Bone and joint infections. Pediatr Infect Dis J. 2017;36:788–799. doi:10.1097/INF.0000000000001635.
[19] McMullan BJ, Andresen D, Blyth CC, Avent ML, Bowen AC, Britton PN, et al. Antibiotic duration and timing of the switch from intravenous to oral route for bacterial infections in children: systematic review and guidelines. Lancet Infect Dis. 2016;16:e139-152. doi:10.1016/S1473-3099(16)30024-X.
[20] Septic Arthritis [revised 2015 Oct.]. Melb Ther Guide Ltd. 2018. https://tgldcdp.tg.org.au/searchAction (accessed August 6, 2018).
[21] Osteomyelitis [revised 2015 Oct.]. Melb Ther Guide Ltd. 2018. https://tgldcdp.tg.org.au/searchAction (accessed August 6, 2018).

Authors: Ali Parsa, Ashok Johari

QUESTION 5: Do steroids have a chondroprotective effect in children with septic arthritis (SA)?

RECOMMENDATION: Based on available pre-clinical and clinical studies it appears that the concurrent use of corticosteroids and antibiotics may have a protective role in the management of SA in the pediatric patient population.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 58%, Disagree: 20%, Abstain: 22% (Simple Majority, NO Consensus)

RATIONALE

SA can lead to severe joint disabilities in about 30% of affected children. These disabilities include restriction of bone growth, chondral destruction, stiffness, pathologic fracture, limb-length discrepancy, subluxation and chronic dislocation of the joint [1,2].

The processes leading to these sequelae are thought to be due more to inflammatory responses than direct damage caused by

microorganisms. Rapid proliferation of bacteria within the joint space activates a cascade of pro-inflammatory cytokines including, interleukin (IL)-1 beta, IL-6, IL-17 and tumor necrosis factor (TNF)-α [3]. These cytokines, in conjunction with the TNF receptor-ligand family receptor activator of nuclear factor kappa-B ligand (RANKL), are believed to play a critical role in the activation and proliferation of osteoclasts, leading to bone resorption. Specifically, the interaction between RANKL and its receptor, RANK, has been shown to be required for osteoclast differentiation. Expression dysregulation of these factors in SA can lead to significant osteolysis [4,5]. In addition, increased synovial fluid and joint effusion in SA can obstruct blood supply of the joint, leading to chondrocyte necrosis, even during the early hours of infection [6].

Glucocorticoids have an established role in suppressing the release of proinflammatory cytokines in almost all acute or chronic diseases [7]. They are used to control inflammatory conditions affecting the joint, such as rheumatoid arthritis and ankylosing spondylitis. Corticosteroids also reduce the production of proteolytic enzymes, such as elastase, collagenase and synovial matrix metallopeptidase-1 (MMP-1), thereby preventing the chondral degradation process [7,8]. Despite the use of corticosteroids in inflammatory conditions, they are avoided in patients who have infections due to their immunosuppressive effect and their potential to exacerbate infection. However, recent evidence suggests that the concurrent use of corticosteroids with antibiotics improved the care of patients with central nervous system infections, pneumonia, upper urinary tract infection and sepsis [9–12].

The chondroprotective effect of glucocorticoids was investigated by two separate studies in 1996. Stricker et al. and Sakiniene et al. investigated the chondroprotective effect of corticosteroids on the course of SA [13,14]. Both studies utilized animal models to investigate if the administration of glucocorticoids had any influence on the levels of circulating inflammatory mediators. Stricker et al. employed the rabbit model and Sakiniene et al. utilized a mouse model to demonstrate that the administration of glucocorticoids resulted in improvement in symptoms in the animals and a significant decrease in serum levels of inflammatory cytokines at two weeks.

Extensive search of the literature revealed four clinical studies that relate to this subject (Table 1). These studies consist of two double-blinded randomized control trials, one non-randomized clinical trial and one retrospective study [15–18]. The findings of the studies are summarized in Table 1. All studies demonstrate improvements in clinical symptoms, length of hospital stay, reduced use of antibiotics or faster return to normal of serum inflammatory markers, such as C-reactive protein (CRP). In 2015 a meta-analysis was published regarding the use of corticosteroids in SA that included three of the aforementioned studies [19]. The finding of the meta-analysis was that the use of corticosteroids combined with antibiotics resulted in an improvement in the outcome of management of SA in children.

