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PEDIATRIC INFECTIOUS DISEASES (I BROOK, SECTION EDITOR)

Diagnosis and Management of Infectious Arthritis in Children

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Abstract

Purpose of Review Septic arthritis is limb and life-threatening condition which necessitates rapid diagnosis and treatment. It is important for a medical practitioner to be familiar with this condition. This review summarizes the epidemiology, risk factors, diagnosis and differential diagnosis, complications, as well as treatment and the following-up of this condition.

Recent Findings Different causative organisms require unique diagnostic and treatment approaches. Establishing the diagnosis often requires multiple diagnostic modalities, some of which are new and innovative. Differential diagnosis requires excluding non-infectious inflammatory causes, such as reactive arthritis, juvenile rheumatoid arthritis, transient synovitis, and pericapsular pyomyositis. There is no consensus regarding the nature or duration of pharmacological or surgical treatment. Treatment includes administration of appropriate antimicrobial therapy and including the use of steroids and drainage. The most common complications are osteonecrosis of the femoral head and chronic osteomyelitis.

Summary Complications of septic arthritis are mostly due to a missed diagnosis. Further studies are required to better evaluate the diagnostic and therapeutic choice.

Keywords Septic arthritis · Pediatric arthritis · Diagnosis · Epidemiology

Introduction

Epidemiology

The annual incidence of septic arthritis in children is 4:100,000 (range 1 to 37 cases per 100,000 [1, 2•, 3•]. However, the rate is lower in many developed regions of the world (e.g., western European countries including Israel) where the incidence is lower (1 in 100,000) [4••]. The condition is more common in males, perhaps due to greater physical activity [3•, 5, 6•]. It is more prevalent than isolated osteomyelitis under 2 years of age, and, at any age group, up to 68% presents with co-existing osteomyelitis [7].

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Risk Factors

Most children are healthy and do not have any predisposing conditions [8]. Younger age and male gender are associated risk factors. Diseases such as respiratory distress syndrome, host phagocytic defects, and hemoglobinopathies are risk factors [8]. Risk factors also include previous joint surgeries, umbilical artery catheterization, having a urinary tract implant, and urinary or intestinal tract surgeries [8]. Risk factors for co-existing joint and bone infections are newborn or adolescent age, involvement of the shoulder region, and a methicillin-sensitive *Staphylococcus aureus* (MSSA) and methicillin-resistant *Staphylococcus aureus* (MRSA) infection [7].

Risk factors for bacterial arthritis in the neonate (< 1 month) include umbilical vessel catheterization, presence of central venous catheters, femoral vessel blood

sampling, osteomyelitis, and active maternal infection at the time of delivery [9–11].

Preceding trauma or upper respiratory tract infection was recorded in 60% of the cases according to one report [12]. Other reports claimed that joint structure, altered by conditions such as rheumatoid arthritis and Charcot's arthropathy, was the single most important risk factor [13]. Interestingly, it was found that disease-modifying antirheumatic drugs (DMARDs) may paradoxically increase the rate of septic arthritis [13].

Etiology

Bacterial hematogenous spread is the most common cause of septic arthritis [2•, 3•, 5], and *S. aureus* is the most common pathogen [4••, 5]. *S. aureus* is a frequent cause of septic arthritis, and it should be suspected in those with another foci of infection, such as a foreign body site, pneumonia, osteomyelitis, and endocarditis. Hospital-acquired *MRSA* is typically resistant to multiple antibiotics, while community-acquired *MRSA* is typically sensitive to non-beta-lactam antibiotics [14]. Frequent antibiotic treatment, skin trauma, close contact, crowded environment, and sharing of contaminated items, are known risk factors for acquiring community-acquired *MRSA* [14]. Clinical spectrum of *MRSA* involvement ranges from benign colonization to the most severe life-threatening infections [14].

In infants < 3 months, group B *Streptococcus* (GBS), *S. aureus*, and Gram-negative bacilli are the predominant organisms. Ages between two and five years are associated with *Streptococcus pyogenes* and *Streptococcus pneumoniae* [6•]. *S pneumoniae* had caused about 6% of septic arthritis prior to the universal vaccination. However, the rate of infections due to strains included in the pneumococcal conjugate vaccine decreased after the introduction of vaccination. Up to a third of *S. pneumoniae* isolates show reduced susceptibility to penicillin in children under age four years, with the exception of the neonatal period. In infants, an adjacent spread of osteomyelitis into the joint, as opposed to hematogenous spread, is the most common pathway. Up to 76% of neonatal epiphyseal osteomyelitis can lead to septic arthritis [7]. A metaphyseal spread is also possible in older children, especially in joints with an intra-capsular metaphysis, such as the hip, shoulder, ankle, and elbow. Transphyseal blood flow in infants younger than 18 months might also account for the metaphyseal spread of infection into the joint. The mechanism may be due to direct damage by the bacteria or its endotoxins and inflammatory or ischemic damage. The ischemia is caused by joint effusion which occludes the nutrient blood vessels. This is especially relevant in the hip [4••]. Penetrating injuries or procedure might cause direct inoculation of intra-arthritic bacteria [1, 2•, 4••, 15].

