Diagnostic

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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.

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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].