Despite the availability of evidence to support the use of corticosteroids in pediatric patients with SA, some concerns still remain. These concerns are:

1. The studies do not specifically seek adverse effects associated with the administration of corticosteroids.
2. Long term follow-up on patients receiving steroids is not available.
3. Total participant number of these studies is low.
4. Optimum dose, duration and route of prescription of corticosteroids is not clear yet.

TABLE 1. Summary of studies

Author (Year)	Study Design	Participants	Treatment Protocol	Results (Follow-up)
Odio et al. (2003) [15]	Randomised clinical trial	100 children	4 days of dexamethasone + AB	Significant decrease of joint dysfunction (12m) Quicker normalization of CRP Earlier symptoms relief Decreased IV antibiotics days
Harel et al. (2011) [16]	Randomised clinical trial	49 children	4 days of dexamethasone + AB	Significant decrease of joint dysfunction (12m) Became afebrile earlier Quicker normalization of CRP Decreased IV antibiotics days Decreased hospitalization
Arti et al. (2014) [17]	Non-randomized clinical trial	60 children	4 days of dexamethasone + AB	Decreased hospitalization Better final ROM Decreased local sign of inflammation Higher ESR reduction rate
Fogel et al. (2015) [18]	Retrospective	116 children	Few days of dexamethasone + AB	Rapid clinical improvement Quicker normalization of CRP Decreased IV antibiotics days Decreased hospitalization

The aforementioned concerns are important enough to justify the need for larger scale prospective studies with a longer follow-up that examine the benefits as well as the potential adverse effects of corticosteroids administered to pediatric patients with SA.