Kingella kingae is a common pathogen responsible for acute osteoarticular infections. The recovery of *Kingella kingae* in septic arthritis has been reported in multiple reports [3•, 6•, 16•, 17, 18•]. It is a Gram-negative component of the normal pharyngeal flora and usually affects the large lower limb joints [16•]. It is more common in children younger than 5 years [19, 20]. The infection has a subtler clinical course and necessitates greater suspicion. There is often no leukocytosis, body temperature is normal or slightly elevated, and acute-phase reactant levels are elevated only in about half of the patients [18•]. Refusal to bear weight is the most sensitive sign of infection by *K. kingae* [18•]. *K. kingae* is difficult to culture from synovial fluid. However, it is easier to detect using nasopharyngeal culture and plating of the aspirated synovial fluid in blood culture media [16•]. Utilizing aerobic blood culture in addition to agar plates is required to detect *K. kingae* [3•, 6•], and it is believed that the increasing utilization of polymerase chain reaction (PCR) will increase the detection of this organism [17]. The increasing utilization of newer culture methodologies, such as nucleic acid amplification (NAA) assays, had shed new light on this pathogen and suggests that it may be the most common cause of joint infections in ages 6–48 years [17, 18•].

Neisseria gonorrhoeae is an important cause of bacterial arthritis in newborns and sexually active adolescents. In newborns, it has non-specific prodromal symptoms; poor feeding, irritability, and fever. The hip is usually involved; however, knee, ankles, and metatarsals may be affected [21, 22]. In adolescence, gonococcal arthritis usually occurs as a manifestation of disseminated infection, including fever, rash, and tenosynovitis or small joints.

Neisseria meningitidis arthritis may be preceded by upper respiratory infection, involve more than one joint, and be associated with a maculopapular rash [21, 22].

Haemophilus influenzae may cause bone and joint infections in young children in areas with low Hib immunization rates [23].

Salmonella species may cause bacterial arthritis in children with sickle cell disease and related hemoglobinopathies.

Other Gram-negative organisms occasionally cause bacterial arthritis in particular circumstances. Non-Salmonella Gram-negative bacilli (e.g., *Serratia*, *Aeromonas*, *Enterobacter*, *Bacteroides*, *Campylobacter*) are more relevant in immunocompromised patients, patients with direct inoculation, and those with a history of recent gastrointestinal or genitourinary instrumentation [24–29]. *Pseudomonas aeruginosa* may cause arthritis in patients with puncture wounds or injection drug use [24, 30–32]. *Brucella melitensis* may cause arthritis in children with foreign travel or other exposure to the organism, usually after consuming unpasteurized dairy products [33].

Anaerobic arthritis may occur in children with a history of joint surgery, trauma, or oropharyngeal infection [34]. The most common anaerobes causing bacterial arthritis are the anaerobic Gram-negative bacilli, such as *Bacteroides fragilis group*, *Fusobacterium* spp., *Peptostreptococcus* spp., and

Cutibacterium acnes [34]. Anaerobes are rarely reported as a cause of septic arthritis in children [34]. Most of the cases usually involve a single isolate and are due to hematogenous spread. See Table 1 for a summary of the most common pathogen according to age group.

Diagnosis

Clinical Presentation

Children with septic arthritis most commonly present with an acute onset of pain around the affected joint, redness, active and passive restriction of joint movement, pseudoparalysis, and fever [3•]. Arthritis of the lower limbs mostly affects the knee, hip, and ankle [2•]. It causes limping and partial or non-weight bearing. Superficial joints, such as the knee, ankle, shoulder, or elbow, may show redness, warmth, and swelling around the joint [3•]. Clinical identification of effusion in the deeper joints, such as the hip or shoulder, is more challenging. The child will usually be in a position where the joint capsule is the least tense. Knee flexion, hip flexion, abduction, and internal rotation are anticipated [2•].

Fever and other systemic signs are frequently absent in neonates. A child with a hip infection usually presents with flexion, abduction, and external rotation of the limb [1, 2•, 3•, 4••, 5, 35]. The classical clinical pattern is more common in cases caused by *S. aureus*, while a milder clinical course is more characteristic for *K. kingae* infection [3•, 36]. An initial high temperature generally correlates with the need for prolonged treatment [12]. However, low temperature does not rule it out, as variations in temperature occur [12].

Monitoring patient's temperature can be useful in accurately and reliably evaluating the response to therapy [12]. A high temperature can be regarded as core temperature > 38.3 °C (101 °F) for patients 3 months of age and older or > 38 °C (100.4 °F) for infants < 3 months of age [37].

Table 1 Organism causing septic (pyogenic) arthritis in children

Under 3 months of age	Between 3 months and 5 years of age	Above 5 years of age
Common organisms: *Staphylococcus aureus* (MSSA and MRSA) Group B *Streptococcus* (*Streptococcus agalactiae*), Gram-negative bacilli	Common organisms: *Staphylococcus aureus* (MSSA and MRSA) Group A *Streptococcus*, *K. kingae*, *Streptococcus pneumoniae*	Common organisms: *S. aureus* (MSSA and MRSA) Group A *Streptococcus*
Other organisms: *N. gonorrhoeae* *Candida* spp.	Other organisms: *Haemophilus influenzae* type b (Hib) (in low Hib immunized children)	Other organisms: *S. pneumoniae* Beta-hemolytic streptococci other than groups A and B, *Salmonella* spp., *N meningitidis*, *N. gonorrhoeae* (in sexually active) *Pseudomonas aeruginosa* and *Candida* spp. (in drug abusers) Anaerobic bacteria

Laboratory Work-up

Aspiration of synovial fluid should not be delayed once bacterial arthritis is suspected. Recovering an organism(s) in the synovial fluid is the primary way to establish a diagnosis [38–40]. Moreover, drainage of the synovial fluid relieves the patient symptoms by decompressing the joint. Aspiration of the hip joint is best done utilizing imaging guidance. Collection of the synovial fluid is usually done with a heparinized syringe to avoid clot formation. Cell count, culture, Gram stain, and susceptibility testing are routinely performed on the aspirated fluid [38]. If no synovial fluid can be aspirated, injection of 3–5 ml normal saline to the joint followed by aspiration for microbiology studies can be performed [8].

