Septic Arthritis in Children: Clinical Update

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Introduction

Septic arthritis is commonly encountered in children and results from a purulent inflammatory response to a bacterial infection, most commonly *Staphylococcus aureus*. The most common mode of transmission is hematogenous dissemination to the synovial joint. Septic arthritis of the hip joints is a medical emergency, needing prompt diagnoses, drainage of the synovial space, and antimicrobial therapy to prevent poor outcomes [1]. The purpose of this chapter is to provide an overview of the etiology, microbiology, epidemiology, pathogenesis, approach to diagnosis, and treatment of septic arthritis in children.

Etiology/Microbiology

The microorganisms causing infectious arthritis include most commonly bacteria, followed by viruses and fungal organisms. Bacterial causes of pyogenic arthritis vary with age, immunization status, and certain predisposing risk factors and/or medical conditions such as immunosuppressive states or hemoglobinopathies. In the neonatal age group up to 2 months of age, the most frequently isolated organisms are *Staphylococcus aureus* and *Streptococcus agalactiae* (known as group B streptococcus) followed by enteric gram-negative organisms (*Enterobacteriaceae*) and *Streptococcus pneumoniae* [2, 3]. Other rare but important organisms in the neonates are *Salmonella* spp., *Neisseria gonorrhoeae*,*Candida albicans*, and the emerging *Candida* non-albicans species [4–7]. One notable non-albicans species is *C. parapsilosis*, with increasing prevalence over the past two decades and which is the second most commonly reported cause of systemic candidiasis in a cohort of neonates weighing less than 1000 g at birth (extremely low-birth-weight neonates) [8–10]. Past the neonatal age, infections with enteric gram-negative bacteria are rare in the pediatric population; nonetheless, they can be observed in association with direct inoculation by intravenous drug use (IDU), surgical instrumentation, and trauma and in hosts that are immunocompromised [5].

Pseudomonas aeruginosa has been associated with septic arthritis in infants at sites of puncture wounds and in adolescents with IDU and following nail injuries through a sneaker [11–13]. In infants and young children up to 59 months of age, *Haemophilus influenzae* type b (Hib) was the most frequent bacterium isolated in pyogenic arthritis; however, with the implementation of the Hib vaccine for children in 1987 and infants in 1990, the incidence of typeable invasive *H. influenzae* has dramatically decreased [14–16]. With this decrease in invasive Hib, *Staphylococcus aureus* has predominated as the most common etiologic cause of septic arthritis in all age groups [14, 17]. In children younger than 5 years of age, methicillin-susceptible *S. aureus* (MSSA), community-associated methicillin-resistant *S. aureus* (MRSA), *Kingella kingae*, *Streptococcus pyogenes*, and *Streptococcus pneumoniae* are common causes of pyogenic arthritis [3]. Although *S. aureus* continues to be the most common pathogen isolated from osteoarticular infections in children, *Kingella kingae* is being reported more frequently in the United States [18–21]. In a retrospective case series from 1999 to 2002, *Kingella kingae* was the most isolated organism in children under 36 months of age with a statistically significant value (p: 0.0003) [22]. In another series from Israel, *Kingella kingae* was the primary cause of septic arthritis in patients younger than 24 months of age, found in 48% of cases [23]. A rise in the diagnosis of *Kingella kingae*

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osteoarticular infections is attributable to improvements in culture methods, growing best in aerobic conditions with carbon dioxide, and utilization of real-time polymerase chain reaction (PCR) [18, 24, 25].

Emphasis to underlying medical condition and immunosuppressed state must be considered as certain conditions predispose to certain bacteria. For instance, in the patient with sickle cell anemia, *Salmonella* spp. is a common cause of septic arthritis; however, atypical osteomyelitis and concurrent septic arthritis due to *Salmonella typhi* have been documented in normal hosts [26]. Patients with malignancy and immunosuppression can present with septic arthritis due to *Aeromonas* spp., *Enterobacter* spp., *Serratia* spp., *Bacteroides* spp., *Pseudomonas* spp., *and Campylobacter* spp. [13, 27].

The exposure history must be considered in evaluating for possible bacterial etiologies of septic arthritis. If clinical findings of septic arthritis arise after an animal bite, multiple organisms must be considered depending on the animal. Bites by cats, dogs, or mammals have multiple organisms that can be pathogenic including *Pasteurella* spp., *Staphylococcus aureus*, *Streptococcus* spp., *Capnocytophaga* spp., *Moraxella* spp., *Corynebacterium* spp., and *Neisseria* spp. [28]. In cases of cat or dog scratches or bites, *Bartonella henselae*, etiology of cat-scratch disease, has to be in the differential as a rare cause of septic arthritis. For reptile bites, enteric gram-negative bacteria and anaerobes are considered. For human bites those considered include *Streptococci* spp., *S. aureus*, *Eikenella corrodens*, *Haemophilus* spp., and anaerobes. In rat bites a disease known as rat-bite fever can rarely present with septic arthritis and is attributable to *Streptobacillus moniliformis* and *Spirillum minus* [29]. It is important to recognize rat-bite fever as the case fatality rate is 7–13% in patients that do not receive therapy [29]. Another exposure history to consider is tick bites or finding of the characteristic rash of erythema migrans in endemic areas as a cause of Lyme arthritis secondary to *Borrelia burgdorferi*; refer to the chapter on Lyme arthritis for further details. A detailed travel history and exposure history including consumption of raw food and unpasteurized milk or cheese must be inquired as they can be associated with septic arthritis *caused by Brucella* spp. [3, 5].