REFERENCES

[1] Welkon CJ, Long SS, Fisher MC, Alburger PD. Pyogenic arthritis in infants and children: a review of 95 cases. Pediatr Infect Dis. 1986;5:669–676.
[2] Weston VC, Jones AC, Bradbury N, Fawthrop F, Doherty M. Clinical features and outcome of septic arthritis in a single UK Health District 1982-1991. Ann Rheum Dis. 1999;58:214–219.
[3] Colavite PM, Sartori A. Septic arthritis: immunopathogenesis, experimental models and therapy. J Venom Anim Toxins Trop Dis. 2014;20:19. doi:10.1186/1678-9199-20-19.
[4] Kwan Tat S, Padrines M, Théoleyre S, Heymann D, Fortun Y. IL-6, RANKL, TNF-alpha/IL-1: interrelations in bone resorption pathophysiology. Cytokine & Growth Factor Rev. 2004;15:49–60.
[5] Roux S, Amazit L, Meduri G, Guiochon-Mantel A, Milgrom E, Mariette X. RANK (receptor activator of nuclear factor kappa B) and RANK ligand are expressed in giant cell tumors of bone. Am J Clin Pathol. 2002;117:210–216. doi:10.1309/BPET-F2PE-P2BD-J3P3.
[6] Smith RL, Merchant TC, Schurman DJ. In vitro cartilage degradation by Escherichia coli and Staphylococcus aureus. Arthritis Rheum. 1982;25:441–446.
[7] Buttgereit F, Burmester G-R, Straub RH, Seibel MJ, Zhou H. Exogenous and endogenous glucocorticoids in rheumatic diseases. Arthritis Rheum. 2011;63:1–9. doi:10.1002/art.30070.
[8] Townsend HB, Saag KG. Glucocorticoid use in rheumatoid arthritis: benefits, mechanisms, and risks. Clin Exp Rheumatol. 2004;22:S77-82.
[9] Brouwer MC, McIntyre P, Prasad K, van de Beek D. Corticosteroids for acute bacterial meningitis. Cochrane Database Syst Rev. 2013:CD004405. doi:10.1002/14651858.CD004405.pub4.
[10] Kil H-R, Lee J-H, Lee K-Y, Rhim J-W, Youn Y-S, Kang J-H. Early corticosteroid treatment for severe pneumonia caused by 2009 H1N1 influenza virus. Crit Care Lond Engl. 2011;15:413. doi:10.1186/cc10082.
[11] Pohl HG, Rushton HG, Park JS, Chandra R, Majd M. Adjunctive oral corticosteroids reduce renal scarring: the piglet model of reflux and acute experimental pyelonephritis. J Urol. 1999;162:815–820.
[12] Annane D, Bellissant E, Bollaert P-E, Briegel J, Confalonieri M, De Gaudio R, et al. Corticosteroids in the treatment of severe sepsis and septic shock in adults: a systematic review. JAMA. 2009;301:2362–2375. doi:10.1001/jama.2009.815.
[13] Stricker SJ, Lozman PR, Makowski AL, Gunja-Smith Z. Chondroprotective effect of betamethasone in lapine pyogenic arthritis. J Pediatr Orthop. 1996;16:231–236.
[14] Sakiniene E, Bremell T, Tarkowski A. Addition of corticosteroids to antibiotic treatment ameliorates the course of experimental Staphylococcus aureus arthritis. Arthritis Rheum. 1996;39:1596–1605.
[15] Odio CM, Ramirez T, Arias G, Abdelnour A, Hidalgo I, Herrera ML, et al. Double blind, randomized, placebo-controlled study of dexamethasone therapy for hematogenous septic arthritis in children. Pediatr Infect Dis J. 2003;22:883–888. doi:10.1097/01.inf.0000091293.32187.7b.
[16] Harel L, Prais D, Bar-On E, Livni G, Hoffer V, Uziel Y, et al. Dexamethasone therapy for septic arthritis in children: results of a randomized double-blind placebo-controlled study. J Pediatr Orthop. 2011;31:211–215. doi:10.1097/BPO.0b013e3182092869.
[17] Arti H, Mousapour A, Alavi SM. The effect of intravenous dexamethasone in the treatment of septic arthritis. Pak J Med Sci. 2014;30:955–7. doi:10.12669/pjms.305.5217.
[18] Fogel I, Amir J, Bar-On E, Harel L. Dexamethasone therapy for septic arthritis in children. Pediatrics. 2015;136:e776–782. doi:10.1542/peds.2014-4025.
[19] Farrow L. A systematic review and meta-analysis regarding the use of corticosteroids in septic arthritis. BMC Musculoskelet Disord. 2015;16:241. doi:10.1186/s12891-015-0702-3.

Author: Mahzad Javid

QUESTION 6: What is the optimal management of septic arthritis/osteomyelitis (SA/OM) caused by methicillin-resistant *Staphylococcus aureus* (MRSA)?

RECOMMENDATION: Patients with MRSA infection should be started on an antibiotic regimen, such as vancomycin, intravenously followed by linezolid, which is effective against this organism. Early consideration for surgical treatment and close monitoring is essential in pediatric patients with musculoskeletal MRSA infection to reduce the high prevalence of complications and late sequelae that are often seen.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 85%, Disagree: 11%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE:

In past decade, the prevalence of MRSA in SA and acute OM has dramatically risen between 3- to 10-fold [1–3]. Compared to methicillin-susceptible *Staphylococcus aureus* (MSSA) infections, patients with MRSA have more extensive areas of soft tissue destruction, more rapid spread of infection and experience higher mortality rates [2–4]. The course of treatment of these patients is also protracted with a longer length of hospital stay, need for surgical intervention and an increased risk of complications, such as persistent bacteremia, deep vein thrombosis, pulmonary embolus, pathologic fractures and other long-term sequelae [1,2,5–10].

The severity of MRSA infections may be related to virulence factors, such as Panton-Valentine Leukocidin (PVL) found in many MRSA strains [11,12]. MRSA strains may also contain specific virulence factors that are linked to increased soft tissue destruction, such as α-hemolysin and α-type phenol-soluble modulin [3].

Pediatric patients with MRSA infections are more systematically unwell with higher temperatures and increased tachycardia. In addition, they present with even higher leukocytosis (or absolute neutrophil count), greater elevations in erythrocyte sedimentation rate and C-reactive protein but lower hematocrit values [5,7,10,13].