Because synovial fluid is bacteriostatic, some organisms seen on the Gram-stained smear may not grow in culture. Up to half of joint aspirate culture do not yield bacterial growth even in those with a positive blood culture. Synovial fluid should be cultured for aerobic and anaerobic bacteria, mycobacteria, and fungi. There is no general agreement regarding the necessary laboratory work-up and its interpretation for establishing the diagnosis of pediatric septic arthritis. Peripheral blood cell count, ESR, CRP, Gram stain, and aerobic and anaerobic cultures are commonly the initial studies performed before considering arthrocentesis according to several studies [15, 16•, 26, 41]. A reliable single laboratory marker which is sensitive and specific enough in diagnosing joint infections is yet to be established. Blood cell count, ESR, and CRP are not specific enough and can be elevated in non-pyogenic inflammatory disorders [42]. Blood culture has varied sensitivity rates of 40–70% [40, 42–45]. ESR and CRP are the most sensitive clinical parameters used for diagnosis according to Pääkkönen and Peltola [3•]. If clinically relevant, synovial fluid white blood cell (WBC) count of ≥ 50,000/mm^3 and polymorphonuclear cell fraction > 90% are highly indicative of septic arthritis [4••]. However, a lower number of WBC can be found in septic arthritis caused by Brucella. Furthermore, juvenile idiopathic arthritis, serum sickness, or reactive arthritis may demonstrate synovial fluid WBC > 50,000 cells/μl [33, 45–47].

CRP > 20 mg/l and peripheral white blood cell count > 12 × 109 cells/l offer a predictive probability of 87% for septic

arthritis [10]. Normal-range WBC, ESR, and CRP do not rule out septic arthritis [5]. It is important to send synovial fluid for cell count, Gram stain, culture, and sensitivities in suspected cases of septic arthritis and identify the causative organism prior to antibiotic treatment [2•, 3•, 4••, 8]. Because Gram staining of the synovial fluid has high false negative rates, it is used to confirm the diagnosis but cannot be used to rule out septic arthritis [2•, 5]. Cellular debris, which can sometimes be misinterpreted as bacteria, makes this study not definitive on its own [39, 40, 43, 44].

CRP changes rapidly enough to allow for monitoring response to treatment and follow-up [3•, 16•]. This is not the case for ESR, which increases rapidly but decreases significantly slower than the CRP level. This makes it less useful for monitoring the infection [48]. CRP is generally elevated and peaks within 48 h of the establishment of septic arthritis [3•, 16•, 48]. CRP may decline within 6 h of antibiotic therapy and may normalize within 7 to 10 days. ESR peaks at about 3 to 5 days. However, as the infection resolves, normalization is slow and may take about 6 weeks [3•, 16•, 48]. A markedly elevated CRP (> 100 mg/l) may suggest that a prolonged therapy may be needed [48]. Moreover, the CRP responds faster to effective treatment, whereas ESR can stay elevated for several weeks in the face of a good clinical response [12].

Measurement of serum procalcitonin (PCT) became a focus of research because of its diagnostic abilities of septic joints. A level of 0.5 ng/ml is regarded as a reliable marker for pyogenic infections [3•, 42]. Under normal circumstances, its serum level is very low (< 0.1 ng/ml) and rises quickly under the systemic effect of bacterial endotoxin. Procalcitonin requires more time to become elevated than CRP and is more expensive to perform [3•]. However, with a half-life of 22 to 29 h and high specificity, it is a good way to diagnose and monitor bacterial infections. Serum cut-off level is still debated, as PCT is very low under healthy circumstances [42].

Brook et al. [49•] had described the role of lactic acid in synovial fluid analysis. Lactic acid measurements can be used as an additional valuable diagnostic tool in differentiation between gonococcal and non-gonococcal septic arthritis, especially in cases where other diagnostic data are overlapping and are not conclusive [50]. It may differentiate between septic arthritis other than gonococcal and other sterile conditions in the joints. Joint fluid lactate levels might be confounded by antibiotic treatment in septic arthritis and should not be used as a basis for withholding necessary antibiotic therapy. Decrements in oxygen partial pressures in joint fluids were accompanied by a decrease in pH and an increase in pCO_2 and lactic acid concentration [51]. These changes were a signal of the largely anaerobic metabolism process in the joint. An inverse relationship between lactic acid synovial levels and glucose was also found [51]. Lactic acid measurement in the synovial fluid above 50 mg/100 ml was detected in bacterial arthritis other than gonococcal. Levels lower than 50 mg/100 ml were found in sterile inflammatory and non-inflammatory conditions [49•, 50–52]. Lactic acid measurement, therefore, appears to be a valuable diagnostic tool in the early differentiation between gonococcal and non-gonococcal septic arthritis and between non-gonococcal septic arthritis and non-septic arthritis before bacterial cultures are available [50].