Unusual organisms reported to cause pyogenic arthritis in children include *Actinomyces pyogenes*, *Propionibacterium acnes*, and *Pasteurella multocida* [13, 30–32]. Chronic monoarticular septic arthritis can arise due to brucellosis, *Mycobacterium tuberculosis* or non-tuberculosis mycobacterium, *Candida* spp. (seen in intravenous drug users), and *Nocardia asteroides* [12, 13]. Besides *Candida* spp., other fungal infections have been attributed to septic arthritis, and travel history or having lived in an endemic area for a dimorphic fungus has to be elicited. Dimorphic fungi known to cause septic arthritis by dissemination are *Histoplasma capsulatum*, *Coccidioides immitis*, *Blastomyces dermatitidis*, *Cryptococcus neoformans*, and *Sporothrix schenckii* [33–36]. Viral etiologies are less likely to cause infectious arthritis in comparison to bacterial etiologies. The most common viruses include parvovirus B19, rubella virus, arboviruses (dengue, chikungunya), and hepatitis B [3]. Other less common viruses include varicella-zoster virus, enterovirus, Epstein-Barr virus, mumps virus, cytomegalovirus, and human immunodeficiency virus [3, 13].

Epidemiology

The incidence of septic arthritis is more common in children; the estimated incidence is 1–37 cases per 100,000 people, with a male-to-female predominance of approximately 2:1 [37, 38]. In a Norwegian prospective population-based, multicenter study from 2004 to 2005, children under 16 years old suspected of having arthritis were referred to the local department of pediatrics or rheumatology. The incidence of arthritis was 71 per 100,000 children, septic arthritis was found in 5 per 100,000 children, and the incidence was higher in children younger than 8 years old with a male predominance [37]. The epidemiology observed in the Norwegian study is similar to multiple case series, highlighting that most cases occur in children younger than 6 years of age, that peak incidence occurs in children younger than 3 years old, and that boys are affected twice as more compared to females [14, 17, 37, 39–43]. A history of trauma may precede the development of pyogenic arthritis and is temporally associated with acquisition by *Staphylococcus aureus*; however, eliciting a history of trauma is less common in septic arthritis in comparison to osteomyelitis [14, 44–46]. A preceding history of an upper respiratory infection often precedes pyogenic arthritis that is caused by HiB and *Kingella kingae*. Both *Kingella kingae* and HiB can colonize the human posterior pharynx [25]. With an upper respiratory infection, the oral pharyngeal mucosa is damaged which predisposes the colonized microorganisms to spread to the blood. Bacteremia occurs with potential hematogenous spread to the synovial fluid (explained in more detail in the pathophysiology section). In the case of *Kingella kingae*, gastroenteritis, aphthous stomatitis, or an upper respiratory infection can increase the likelihood of transient bacteremia due to mild traumatic injuries to the mucosa and often precede septic arthritis by hematogenous spread to the affected joint [14, 19, 25, 40, 47–49]. Outbreaks of child-to-child transmission have been reported in child care centers resulting in osteoarticular infections [50, 51]. In children younger than 4 years of age, *Kingella kingae* has replaced *H. influenzae* as the main pathogen of gram-negative hematogenous pyogenic arthritis [19, 23, 47, 49]. Overall, many children do not have an underlying risk factor for septic arthritis; nonetheless, risk factors that predispose to septic arthritis include immunodeficiency, hemoglobinopathy, recurrent

hemarthrosis, diabetes, intravenous drug use, and rheumatoid arthritis. Extra-articular spread of infection for septic arthritis, other than osteomyelitis in 9–33%, does not frequently occur in the modern age of antibiotic use [13, 52–55].