Commencing appropriate empiric antibiotics in these patients is paramount to improve outcomes. Children with suspected MRSA SA or OM should be started on intravenous vancomycin or clindamycin. Daptomycin or Linezolid are alternatives for the treatment of MRSA infections in children. The duration of therapy should be individualized based on the response to treatment. A minimum course of three to four weeks for SA and four to six weeks of antibiotics for OM is recommended [4,14].

Cultures should ideally be obtained before initiating antibiotics in patients with musculoskeletal infection, especially if MRSA is suspected. Aspiration of the affected joint and obtaining blood cultures helps isolate the infective organism and should be part of the initial work up of these patients [14,15]. New diagnostic methods, such as real time polymerase chain reaction (PCR), may be useful in the rapid identification of MRSA or other infective organisms [5].

Appropriate imaging, such as magnetic resonance imaging (MRI), should also be part of the work up since this allows for localization of the infection and determination of the extent of disease. MRI may also help with surgical planning to ensure a more thorough debridement and decompression of infected areas [10,15,16].

Images may also reveal subperiosteal abscess formation or the presence of SA in the hip. The presence of such findings lead to the need for early surgical intervention since antibiotics cannot typically penetrate large abscess cavities. Compared to MSSA infections, MRSA infections are more invasive and have a higher rates of abscess formation. Thus, they require surgical intervention more frequently and a higher number of repeat procedures [5].

Aggressive surgical management during the initial procedure, involving opening a surgical window and intramedullary irrigation, is necessary to prevent the need for subsequent reoperation. Close monitoring of patients is critical to prevent complications and reduces long-term sequelae. Patients who fail to respond to antibiotics should undergo prompt surgical interventions. Repeat imaging should also be considered in patients who are not responding to treatment in order to determine persistent infection and assess the extent of bony and soft tissue involvement [6,10,11,14,16].

In summary, MRSA infections of the musculoskeletal system in children may have serious complications. They require early administration of antibiotics and may necessitate multiple surgical interventions. These patients often have a protracted hospital course and require vigilant monitoring to minimize the risk of complications.

REFERENCES

[1] Sarkissian EJ, Gans I, Gunderson MA, Myers SH, Spiegel DA, Flynn JM. Community-acquired methicillin-resistant Staphylococcus aureus musculoskeletal infections: emerging trends over the past decade. J Pediatr Orthop. 2016;36:323–327. doi:10.1097/BPO.0000000000000439.

[2] Arnold SR, Elias D, Buckingham SC, Thomas ED, Novais E, Arkader A, et al. Changing patterns of acute hematogenous osteomyelitis and septic arthritis: emergence of community-associated methicillin-resistant Staphylococcus aureus. J Pediatr Orthop. 2006;26:703–708. doi:10.1097/01.bpo.0000242431.91489.b4.

[3] Davis WT, Gilbert SR. Comparison of methicillin-resistant versus susceptible Staphylococcus aureus pediatric osteomyelitis. J Pediatr Orthop. 2018;38:e285–291. doi:10.1097/BPO.0000000000001152.

[4] Arkader A, Brusalis CM, Warner WC, Conway JH, Noonan K. Update in pediatric musculoskeletal infections: when it is, when it isn't, and what to do. Instr Course Lect. 2017;66:495–504.

[5] Hawkshead JJ, Patel NB, Steele RW, Heinrich SD. Comparative severity of pediatric osteomyelitis attributable to methicillin-resistant versus methicillin-sensitive Staphylococcus aureus. J Pediatr Orthop. 2009;29:85–90. doi:10.1097/BPO.0b013e3181901c3a.

[6] Vander Have KL, Karmazyn B, Verma M, Caird MS, Hensinger RN, Farley FA, et al. Community-associated methicillin-resistant Staphylococcus aureus in acute musculoskeletal infection in children: a game changer: J Pediatr Orthop. 2009;29:927–931. doi:10.1097/BPO.0b013e3181bd1e0c.