Polymerase Chain Reaction

These methods are especially effective for detecting infection in cases where cultures are negative or when antibiotic treatment was started before arthrocentesis. A pathogen could be detected this way up to 6 days into antibiotic treatment [53, 54]. The test targets bacterial DNA or RNA that codes the 16S ribosomal RNA. It is especially useful in detecting slow-growing or difficult-to-grow bacteria, such as *K. kingae*, and anaerobic bacteria. It is also helpful in detecting *S. pneumoniae*, *S. pyogenes*, *Salmonella* spp., and *S. aureus*. An additional advantage is a distinction between Gram-positive and Gram-negative bacteria by universal PCR [53]. However, it necessitates post-PCR visualization on agar which may potentially cause crossover contamination and increased false positive rates. Another limitation of PCR in the clinical setting is the current inability to provide antibiotic sensitivity [54]. However, PCR methodology is capable of detecting some resistant organisms, such as MSSA and MRSA [55].

PCR was able to detect organisms in 23% of negative cultures from suspected cases for septic arthritis. Its sensitivity is higher [56] than the gold standard microbiologic sensitivity results (2.4–18% vs 30–90%) [12, 13, 53, 56].

Real-time PCR, a newer version of the technique, is gaining wider availability and usage. In comparison with conventional PCR, the real-time technique is considered faster, has lowered cross-contamination rates, and is easier to interpret. It has also ten times higher detection rates in comparison with conventional PCR [54].

Imaging

Radiographs

Radiographic imaging is required to exclude other bone pathologies, such as osteomyelitis, fractures, and tumors. Plain radiography is the first imaging study method to be performed when septic arthritis is suspected [1, 2•, 16•]. In acute septic arthritis setting, radiography imaging may also be normal. Similar to osteomyelitis, where the typical "rat bite" sign only becomes visible on plain radiographs 2 to 3 weeks after the onset of symptoms [48], a normal radiograph does not rule out either osteomyelitis nor septic arthritis in the acute setting [48]. Hence, if other diagnostic

tools are not performed, cases can potentially be missed [7], especially with underlying osteomyelitis.

The first radiographic signs may appear between days 4 and 10 of infection and may even appear only after days 10–15 as the child age progresses [15]. Soft tissue swelling around the joint capsule is anticipated first (see Fig. 1). In the hip, eccentric femoral head of the femur can be seen. It may be due to the adductors contracting than the capsular effusion itself [15]. In advanced stages, an increased joint space may represent even a dislocation in neonates and infants [1, 4••].

Ultrasound

Ultrasound is especially helpful in ruling out deep joint, shoulder and hip, infections [4••, 15, 16•]. It can distinguish the size and nature of the intra-articular fluid, follow the changes of the joint capsule in the child, and help demonstrate damage to the epiphyseal nuclei, especially in the femur [15]. In addition, metaphyseal subperiosteal abscesses may also be detected. This can progress to show elevated periosteum far from the bone representing an anechoic abscess. Ultrasound-guided arthrocentesis can improve the yield of the aspirate [15].

The presence of fluid suggests an infection, but there is no correlation between the size or echogenicity of the effusion with the severity of the inflammatory process [1, 2•, 15]. Under the relevant clinical and laboratory setting, sonographically guided aspiration of the hip can decrease the damage to the articular surfaces [1, 2•]. Sensitivity and specificity are high, as even small (1–2 ml) effusions can be detected [4••, 16•]. Generally, ultrasonography does not play an important role in the diagnosis of concurrent osteomyelitis, and other imaging modalities are used for this condition [48].

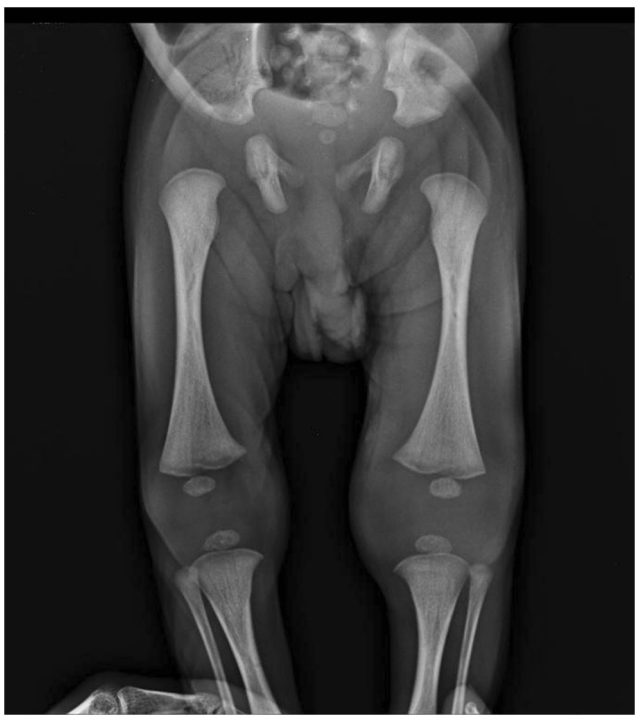

Fig. 1 Radiograph of a 13-day-old neonate. Note the epiphyseal lucent band which is normal in infants. Note the soft tissue swelling around the knee. Case courtesy of Dr. Maulik S. Patel, Radiopaedia.org. From the case rID: 13358

Bone Scan

In the absence of fluid, skeletal scintigraphy can be performed in order to exclude osteomyelitis [48]. Its sensitivity is higher in long bones and when symptoms are hard to precisely locate, when a multifocal disease is suspected, and in neonates and MRSA infections [4•, 48]. In septic arthritis, diffuse, faint increased tracer uptake on both sides of the joint is observed [1]. Different from osteomyelitis, the uptake is limited to the bony structures near the joint. Pus and fluid inside the joint, particularly in the hip, increase the intracapsular pressure and can damage epiphyseal perfusion, which can result in decreased tracer uptake in the epiphysis and false negative results with up to 50% of cases [16•]. This makes the use of bone scans highly controversial [1, 15].

