**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].

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# 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.

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