[7] Gonzalez BE, Teruya J, Mahoney DH, Hulten KG, Edwards R, Lamberth LB, et al. Venous thrombosis associated with staphylococcal osteomyelitis in children. Pediatrics. 2006;117:1673–1679. doi:10.1542/peds.2005-2009.

[8] Bouchoucha S, Benghachame F, Trifa M, Saied W, Douira W, Nessib MN, et al. Deep venous thrombosis associated with acute hematogenous osteomyelitis in children. Orthop Traumatol Surg Res. 2010;96:890–893. doi:10.1016/j.otsr.2010.05.006.

[9] Belthur MV, Birchansky SB, Verdugo AA, Mason EO, Hulten KG, Kaplan SL, et al. Pathologic fractures in children with acute Staphylococcus aureus osteomyelitis. J Bone Joint Surg Am. 2012;94:34–42. doi:10.2106/JBJS.J.01915.

[10] Saavedra-Lozano J, Mejías A, Ahmad N, Peromingo E, Ardura MI, Guillen S, et al. Changing trends in acute osteomyelitis in children: impact of methicillin-resistant Staphylococcus aureus infections. J Pediatr Orthop. 2008;28:569–575. doi:10.1097/BPO.0b013e31817bb816.

[11] Martínez-Aguilar G, Avalos-Mishaan A, Hulten K, Hammerman W, Mason EO, Kaplan SL. Community-acquired, methicillin-resistant and methicillin-susceptible Staphylococcus aureus musculoskeletal infections in children. Pediatr Infect Dis J. 2004;23:701–706.

[12] Bocchini CE, Hulten KG, Mason EO, Gonzalez BE, Hammerman WA, Kaplan SL. Panton-Valentine leukocidin genes are associated with enhanced inflammatory response and local disease in acute hematogenous Staphylococcus aureus osteomyelitis in children. Pediatrics. 2006;117:433–440. doi:10.1542/peds.2005-0566.

[13] Dietrich LN, Reid D, Doo D, Fineberg NS, Khoury JG, Gilbert SR. Predicting MSSA in acute hematogenous osteomyelitis in a setting with MRSA prevalence. J Pediatr Orthop. 2015;35:426–430. doi:10.1097/BPO.0000000000000301.

[14] Pendleton A, Kocher MS. Methicillin-resistant Staphylococcus aureus bone and joint infections in children. J Am Acad Orthop Surg. 2015;23:29–37. doi:10.5435/JAAOS-23-01-29.

[15] Ju KL, Zurakowski D, Kocher MS. Differentiating between methicillin-resistant and methicillin-sensitive Staphylococcus aureus osteomyelitis in children: an evidence-based clinical prediction algorithm. J Bone Joint Surg Am. 2011;93:1693–1701. doi:10.2106/JBJS.J.01154.

[16] Copley LAB. Pediatric musculoskeletal infection: trends and antibiotic recommendations. J Am Acad Orthop Surg. 2009;17:618–626.

Authors: Ali Parsa, Parham Sendi, Ashok Johari, Ed McPherson

QUESTION 7: What is the best management for mycobacterium tuberculosis (TB) of the musculoskeletal system in children?

RECOMMENDATION: Mycobacterium TB periprosthetic joint infection (PJI) must be treated in collaboration with an infectious disease specialist, noting that the duration of treatment (minimum six months and up to two years) and the type of antimicrobials (usually a combination of four drugs) is determined based on the resistance profile of the pathogen.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 86%, Disagree: 2%, Abstain: 12% (Super Majority, Strong Consensus)

RATIONALE

There is an agreement that anti-TB medications can eradicate most of the bacilli and prevent both relapse and drug resistance. The current recommendation for treatment length of extra-pulmonary TB in children is six months. However, these recommendations do not apply to osteoarticular infections and meningitis. Almost all available guidelines strongly recommend 12 months of anti-TB treatment for osteoarticular TB [1–5].

The recommended regimen for children with suspected or confirmed osteoarticular TB is a four-drug regimen consisting of Isoniazid (INH), Rifampin (RIF), Pyrazinamide (PZA) and Ethambutol (EMB) for 2 months, followed by a two-drug regimen of Isoniazid and Rifampin (HR) for 10 months [6].