Computed Tomography and Magnetic Resonance Imaging

Computed tomography (CT) and magnetic resonance imaging (MRI) may help the clinician detect the involvement of bone and cartilage [15]. CT scans can detect effusions and guide joint aspirations in septic arthritis, but they are considered inferior to MRI for septic arthritis [4••]. Early MRI can classify the position and size of the disease for surgical planning. Gadolinium enhancement may help to differentiate between causative organisms and is recommended when the suspected pathology is located in the non-ossified cartilage of bones [16•].

Some authors consider MRI to be the best imaging method for musculoskeletal pediatric infections. It is also in use for diagnosis osteomyelitis, especially in challenging cases [57]. Monsalve et al. recommend that every child with suspected musculoskeletal infection should undergo an MRI scan (preferably within 12 h from clinical presentation) [7]. This scan should include the nearest joint to rule out its concurrent involvement in an adjacent infection [58]. Because of the high incidence of co-existing osteomyelitis, it is recommended that an MRI should be performed and compared with the ultrasound [7, 58]. Performing MRI may delay the initiation of treatment, but the significance of this is hard to evaluate. It is logical to assume that risk of missing the extent of the infection, such as with concurrent osteomyelitis of periarticular abscess, may justify the treatment delay [7]. MRI should be considered in children who fail to improve after 48 h of antibiotic treatment. MRI may not be available, especially in developing countries. It requires sedation for young children, and it is costlier. In septic arthritis, MRI signal

intensity differs in the bone marrow and adjacent soft tissues, with a brighter T2 signal [4••] (see Fig. 2). Contrast enhancement is anticipated in adjacent soft tissues. Different diseases, such as transient synovitis, will not show signal marrow and soft tissue changes [4••].

Differential Diagnosis

It is imperative that the clinician is familiar with the differential diagnosis of septic arthritis. It includes trauma, tumors, Perthes disease, or slipped upper femoral epiphysis (SUFE) when considering the hip specifically, other types of infections, such as osteomyelitis or cellulitis, and inflammatory causes, such as reactive arthritis, juvenile rheumatoid arthritis, and transient synovitis (toxic synovitis) in the hip [2•, 4••]. Here, we elaborate on some of these.

Transient Synovitis

This etiology may have a similar initial presentation to septic arthritis and may pose a diagnostic dilemma [2•, 8, 13, 59]. Limping and joint irritability with no fever is more compatible with transient synovitis [2•, 13]. History of non-weight bearing and a temperature greater than 38.5 °C are reliable clinical signs differentiating it from septic arthritis [2•, 13]. A cut-off of 50,000 white blood cells (WBCs)/mm^3 of synovial fluid, ESR > 40 mm/h, and CRP > 20 mg/l were used by many authors for differentiating septic arthritis from transient synovitis [2•, 13]. However, especially in immunosuppressed or children who were pretreated with antibiotics, there is lower WBC count [2•, 4••, 12, 13]. CRP > 20 and refusal to bear weight may be reliable for differentiation in from septic arthritis [8].

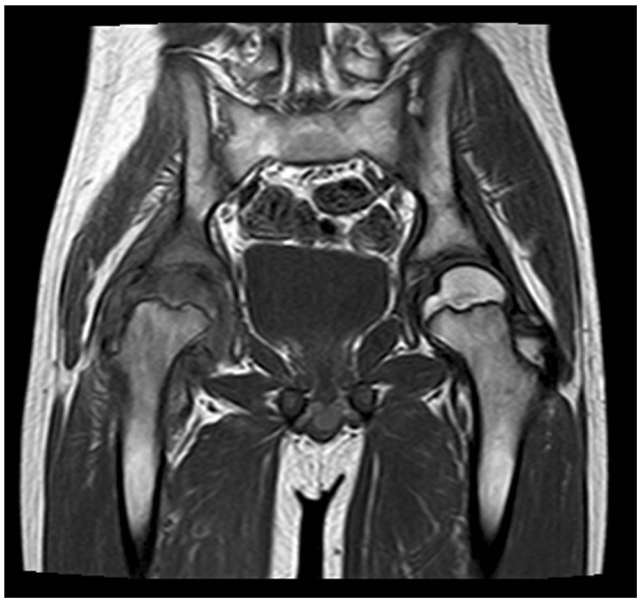

Fig. 2 Magnetic resonance image of a 10-year-old child. Note the irregularity of the right femoral epiphysis and opposing acetabular surface displaying low signal in T1 and bright signal in STIR/T2 FATSAT due to marrow edema. There is loss of joint space at the superior aspect of the right hip joint with moderate joint infusion. Case courtesy of Dr. Ahmed Abdrabou, Radiopaedia.org. From the case rID: 27744

