

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- α /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] Buttgeriet 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;15:213. 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.

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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 neutro-

phil 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, Nessim 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. Pantone-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.

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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 Rifampin, the recommendation is for 6-9 months of a three-drug regimen consisting of the other susceptible antibiotics from