There is limited literature that describes how to treat children with drug-resistant TB. For mono-drug resistance to either Isoniazid or Rifampicin, the recommendation is for 6-9 months of a three-drug regimen consisting of the other susceptible antibiotics from

TABLE 1. Recommendations for treatment of resistant TB in pediatrics

	Initial Phase	Maintenance Phase
INH-monoresistance TB	RIF + PZA + EMB (2 months)	RIF + PZA + EMB (4-7 months)
RIF-monoresistance TB	INH+ PZA + EMB + FQN (2 months)	INH + EMB + FQN (10-16 months)

INH, Isoniazid; EMB, Ethambutol; RIF, Rifampicin; PZA, Pyrazinamide; FQN, Fluoroquinolones; TB, Tuberculosis

the conventional four-drug regimen (Table 1) [3,7,8]. For multi-drug resistant (MDR) TB, all guidelines recommend a longer treatment period of up to 24 months with all four anti-TB drugs [3,7,9]. Evaluation of the organism's drug susceptibility profile should also be conducted [3,7,9].

While some authors have reported favorable results with chemotherapy and non-operative splinting of the affected joint(s), others have recommended debridement of focal bony involvement and arthroscopic or open synovectomy to decrease the overall bioburden of infected material [10,11].

Arthrodesis, especially of the hip joint, may be an option in the event of severe destruction of the joint secondary to infection [12]. Orthopaedic interventions in spinal TB may occasionally be recommended to prevent deformity of the spine in pediatric patients. These procedures may include surgical intervention, application of a brace or cast in addition to standard chemotherapy. Proper immobilization of the growing spine in pediatric patients may help achieve a solid fusion without surgical procedures.

Surgical intervention is reserved for patients with formation of a large anterior column abscess, severe kyphotic deformity or progressive spinal deformity despite chemotherapy [13,14].

REFERENCES

[1] Schaberg T, Bauer T, Castell S, Dalhoff K, Detjen A, Diel R, et al. [Recommendations for therapy, chemoprevention and chemoprophylaxis of tuberculosis in adults and children. German Central Committee against Tuberculosis (DZK), German Respiratory Society (DGP)]. Pneumol Stuttg Ger. 2012;66:133–171. doi:10.1055/s-0031-1291619.

[2] Rapid Advice: Treatment of Tuberculosis in Children. Geneva: World Health Organization; 2010.

[3] Gale-Rowe M, Menzies D, Sutherland J, Wong T, editors, chapter authors. Highlights of the new 7th edition of the Canadian Tuberculosis Standards. Can Commun Dis Rep. 2014;40:113–116.

[4] Guidance for National Tuberculosis Programmes on the management of tuberculosis in children. Chapter 1: introduction and diagnosis of tuberculosis in children. Int J Tuberc Lung Dis. 2006;10:1091–1097.

[5] Safdar N, Hinderaker SG, Baloch NA, Enarson DA, Khan MA, Morkve O. Childhood tuberculosis deskguide and monitoring: an intervention to improve case management in Pakistan. BMC Health Serv Res. 2011;11:187. doi:10.1186/1472-6963-11-187.

[6] Berti E, Galli L, Venturini E, de Martini M, Chiappini E. Tuberculosis in childhood: a systematic review of national and international guidelines. BMC Infect Dis. 2014;14:S3. doi:10.1186/1471-2334-14-S1-S3.

[7] Red Book: 2012 Report of the Committee on Infectious Diseases. 29th Edition (2012). American Academy of Pediatrics. Elk Grove Village, IL. 2012.

[8] Falzon D, Jaramillo E, Schünemann HJ, Arentz M, Bauer M, Bayona J, et al. WHO guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. Eur Respir J. 2011;38:516–528. doi:10.1183/09031936.00073611.

[9] Voss LM, Australasian Subgroup in Paediatric Infectious Disease of the Australasian Society for Infectious Diseases; Australasian Paediatric Respiratory Group. Management of tuberculosis in children. J Paediatr Child Health. 2000;36:530–536.