Pathogenesis

Septic arthritis is caused by various mechanisms. The most commonly observed mode of acquiring pyogenic arthritis in children is by direct seeding of bacteria by hematogenous spread to the synovial membrane [56]. Other mechanisms include direct inoculation by trauma or surgical infection and from spread from a contiguous focus of infection (as seen with osteomyelitis). The synovial joints are composed of synovia (transparent synovial fluid which is viscous with hyaluronic acid and IgG) [44]. The synovium, also known as the synovial membrane, is embarked with the formation of synovia. The synovial membrane is a highly vascularized region with a vast capillary supply that functions to nourish, lubricate, and cushion the avascular cartilage of the joints [44]. Noticeably, the synovium has a rich blood supply and lacks a barrier basement membrane, making it prone to hematogenous spread and seeding to the synovial space [10, 44]. Children, particularly younger than 18 months, have increased vasculature connecting the metaphysis and epiphysis, termed transphyseal blood vessels, allowing contiguous spread from a primary metaphyseal osteomyelitis into the joint space through the epiphyseal growth plates or vice versa with the spread to the metaphyseal bone from the infected synovium [57, 58]. The extension from a primary septic arthritis of the hip or shoulder to a secondary osteomyelitis of the femur or humerus most notably occurs in neonates and in children with *K. kingae* [3, 55]. Septic arthritis may also occur through direct inoculation of a pathogen into the sterile joint space by surgical procedures such as arthroscopy, prosthetic joint implantation or revisions, intra-articular injection of corticosteroids or other medications, and penetrating trauma to the joint space [44, 59–61].

The pathophysiology of septic arthritis consists of adherence of the organism to the synovial membrane and bacterial proliferation in the synovial fluid that results in an inflammatory response [62]. Various experimental animal models have been studied to further comprehend the pathogenesis of septic arthritis. The synovial fluid inhibits growth of bacteria in vitro; however, *Staphylococcus aureus*, one of the bacteria most studied in the pathogenesis of septic arthritis, has developed methods of resistance to overcome the defense mechanism of the synovial fluid. *Staphylococcus aureus* adheres to the bone matrix (laminin, fibronectin, collagen, and bone sialoglycoprotein) by bacterial adhesins or microbial surface components that recognize matrix molecules (MSCRAMMs) [44, 63–67]. The strains of *Staphylococcus aureus* lacking the genes encoding MSCRAMMs are less likely to result in osteoarticular infection in animal models [64, 66–68]. Once the bacteria enter and adhere to the joint space, virulence factors, such as formylated peptides, mediate the recruitment of neutrophils [69]. Neutrophils are essential in bacterial clearance but also contribute to tissue damage via enzyme release and free radical formation [67]. Bacterial exotoxins recruit T cells and activated macrophages to the joint space, resulting in the release of an inflammatory cytokine cascade. Cytokines released include gamma interferon, tumor necrosis factor, interleukin 1, interleukin 2, interleukin 6, and interleukin 7 [67, 70]. These cytokines stimulate the release of proteolytic enzymes by the cells in the synovial lining and chondrocytes that enhance leukocyte migration and also promote increased intra-articular pressure [44]. This increase in pressure by accumulation of purulent synovial fluid leads to ischemia and destruction of the synovium and cartilage [44, 56]. It is the host's inflammatory response to a pathogen that leads to most of the damage to the joint as early as 3 days [71, 72].

Clinical Manifestations

Septic arthritis initially presents with systemic manifestations of fever, irritability, or decreased appetite. Neonates or infants present with nonspecific symptoms of hyperthermia or hypothermia, decreased activity, decreased appetite, desaturations, lethargy, irritability, and/or pseudoparalysis of the extremity involved. Subtle signs and symptoms, such as fever, can be absent in a neonate with septic arthritis; thus, a high index of suspicion has to remain in this vulnerable population [44]. The hip and knee joints are most commonly affected in neonates [73, 74]. More localized findings are observed in older children such as pain in the involved joint progressing to edema and rubor of the overlying skin. Septic arthritis presents in a monoarticular fashion in more than 90% of cases [40]; however, polyarticular presentations can occur with *Neisseria meningitidis*, *Neisseria gonorrhoeae*, and *Salmonella* spp. [3]. The weight-bearing joints of the lower extremities are affected in approximately 75% of cases, with the knee being most commonly affected followed by the hip and ankle [40, 75]. The elbow and shoulder can also be affected with less frequency [48]. When the upper extremity is affected, pseudoparalysis of the affected joint can be seen with associated point tenderness on palpation and decreased range of passive or active motion with associated pain [3]. In the infant population, the hip is also one of the most affected joints; interestingly, rubor and edema may not be present which makes it difficult to diagnose [3, 13]. Overall, the smaller distal joints are less affected in comparison to the proximal larger joints [44].