Inflammatory Arthritis

Synovial fluid WBC counts, polymorphonuclear (PMN) percentage, TNF-a, ESR, and serum PCT were found useful by Talebi-Taher et al. [46] in differentiating between septic and non-septic arthritis. Synovial WBC count above 50,000/mm^3 lacks the sensitivity to be clinically useful to rule out infectious arthritis. Patients with infection had a much higher CRP in comparison to those with inflammation [46], making a high CRP a moderately sensitive parameter. Low ESR was found to be a good negative predictor; high ESR, on the other hand, was not a good positive predictor for the disease [46]. Tumor necrosis factor alpha (TNF-a) was significantly elevated in infectious cases in comparison to inflammatory arthritis [46]. Interleukin 6 (IL-6) level, however, did not differ among the two groups [46]. Serum procalcitonin level (PCT) was not more useful than CRP, ESR, and serum PCT in differentiating septic arthritis from non-septic arthritis [46]. Lactic acid measurements can also be used in the differential diagnosis of septic and non-septic arthritis [49•].

Pericapsular Pyomyositis

Mignemi et al. [35] described their findings distinguishing between septic arthritis and pericapsular pyomyositis. Pericapsular pyomyositis is twice as common as septic arthritis in children presenting with an acutely irritable hip [35]. The synovial fluid aspiration is usually "non-septic" (< 50,000 WBC count, negative Gram stain and cultures) as it is an extra-articular infection [35]. The importance of distinguishing between septic arthritis and pericapsular pyomyositis is important, because arthrocentesis through infected musculature can contaminate the joint. It is hard to clinically differentiate between pericapsular pyomyositis and septic arthritis in a child presenting with an irritable hip [35]. There were no significant differences in CRP, ESR, and serum WBC between the two entities, and body temperature and weight-bearing also did not differ significantly [35]. The two entities could only be differentiated in the study by Mignemi et al. [35] by ultrasound and MRI. Pericapsular pyomyositis was found to present a smaller hip effusion on ultrasound in comparison to septic arthritis [35]. The authors concluded that MRI is the method of choice to distinguish between the two entities.

Adjacent Infection

Children with osteomyelitis showed symptoms longer than those with septic arthritis, and it was suggested that the intense inflammatory response may facilitate the spreading of the infection in an adjacent joint [58]. Five independent predictors of adjacent infection were age above 3.6 years, CRP > 13.8 mg/l, duration of symptoms >3 days, platelets < $314 \cdot 10^3$ cells/ml, and absolute neutrophil count (ANC) > $8.6 \cdot 10^3$ cells/ml [58]. The presence of three or more of those indicators was associated with a higher risk for adjacent infection to a septic joint. It was advised, however, that any child with septic arthritis should undergo an MRI to avoid a 10% false negative result in cases designated as "low risk" [58].

Treatment

Surgical Treatment

In case that purulence is found in the synovial fluid, immediate operative treatment is recommended [2•, 8, 13, 59]. Historically, open arthrotomy was the standard of care for infected joint operative treatment. However, newer arthroscopy and irrigation techniques are now considered safe and effective [2•, 13]. Arthritic joints, associated osteomyelitis, or failed arthroscopic drainage is generally operated with open arthrotomy; however, no definite evidence exists regarding which of the two methods is more suitable for different joints [13].

Early diagnosis (< 4 days) may allow daily aspirations until no pus can be found [4••, 8]. In complicated settings or large pus collections which involves surrounding tissues, arthroscopic or open arthrotomy is strongly recommended [2•]. The knee and shoulder are usually approached arthroscopically, and arthroscopic debridement for septic hips showed improved outcomes and significantly shorter hospital stay compared with open debridement [16•].

However, some reports still suggest approaching the hip and ankle joints with open arthrotomy due to the serious sequel of septic infection [4••]. Normal saline lavage followed by a drain insertion for 48 h is recommended, with an optional immobilization of the limb for that duration with a splint or traction device [4••]. It is encouraged to start physiotherapy and ambulation as early pain allows to retain the joint range of motion.

Pharmacological Treatment

There is no consensus regarding the best antibiotic treatment regime or the mode of administration [6•]. Empiric antibiotic treatment is started once the synovial fluid is aspirated and sent for analysis [2•, 3•, 8, 16•]. Gram stain findings can assist in the initial empiric antimicrobial selection. Once there are culture and sensitivity results, the antibiotic cover is adjusted accordingly. Empirical treatment is continued, depending on clinical response in case the causative organism is not identified [2•].

Suggested guidelines for switching from parenteral to oral therapy include the following [4••, 29, 31, 32, 60–62]:

1. The child is ≥ 1 month of age. This is due to the less predicted pattern of gastrointestinal absorption of oral antibiotics in neonates [34, 63].
2. Parenteral therapy shows clinical improvement (Unfortunately, 10% of children need continuous intravenous antibiotic treatment as they do not respond to oral treatment [4••]).
3. Immunocompetent and fully immunized child against Hib and *S. pneumoniae* according to age.
4. Ability to use oral medication
5. Compliant and well-informed patient and family.
6. Identification of the pathogen and its sensitivity. Or, in case of negative culture, the child has responded as expected to empiric oral therapy during hospitalization
7. Uncomplicated clinical course

Empiric therapy for bacterial arthritis in infants < 3 months of age should be directed against *Staphylococcus*, group B *Streptococcus* (GBS), and Gram-negative bacilli. Gentamycin, nafcillin, oxacillin, or vancomycin in combination with cefotaxime, or ceftazidime if *Pseudomonas* is considered is the treatment of choice [16•, 64].