[10] Titov AG, Nakonechniy GD, Santavirta S, Serdobintzev MS, Mazurenko SI, Konttinen YT. Arthroscopic operations in joint tuberculosis. The Knee. 2004;11:57–62. doi:10.1016/S0968-0160(03)00035-8.

[11] Agarwal A, Qureshi NA, Khan SA, Kumar P, Samaiya S. Tuberculosis of the foot and ankle in children. J Orthop Surg. Hong Kong. 2011;19:213–217. doi:10.1177/230949901101900217.

[12] OZdemir HM, Yensel U, Cevat Ogün T, Senaran H, Kutlu A. Arthrodesis for tuberculous coxarthritis: good outcome in 32 adolescents. Acta Orthop Scand. 2004;75:430–433.

[13] Jain AK. Tuberculosis of the spine: a fresh look at an old disease. J Bone Joint Surg Br. 2010;92:905–913. doi:10.1302/0301-620X.92B7.24668.

[14] Zhang H-Q, Wang Y-X, Guo C-F, Liu J-Y, Wu J-H, Chen J, et al. One-stage posterior approach and combined interbody and posterior fusion for thoracolumbar spinal tuberculosis with kyphosis in children. Orthopedics. 2010;33:808. doi:10.3928/01477447-20100924-10.

Authors: Ali Parsa, Irene Kalbian

QUESTION 8: What is the role of host gene expression and severity of acute osteoarticular infection in children, especially methicillin-resistant *Staphylococcus aureus* (*S. aureus*), or MRSA, infection?

RECOMMENDATION: Unknown. The limited literature available suggests altered host gene transcription related to the balance of the body's adaptive and innate immune responses may increase pediatric patients' susceptibility to severe osteoarticular infection, particularly in cases of MRSA. However, much more investigation is needed to determine which genes are most useful and how they can be utilized to help physicians anticipate the course of infection in a given patient.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 75%, Disagree: 3%, Abstain: 22% (Super Majority, Strong Consensus)

RATIONALE

The severity of osteoarticular infection in otherwise healthy children varies greatly, even in the setting of infection by the same pathogen. Some pediatric patients experience a mild course that allows them to be discharged after a few days of hospital admission with antibiotic therapy. Other patients experience a protracted course and require major surgical intervention as well as intensive care management [1–3]. The contribution of genetic mechanisms to this wide range of clinical manifestations has been investigated to a limited extent. A similar diversity in illness severity has been observed in neoplastic and rheumatologic disorders, where there is evidence that ribonucleic acid expression plays a role in the presentation of these conditions [4–6]. Chaussabel et al. used gene expression microarrays in patients with seven autoimmune-related conditions and identified transcriptional changes ("diagnostic signatures") that could be used to distinguish between these respective conditions [7]. Identifying a parallel set of transcriptional diagnostic indicators for the severity of osteoarticular infection may enhance the ability of physicians to treat this condition.

S. aureus is one of the leading pathogens causing hospital-acquired infection and MRSA infection is associated with over 6,000 deaths/year in the United States [8]. In a series of 99 children hospitalized with *S. aureus* infection, investigators used microarray analysis to characterize the transcriptional profiles in whole blood. Significant heterogeneity was observed in host signatures and transcriptional changes were identified. Furthermore, this heterogeneity was found to be associated with a more severe course of disease. Overall, patients with invasive *S. aureus* infection had an exaggerated expression of genes associated with the innate immune response and a diminished expression of adaptive immunity [9].

Ardura et al. conducted a study comparing gene expression in peripheral blood monocyte cells (PBMC) between 53 children with invasive *S. aureus* infection and 24 healthy children. Analysis of PBMC gene expression showed that patients with invasive *S. aureus* had lower numbers of central memory CD4+ and CD8+ T-cells and increased numbers of CD14+ monocytes versus healthy controls [10]. Ramilo et al. compared the immune system response in patients with *Escherichia coli* infection versus those with *S. aureus* infection. Their findings support the specific pattern described by Ardura et al. They found that patients with *S. aureus* infection had altered host gene expression associated with their adaptive immune response [11]. Gaviria-Agudelo et al. reported on a cohort of 12 pediatric patients with acute hematogenous osteomyelitis caused by MRSA, and they identified specific genes which correlated with the severity of disease in the early hospitalization period. Among the five distinct genes that were identified, three were up-regulated (P2RX1, SORT1, RETN) and two were down-regulated (LOC641788, STAT 4). STAT4 down-regulation showed the strongest correlation with disease severity [12].