Physical examination and clinical findings vary with the age group affected. In general, focal joint tenderness can be

elicited with erythema of the overlying skin and effusion or edema. Passive joint movements increase intracapsular pressure causing pain and decreased range of motion. The neonate and infant with hip involvement may cry or become irritable with diaper changes or when the joint is moved [3]. Diminished movement of the affected limb is often observed, temporally unrelated to birth trauma [74, 76]. On further evaluation, tissue edema around the hip joint can be seen, often encompassing the entire leg [3]. An infant or child with septic arthritis of the hip is seen to lie with the affected leg held in a flexed, externally rotated, abducted position, resisting passive range of motion [77]. The affected joint can dislocate due to the edema and buildup of pressure [77]. Older children with pyogenic arthritis of the hip often complain of pain, especially when weight bearing or when the head of the femur is compressed into the acetabulum. The hip pain can be associated with referred pain to the knee [77].

Neonates are a special population in which osteomyelitis and septic arthritis often occur concomitantly [44]. They have an increased vascular supply connecting the metaphysis blood vessels directly through the physis and into the epiphysis [44, 78]. This direct blood supply predisposes neonates to contiguous spread of pathogens to the epiphyseal end of the bones resulting in a concomitant osteomyelitis [57]. Vigilance is needed in patients with central line-associated bloodstream infections, with attention to premature neonates and immunosuppressed populations, as hematogenous spread of pathogens (such as MSSA, MRSA, and coagulase-negative staphylococci) to distant sites can result in osteomyelitis and septic arthritis as part of disseminated disease [79, 80].

Diagnostic Evaluation

A clinical suspicion of septic arthritis is based on history and physical exam that should lead to a laboratory, radiographic, and surgical intervention for therapeutic and diagnostic reasons. Evaluation of the joint fluid is essential as the identification of the organism establishes a diagnosis. Initial laboratory evaluation includes a serum complete blood count and differential looking for leukocytosis and neutrophil predominance, erythrocyte sedimentation rate (ESR), C-reactive protein, blood culture, and PCR analysis of synovial fluid looking for *K. kingae* or other fastidious-growing organisms in the pertinent patient population.

Laboratory and Joint Fluid Findings

The laboratory evaluation of pyogenic arthritis often shows peripheral leukocytosis with neutrophil predominance and acute-phase reactants such as elevated erythrocyte sedimentation rate (ESR) with values more than 20 mm/h and elevated C-reactive protein (CRP) with a mean value of 8.5 mg/dL [3, 81–83]. These tests are nonspecific for septic arthritis as they can be elevated with any infectious/inflammatory process and must be used as supportive evidence of septic arthritis in the right clinical context. Sensitivity for the diagnosis of osteoarticular infections increases with the combination of an elevated CRP and ESR; however, children with osteoarticular infections with *K. kingea* frequently do not have elevated inflammatory markers [3, 83, 84]. The ESR is a nonspecific value of inflammation that reflects concentrations of fibrinogen and immunoglobulins in the plasma [44]. ESR rises in 24 h after the onset of an inflammatory trigger, slower than C-reactive protein, slowly returning to normal in approximately 4 weeks [44, 85]. The CRP is a better positive predictor of septic arthritis in comparison to ESR with a positive predictive value ranging from 34% to 53%. However, CRP is better utilized as a negative predictor value for septic arthritis ranging from 78% to 87% in CRP values <1.0 mg/dl [86]. Serum procalcitonin (PCT) is also an acute-phase reactant that is being evaluated as a diagnostic marker for septic arthritis. In a meta-analysis in adults, PCT was more sensitive and specific in comparison with ESR and CRP for the diagnosis of osteoarticular infections. In patients with septic arthritis, the sensitivity was 55% and specificity 88%, thus suggesting that PCT can be used to rule in infection rather than for exclusion of osteoarticular infections [87]. Studies are needed in the pediatric population to further evaluate the utility of PCT in osteoarticular infections. CRP is often used, in conjunction with other laboratory data, to follow early response to antibiotic therapy and overall clinical progression [44, 83, 88]. CRP peaks in 48 h, and in uncomplicated cases with proper antibiotic coverage, it can normalize within 1 week [78]. A rise in CRP in a patient who is clinically decompensating is concerning for recrudescence of a primary infectious process and suboptimal source control of pyogenic arthritis [44, 89].

The synovial fluid of the affected joint must be collected in a heparinized syringe to prevent clot formation and optimize the enumeration of leukocytes [13]. The synovial fluid is usually observed to be turbid and purulent [44]. It should be analyzed using a Gram stain, aerobic and anaerobic culture, and cell and differential count. A leukocyte count greater than 50,000 cell/mm^3 with predominance of polymorphonuclear neutrophils is suggestive of a septic arthritis; nonetheless, counts greater than 50,000 cells/mm^3 can occur in juvenile rheumatoid arthritis or Lyme disease, and lower WBC counts do not necessarily exclude a diagnosis of septic arthritis [44, 52, 56, 90–93]. Table 4.1 depicts the synovial fluid characteristics in various types of infectious arthritis. Synovial fluid glucose may be low and protein and lactate dehydrogenase may be elevated; however, these tests have low sensitivity and specificity, not allowing for a reliable differentiation of infectious and inflammatory pro-