Empiric therapy for bacterial arthritis in children ≥ 3 months should be directed toward *S. aureus* and other Gram-positive organisms (e.g., group A *Streptococci*, *S. pneumoniae*). A 10-day clindamycin therapy with 2–4-day high initial intravenous dose or 1st-generation cephalosporin seems to be a proper treatment. If the child is not vaccinated against *Haemophilus influenzae*, ampicillin or amoxicillin should be administered additionally [3•, 8]. If < 10 to 15% of community *S. aureus* isolates are methicillin-resistant and the child is hemodynamically stable, cefazolin and nafcillin/oxacillin are the treatment of choice. If ≥ 10 to 15% of the community *S. aureus* isolates are methicillin-resistant, clindamycin and vancomycin are suggested [4••, 38, 65]. For penicillin non-susceptible *S. pneumonia*, vancomycin and clindamycin may also provide coverage. However, a large proportion of serotype *19A* isolates is resistant to clindamycin [66]. Second- or third-generation cephalosporin should be added to empiric anti-staphylococcal therapy if Gram-negative organisms are suspected or observed on the Gram stain [67].

K. kingae is often the offensive agent in children 6 to 36 months of age. *K. kingae* can usually be treated with cephalosporins, such as cefazolin, cefotaxime, and ceftriaxone, but consistently resistant to vancomycin and often resistant to clindamycin and anti-staphylococcal penicillins (e.g., oxacillin, nafcillin) [4••, 68–73].

Children with sickle cell disease are prone to infection by *Salmonella* which is sensitive to cefotaxime and ceftriaxone and is added to the empiric regimen [65].

For patients with delayed penicillin hypersensitivity, cephazolin 50 mg/kg (max 2 g) IV every 8 h is recommended [2•]. For patients with immediate penicillin hypersensitivity, vancomycin 30 mg/kg (max 1.5 g) IV every 12 h is recommended [2•].

Penetrating trauma may predispose to polymicrobial infection. Empiric therapy should include coverage for *P. aeruginosa* as well as *S. aureus*. Options for empiric therapy are cefepime for coverage against *P. aeruginosa* and MSSA or combination therapy with cefepime or ceftazidime plus an agent with activity against MRSA, such as clindamycin or vancomycin. Pathogen-directed therapy should include agents directed against all organisms recovered.

Children treatment with fluoroquinolones should be limited to cases for which no other good alternative exists [74–80].

The use of steroids is not the standard of care, and further studies are required to study its role in the treatment of septic arthritis. Early treatment with a 4-day course of adjuvant dexamethasone (0.6 mg/kg per 24 h divided for 3 dosages per day) demonstrated an early improvement in clinical and laboratory parameters compared with children treated with antibiotics alone [4••]. This treatment reduced the duration of symptoms and hospital stay, while the level of residual dysfunction was also reduced by the treatment end. Lower synovial fluid concentrations of IL-1b, IL-1, TNF-a, and metalloproteinases and a decrease in cartilage destruction, which is mediated by these cytokines, were associated with adjuvant steroid treatment [13, 16•, 17]. However, another report showed that dexamethasone shortens the disease course but had no effect on the frequency or extent of complications [3•]. As large-joint septic arthritis is less indolent and more easily diagnosed, physicians may not hesitate to treat with corticosteroids that may mask the symptoms [12]. We did not find a report about useful NSAID usage in septic arthritis, although it may potentially alleviate pain.

In contrary to what was suggested in the past, Jagodzinski et al. [12] did not find a correlation between the duration of symptoms prior to surgery and the need for prolonged antibiotic treatment.

Response to Treatment

Response to treatment should be subjected to serial evaluations. Fever, joint pain, swelling, erythema, and joint mobility should be daily evaluated during hospitalization. We suggest that peripheral white blood cell (WBC) count and C-reactive protein (CRP) be measured every two to three days and upon any clinical deterioration. Repeated aspirations are not routinely necessary. If repeat aspiration or a surgical drain is performed, serial synovial fluid analyses should demonstrate no bacterial presence and a decreased WBC count within one to two days under therapy [6•]. Fever is expected to resolve within up to five days of treatment and joint symptoms within two days [29, 81]. Resolution of symptoms and sterilization of the joint fluid is thought to be in correlation with the duration of symptoms before initiation of therapy and the initial synovial WBC count [82–84].

ESR is not as useful as CRP for monitoring treatment response. ESR may rise for three to five days even under treatment. However, ESR may guide decisions about treatment duration as it normalizes when inflammation resolves. Children with a mildly elevated ESR at the end of the prescribed treatment course may not require more therapy if not supported by clinical and radiologic features of osteomyelitis [85–87].

CRP peaks within 36 to 50 h of onset of infection and then normalizes quickly with therapy [85–87]. High WBC counts are expected to normalize within one week of treatment [87], even with appropriate treatment.

The absence of clinical improvement, persistently elevated ESR, CRP, peripheral WBC count, or synovial fluid WBC count, and failure to sterilize the synovial fluid in the expected periods are indications of treatment failure. Those patients may require either arthrotomy or adjustment of antimicrobial therapy or both.

Reevaluation, including the exclusion of osteomyelitis with abscess with MRI, investigation for exposure to unusual organisms (e.g., *Pasteurella multocida*, *C. acnes*), or penetrating trauma should be performed, also considering other conditions mentioned in the "Differential Diagnosis" section.