While these findings provide some initial evidence for the role of host gene expression in the severity of acute osteoarticular infection in children, the literature on this topic remains sparse. Further studies are needed to examine this connection, particularly studies with larger sample sizes. An enhanced understanding of host gene expression patterns and the transcriptome in osteoarticular infection could enable physicians to better anticipate the risk of developing chronic osteomyelitis and, ultimately, facilitate personalized patient management strategies.

REFERENCES

[1] Holmig S, Copley L, Grande L, Wilson P. Deep venous thrombosis associated with osteomyelitis in children. J Bone Joint Surg Am. 2007;89:1517–1523.

[2] Creel AM, Durham SH, Benner KW, Alten JA, Winkler M. Severe invasive community-associated methicillin-resistant Staphylococcus aureus infections in previously healthy children. Pediatr Crit Care Med. 2009;10:323–327. doi:10.1097/PCC.0b013e3181988798.

[3] Gonzalez B, Martinez-Aquilar G, Hulten K, Hammerman W, Coss B, Avalos-Mishaan A, et al. Severe Staphylococcal sepsis in adolescents in the era of community-acquired methicillin-resistant Staphylococcus aureus. Pediatrics. 2005;115:642–648.

[4] Garcia-Romo GS, Caielli S, Vega B, Connolly J, Allantaz F, Xu Z, et al. Netting neutrophils are major inducers of type I IFN production in pediatric systemic lupus erythematosus. Sci Transl Med. 2011;3:73ra20-73ra20. doi:10.1126/scitranslmed.3001201.

[5] Chaussabel D, Quinn C, Shen J, Patel P, Glaser C, Baldwin N, et al. A modular analysis framework for blood genomics studies: application to systemic lupus erythematosus. Immunity. 2008;29:150–164. doi:10.1016/j.immuni.2008.05.012.

[6] Golub T, Slonim D, Tamayo P, Huard C, Gaasenbeek M, Mesirov J, et al. Molecular classification of cancer: class discovery and class prediction by gene expression monitoring. Science. 1999;286:531–537. doi:10.1126/science.286.5439.531.

[7] Chaussabel D. Analysis of significance patterns identifies ubiquitous and disease-specific gene-expression signatures in patient peripheral blood leukocytes. Ann N Y Acad Sci. 2005;1062:146–154. doi:10.1196/annals.1358.017.

[8] Klein E, Smith DL, Laxminarayan R. Hospitalizations and deaths caused by methicillin-resistant Staphylococcus aureus, United States, 1999–2005. Emerg Infect Dis. 2007;13:1840–1846. doi:10.3201/eid1312.070629.

[9] Banchereau R, Jordan-Villegas A, Ardura M, Mejias A, Baldwin N, Xu H, et al. Host immune transcriptional profiles reflect the variability in clinical disease manifestations in patients with Staphylococcus aureus Infections. PLoS ONE. 2012;7:e34390. doi:10.1371/journal.pone.0034390.

[10] Ardura MI, Banchereau R, Mejias A, Di Pucchio T, Glaser C, Allantaz F, et al. Enhanced monocyte response and decreased central memory T cells in children with invasive Staphylococcus aureus infections. PLoS ONE. 2009;4:e5446. doi:10.1371/journal.pone.0005446.

[11] Ramilo O, Allman W, Chung W, Mejias A, Ardura M, Glaser C, et al. Gene expression patterns in blood leukocytes discriminate patients with acute infections. Blood. 2007;109:2066–2077. doi:10.1182/blood-2006-02-002477.

[12] Gaviria-Agudelo C, Carter K, Tareen N, Pascual V, Copley LA. Gene expression analysis of children with acute hematogenous osteomyelitis caused by methicillin-resistant Staphylococcus aureus: correlation with clinical severity of illness. PLoS ONE. 2014;9(7):e103523. doi:10.1371/journal.pone.0103523.