Table 4.1 Synovial fluid findings in infectious arthritis

Diagnosis	White blood cells/mm^3	% polymorphonuclear leukocytes	Glucose (median, mg/dL)
Normal	<200	<25	____
Pyogenic arthritis	40,000–300,000	>90	30
Candida arthritis	10,000–220,000	>90	60
Juvenile rheumatoid arthritis	15,000–20,000	60–75	75
Reactive arthritis	20,000–40,000	50–75	_____
Tuberculous arthritis	40–136,000	>50	_____
Lyme arthritis	180–140,000	>75	_____
Viral arthritis	3000–50,000	<50	_____

Data from references [44, 92, 154, 155]

cesses [44, 94]. In patients who have not previously received antibiotics, the yield of a bacterial organism from joint culture is 60% to 70%, but some studies have reported culture positive rates up to 80–90% [40, 95–98]. To increase the yield of certain fastidious pathogens from joint cultures such as *K. kingae*, it is recommended to have direct inoculation of the synovial fluid into pediatric blood culture media bottles [20, 99].

A limitation of the Gram stain is that it stains in only 50% of positive cultures, but it is still useful since approximately 35% of joint aspirates can have no growth on culture [14, 95]. Gram stains must be evaluated with caution as false-positive results can occur from artifacts in staining or in patients with previous antibiotic administration due to increased cellular debris and/or presence of mucin [100]. It is important to obtain blood cultures and synovial cultures before the initiation of antibiotics to increase the yield of isolating an organism, unless the patient has signs of sepsis. In negative synovial cultures, blood cultures are the only source of isolating an organism in approximately 10% of cases of septic arthritis [100]. Blood culture positivity varies from different studies, ranging from 25 to 70% in adults to approximately 40% in children [56, 96, 99].

An emerging technology since the 1990s is the use of polymerase chain reaction (PCR) in the identification of fastidious pathogens [13]. Real-time polymerase chain reaction (RT-PCR) assay uses specific primers that amplify the genes of bacteria. This targeted approach has increased the yield of pathogens [101–103] by increasing the sensitivity with a faster time to detection without significantly decreasing specificity in comparison to PCR methodologies that use broad-range 16 sRNA primers [13, 103–107]. In a review, the isolation of *K. kingae*, which is a common cause of septic arthritis in children younger than 5 years old, was analyzed using synovial fluid inoculated in blood cultures yielding 29% positivity; with conventional methods of PCR, the yield increased to 41%, and with RT-PCR the yield increased further to 49% [108]. A great advantage of PCR is that rapid results are obtained, and there is a higher likelihood of isolating a pathogen in patients that have been pretreated with antibiotics [100]. Limitations of PCR are that it may not be available in many microbiology laboratories, false-positive results often occur due to sample contamination, and it is unable to provide susceptibilities [103]. Recent advances in diagnosis include the use of matrix-assisted laser desorption/ionization time-of-flight-mass spectrometry (MALDI-TOF MS) which can rapidly identify bacteria at the subgroup level within a species once bacteria grow in agar media [109, 110].

Imaging

In the early presentation of septic arthritis in children, plain radiographs outside the neonatal age group are often normal [111]. Periarticular soft tissue swelling and widening of the joint space secondary to joint effusions can be seen [44, 78]. Early radiographic findings are capsular swelling with obliteration or lateral displacement of gluteal fat lines and asymmetric fullness of the obturator internus and iliopsoas soft tissue planes [112]. As pressure builds up in the joint capsule, especially the hip, the femoral head is displaced upward and outward, resulting in lateral subluxation. The lateral subluxation of the septic hip is particularly seen via plain radiographs in neonates and infants [111]. Erosion of the subchondral bone may be seen 2–4 weeks after the onset of acute infection [112]. The onset of avascular necrosis is evident by the appearance of sclerosis and decreased volume in the proximal femoral epiphysis [44, 78, 113].

In children the plain radiograph can be normal, and a better radiologic modality such as an ultrasound is needed to diagnose septic arthritis of the hip [111]. The best modality to detect early septic arthritis of the hip is ultrasonography since, if performed correctly, it can detect small intra-articular fluid collections [114]. Once fluid is detected in the hip joint, a diagnostic aspiration via arthrocentesis should be performed, without having to perform more advanced imaging, for cell count and cultures and to establish the diagnosis [1, 44, 78, 115]. Keep in mind that false-negative ultrasonography results can occur in the evaluation of septic arthritis within 24 h after the onset of symptoms; therefore, it is imperative to obtain blood cultures, CBC with differential, CRP, and ESR to guide management and to repeat ultrasonography in cases still concerning for septic arthritis or when bilateral disease of the hip occurs [116].