Monitoring drug levels to ensure adequate serum levels is recommended for a patient who fails to improve under pathogen-directed antibiotic treatment.

Duration of Treatment

There is no consensus regarding the duration of the treatment. Intravenous treatment is commonly started immediately, while oral antibiotic therapy is not recommended until CRP and leukocyte count normalization, which usually occurs after 2–3 weeks of treatment [15]. Jagodzinski et al. [12] suggested full 3 days of IV treatment, which can be switched to oral treatment only upon clinical and hematological improvement in an afebrile child [12]. Oral treatment should continue for at least 3 weeks and should be stopped only if the child shows clinical and hematological improvement [12]. Radiographic non-progressive lesion in an asymptomatic child is not a reason for treatment continuation. If the clinical status and CRP improve within 24 h, antibiotics are usually continued for 3 to 4 weeks. In cases this does not occur, surgical intervention is necessary [8]. Acute osteomyelitis complicated by septic arthritis is

usually more chronic, and the CRP level normalizes slowly. This indicates the need for a longer treatment course [48]. Wall et al. suggested 2 days of IV antibiotic treatment for non-complicated cases in which clinical improvement is evident and inflammatory markers are normalizing; this is followed by 3 weeks of oral antibiotic treatment [2•].

Dodwell [16•] suggested 2–4 days of IV treatment followed by 10 days of oral antibiotic therapy. The Infectious Diseases Society of America guideline for MRSA septic arthritis supports individualized decision-making for treatment duration, which is a minimum of 3 to 4 weeks typically. Treatment can be stopped when CRP is below 20 mg/l [3•]. For uncomplicated cases of previously healthy children beyond the neonatal age, there are recommendations for 10 days of high-dose clindamycin or a first-generation cephalosporin in total. This is extended to 20 days of treatment in case of accompanying osteomyelitis [3•]. The treatment is initiated with 2–4 days of intravenous treatment and completed orally. Medical treatment can be stopped once the child demonstrated clinical improvement and when CRP level is below 20 mg/l. In cases of accompanying osteomyelitis, the treatment course is extended to 20 days. This 10-day treatment course was not tested for MRSA cases [3•]. For MRSA cases, the treatment is extended, although there is not enough prospective data for clear guidelines. Agarwal et al. [4•] recommended treating infections with *S. pneumoniae*, *K. kingae*, *H. influenzae*, and *N. gonorrhoeae* for 2–3 weeks. Infections caused by *S. aureus* or Gram-negative bacteria are treated for 3–4 weeks [4••]. If an adjacent bone is affected, treatment is extended for about 20 days. If most symptoms and signs subside within a few days and the serum CRP falls below 20 mg/dl, antibiotics can safely be discontinued [4••]. Bacterial arthritis of the hip and arthritis caused by *Enterobacteriaceae* or other unusual organisms may require longer treatments [86].

Prognosis and Complications

The most common septic joint complications are osteonecrosis of the femoral head and chronic osteomyelitis [5]. Osteonecrosis and growth plate damage are probably due to increases in intracapsular pressure and the lytic enzymes in the inflammatory fluid [2•]. The outcome of septic arthritis depends on the duration of symptoms prior to treatment initiation [1, 2•]. Other risk factors are delayed diagnosis (over 4 days), neonatal infections, concomitant osteomyelitis, and staphylococcal or Gram-negative infections [4••].

Howard-Jones et al. [36] reported that about 10% of children demonstrated clinically significant functional impairment at 12 months follow-up. Misdiagnosis was found to be the most common cause for delay in treatment, which is associated with high rates of complications [36].

Long-term follow-up studies are needed to identify joint and bone complications as they are fully apparent after bone growth has concluded [36]. Physeal and metaphyseal alterations are possible, and it may lead to joint arthrosis, asymmetric epiphysiodesis, or damage to the entire physis with shortenings of the bone [15] and even dislocation in case of the hip [36].

Follow-up

Wall et al. suggest that the child should be followed-up with additional inflammatory markers and physical examination one week after discharge and again one week after the end of antibiotic treatment [2•]. Long-term sequelae of septic arthritis, such as arthrosis, growth disturbance, and avascular necrosis, are to be ruled out through periodic orthopedic follow-up during the first one to two years [2•, 3•, 4•], even though septic arthritis complication can manifest several years after initial infection.

We suggest at least 6 weeks of radiological follow-up after resolution of symptoms to evaluate ongoing bone involvement [2•, 3•, 4••].

Conclusions

Septic arthritis in children is uncommon; yet, it is a serious infection. It has medical and surgical risk factors. Hematogeneous spread of *S. aureus* is the most common etiology although other pathogens are known causes at different age groups. Laboratory studies are reliable for diagnosis; however, no one parameter is adequate by itself. Serum procalcitonin and real-time PCR are newer methods showing good prospects for diagnosis. Many imaging modalities exist; however, all have their limitations, and MRI may be the best choice available. This is especially important in the case of suspected pericapsular pyomyositis, where missing the diagnosis can lead to the spread of the infection. Arthroscopic treatment and serial arthrocentesis pus evacuation are gaining more attention as a surgical treatment option. There is no consensus about the nature or duration of pharmacological treatment, and many suggested protocols are found, including the use of steroids. However, most agree that the duration of treatment should be prolonged. Complications are severe and are mostly due to a missed diagnosis. More studies are needed for better understanding of the proper treatment choice and diagnosis parameters.

Compliance with Ethical Standards

Conflict of Interest All authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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