Scintigraphy, including technetium phosphate radionuclide scanning, is not typically used for the diagnosis of pyogenic

arthritis since it is a sensitive but nonspecific indicator of an osteoarticular infection [117]; nonetheless, it can be used in a nonverbal child or children with ongoing bacteremia to evaluate for another potential focus of infection as multifocal septic arthritis and/or osteomyelitis [113]. Scintigraphy studies in septic arthritis are characterized by an increased uptake in the early "blood-pool" phase and delayed images of the joint [44, 78]. The increased bony uptake is observed in symmetric sides of the joint, which differentiates it from osteomyelitis [3, 44, 78, 111]. Computed tomography (CT) is often used to evaluate deep articulations with complex anatomy and fibrocartilaginous articular structures such as the pubic symphysis, hip, sacroiliac joints, and sternoclavicular joints. CT detects erosive changes to the bone and joint effusions [3, 100, 117–121]. It is frequently used in the evaluation of intravenous drug users with concerns of septic arthritis due to *Pseudomonas aeruginosa*, as this pathogen has an affinity for the fibrocartilaginous structures mentioned. The modality of choice to diagnose septic arthritis is magnetic resonance imaging (MRI), being more sensitive than CT in delineating soft tissue structures and abnormalities of adjacent bone [3, 44, 100, 122]. Some authors advocate for an MRI as the initial evaluation of septic arthritis of the shoulder or elbow due to the high rates of concomitant osteomyelitis given the delay in presentation and complicated disease course [13, 123–126]. In general, MRI has more specificity in comparison to scintigraphy or CT and has replaced them as the modality of choice for the evaluation of osteoarticular infections [127, 128].

Management

In children suspected of having septic arthritis, a multidisciplinary approach is needed including rheumatology and/or orthopedics for prompt assistance with diagnostic arthrocentesis [100]. Orthopedic consultation is necessary for surgical drainage via arthrotomy, arthrocentesis, or open surgical drainage, allowing for drainage, irrigation, and debridement [42, 45]. Pediatric infectious disease doctors provide input for recommendations on empiric antibiotic options, and long-term follow-up is imperative at the initial presentation. A rapid diagnostic evaluation is needed, especially in septic arthritis of the hip in children, as it is an emergency and warrants prompt surgical drainage and irrigation of the joint space with appropriate antibiotic therapy in the first 6–12 h from presentation to decrease long-term associated morbidity [1, 42, 45].

Surgical Treatment

The goal of surgical intervention includes decompression of the joint, sterilization of the joint, and removal of inflammatory debris to prevent articular damage and preserve joint function [3, 129]. Surgical options for drainage include arthroscopy and open arthrotomy, allowing for direct visualization, irrigation, lysis of any adhesions, and removal of purulent material [100, 129–131]. In joints other than the hip, single or multiple needle aspirations may be an option to surgical drainage and are often individualized on clinical progress; however, surgical drainage is recommended when multiple needle aspirations fail to control the infectious process [3, 64, 91, 98, 100, 132–135]. In the case of septic arthritis of the hip, open surgical drainage should be performed immediately [44, 64, 78, 91, 98, 133–137]. To date, a controlled, prospective, randomized trial has not been done to evaluate the multiple surgical procedures [44, 45, 78, 113]. A retrospective study in adults evaluated the outcome of septic arthritis in patients treated by surgical drainage in comparison to repeat needle aspirations. The results showed equivalent results in arthritis of the knee, but overall, repeat aspirations were found to be superior to surgical drainage [44, 78, 138]. Multiple factors influence the modality of drainage such as availability of resources, joint involved, and clinical presentation [100]. Needle aspiration may be considered if the joint is accessible and has high probability of adequate drainage and the patient lacks poor prognostic factors such as neurovascular compromise, sepsis, prolonged duration of symptoms prior to evaluation, and significant comorbidities [64, 98, 100, 134]. In children, there are well-established indications for surgical drainage which include the following: involvement of the hip joint with some authors considering the shoulder as it often has delayed presentation and complicated disease course; presence of bacterial inoculum seen as large amounts of pus, debris, and fibrin or loculation within the joint space; and lack of clinical improvement within 3 days of appropriate antibiotic therapy [44, 67, 78, 95, 126, 132, 139].

Antimicrobial Therapy

A determination of empiric antibiotic choices to target the most common pathogens is based on the patient's age, risk factors, clinical presentation, and physical examination. Antibiotic selection is based on the identification of an organism, susceptibility profile, high synovial fluid-to-serum concentration ratios to guarantee penetration into the joint, and side effect profile [3]. The antibiotics used in septic arthritis achieve penetration into the joint; therefore, there is no indication for intra-articular instillation [3]. As discussed, an appropriate diagnostic evaluation including blood cultures, synovial cultures, and/or PCR evaluation of synovial fluid is needed to attempt to identify a microorganism and appropriately tailor antibiotics based on susceptibilities. In cases where a microorganism is not isolated, the patient is continued on empiric treatment based on the most common pathogen for age and mode of acquisition. Refer to Table 4.2

Table 4.2 Empiric antibiotic treatment of pyogenic arthritis in children with no immunosuppression

Age group	Likely pathogens	Antibiotics[a]
Neonates (<28 days of age)	*Staphylococcus aureus*[b,c] *Streptococcus agalactiae (GBS)* Gram-negative bacilli *Neisseria gonorrhoeae* (consider)	Nafcillin or clindamycin or vancomycin[b,c] + Ampicillin + gentamicin or cefotaxime
Children 3 months–5 years of age	*S. aureus*[b,c] *Kingella kingae* *Haemophilus influenzae* *Streptococcus pyogenes* *Streptococcus pneumoniae*	Nafcillin or clindamycin or cefazolin or vancomycin[b,c] + Cefotaxime or ceftriaxone
Children >5 years of age	*S. aureus*[b,c] *Streptococcus pyogenes*	Nafcillin or clindamycin or cefazolin or vancomycin[b,c]
Adolescents	*S. aureus*[b,c] *Neisseria gonorrhoeae* (consider)	Nafcillin or clindamycin or cefazolin or vancomycin[b,c] + Ceftriaxone

[a]For dosing recommendations, refer to the 2018–2021 *Red Book: Report of the Committee on Infectious Diseases*, 31st edition (Tables of Antibacterial Drug Dosages, pages 914–932) [140]

[b]If more than 10% of community-acquired isolates are MRSA, consider empiric therapy with vancomycin or clindamycin. If 10–20% of MRSA isolates are resistant to clindamycin, consider empiric therapy with vancomycin

[c]In isolates that are MSSA, the antibiotic of choice is nafcillin or cefazolin. Keep in mind that clindamycin MSSA resistance is increasing

for empiric antibiotic therapy based on the age group and specific therapy of choice based on the microorganism isolated. For recommended doses of neonates and children, refer to the 2018–2021 *Red Book: Report of the Committee on Infectious Diseases*, 31st edition (Tables of Antibacterial Drug Dosages) [140]. All cases of septic arthritis with or without concomitant osteomyelitis should initially receive parenteral therapy to ensure adequate serum concentrations and penetration into the affected site.

Regardless of age, all patients should receive an empiric antibiotic regimen with activity against *Staphylococcus aureus* as it is the most common cause of septic arthritis. Many experts advocate for empiric use of vancomycin or clindamycin against community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) when resistant rates to methicillin are greater than 10% [141]. With the use of vancomycin, it is important to closely monitor serum creatinine as it is a nephrotoxic agent and to monitor trough levels for both therapeutic levels and for potential toxicity. In children, trough levels of 15–20 mg/L are acceptable for MIC values greater than 2 mg/L; however, many agree that lower trough levels of 10–15 mg/L are acceptable in children when an MIC value is equal or lower to 1 mg/L as the area under the curve (AUC)/MIC achieved is greater than 400 mg∗h/L. AUC/MIC levels greater than 400 mg∗h/L are associated with early response to vancomycin in MRSA bacteremia [142]. It is important to note that many MRSA strains are acquiring clindamycin-inducible resistance; some advocate to use vancomycin as empiric therapy when clindamycin resistance is greater than 10–20% or when the patient has concomitant MRSA bacteremia or in sepsis. The decision to deescalate to clindamycin from vancomycin can be made once it is confirmed that there is no inducible resistance and the patient does not have MRSA bacteremia (clindamycin is not recommended to treat MRSA bacteremia). To verify if the MRSA strain exhibits clindamycin-inducible resistance, a D-test must be performed by the microbiology department. Other alternatives for MRSA coverage include linezolid and daptomycin which are used when a patient is failing therapy with vancomycin and/or when vancomycin has intermediate resistance and the patient is not clinically responding 3–5 days into vancomycin therapy (vancomycin intermediate resistance is seen when the vancomycin MIC to *Staphylococcus aureus* is 2 ug/ml) or when a patient has a drug allergy to vancomycin [100]. If daptomycin is used, a baseline creatinine kinase needs to be obtained and monitored throughout therapy. Daptomycin is only available in parenteral formulation, and no formal randomized study has been performed in pediatrics or adults for daptomycin use in native joint septic arthritis. Linezolid has been used in some instances of severe MRSA infection. It has an oral formulation with equivalent bioavailability to the parenteral formulation; however, the side effect and drug adverse event profile of bone marrow suppression (leukopenia, anemia, thrombocytopenia), lactic acidosis after 2–3 weeks of therapy, optic neuropathy, and nonreversible peripheral neuropathy limits long-term use [3, 100]. For isolates that are methicillin-susceptible *Staphylococcus aureus* (MSSA), therapy should be narrowed to a penicillinase-resistant penicillin such as oxacillin or nafcillin or cefazolin (first-generation cephalosporins) [100]. MSSA strains may be resistant to clindamycin. Ceftriaxone does have in vitro MSSA activity, but it is intrinsically less active than cefazolin and is not advocated for use in infections due to MSSA [100].

Empiric antimicrobial therapy in infants younger than 3 months of age should include activity against *S. aureus*, *Streptococcus agalactiae* (also known as group B streptococcus, GBS), and gram-negative organisms [3]. In both neonates and sexually active adolescents suspected of having septic arthritis secondary to *Neisseria gonorrhoeae*, ceftriaxone or

cefotaxime should be started empirically [4]. A good empiric coverage for infants younger than 3 months of age is anti-staphylococcal antibiotics discussed above and cefotaxime for GBS and gram-negative coverage. In infants and children aged 3 months to 5 years, empiric coverage for *S. aureus*, *K. kingae*, *S. pneumoniae*, and *S. pyogenes* (group A streptococcus) is recommended. Appropriate empiric therapy for the 3 months to 5 years old age group must target *S. aureus* coverage previously discussed and include the addition of ceftriaxone for *K. kingae*, GAS, and *S. pneumoniae* coverage [143]. In patients younger than 2 years of age who have not been immunized or completed a full course of HiB immunization, empiric therapy against *H. influenzae* type B (Hib) with a second- or third-generation cephalosporin should be started [13]. Keep in mind that Hib infection is not common in immunized children, but other typeable or non-typeable *H. influenzae* can rarely cause septic arthritis in children [3, 144]. Children older than 5 years of age are treated empirically for *S. aureus* and streptococci [3]. Special populations, such as children that are in immunosuppressive states or with hemoglobinopathies, are prone to gram-negative coliform bacteria or other gram-negative organisms such as *Salmonella* spp. Broad-spectrum antibiotics are needed in immunocompromised populations (such as patients with cancer, neutropenia, etc.) to provide coverage against *S. aureus* and gram-negative pathogens (e.g., a third- or fourth-generation cephalosporin such as ceftazidime or cefepime) [44, 78]. Patients with IDU are at risk of septic arthritis in the fibrocartilaginous articular structures with *Pseudomonas aeruginosa*, and empiric coverage is necessary with ceftazidime, cefepime, piperacillin/tazobactam, or meropenem.

All children with septic arthritis are started on parenteral therapy. Transition to an appropriate oral antibiotic option that has good gastrointestinal absorption and bioavailability is considered when defervescence occurs, control of infection has been achieved (source control), physical findings (joint pain, edema, rubor, erythema) resolve, and markers of acute-phase reactants normalize or significantly improve. Patients are frequently transitioned from parenteral to oral antibiotic therapy within 1 week in uncomplicated cases, when clinical improvement is established, CRP normalizes, and adherence and clinical follow-up are ensured [3, 85, 145–148]. Joint symptom resolution and clearance of infection from a septic joint are proportional to the duration of symptoms before surgical drainage and initiation of the appropriate antibiotic [13, 149, 150]. Duration of therapy depends on the specific causative organism, clinical response and time to sterility of the joint from drainage/initiation of appropriate antibiotics, laboratory response, and potential for a concomitant osteomyelitis [3]. Many authors consider a total duration of 3–4 weeks of therapy in septic arthritis due to *S. aureus* or gram-negative enteric organisms due to the frequent observance of a concomitant osteomyelitis [3, 58]. Septic arthritis due to other organisms is usually treated for 2–3 weeks.

Appropriate oral antibiotic choices for septic arthritis include cephalexin (100 mg/kg/day in three to four divided doses), clindamycin (30–40 mg/kg/day in three divided doses), and dicloxacillin (75–100 mg/kg/day in four divided doses) [3].

Prognosis

In modern medicine the case fatality rate of septic arthritis is less than 1%, but poor outcomes still occur [44, 75, 78, 151]. The weight-bearing joints of the hip, ankle, and knee are the most common to have sequelae [75]. Involvement of the hip joint has the worst prognosis with sequelae in up to 50% of patients in comparison to 12% with involvement of other joints [42]. The shoulder also has a propensity for poor outcomes and a complicated disease course due to delay in diagnosis and surgical intervention [126]. Complications of septic arthritis include articular destruction with ankylosis, growth disturbances, concomitant osteomyelitis or soft tissue extension, and hip dislocation [112, 126, 137]. The main predictors of a poor outcome include age less than 1 year, involvement of the hip and shoulder, concomitant metaphyseal osteomyelitis, duration of symptoms for 4 or more days before surgical intervention and initiation of antibiotic therapy, and a prolonged time in clearing the infection from the synovial fluid [40, 42, 45, 64, 77, 107, 117, 137, 150, 151]. *Enterobacteriaceae* is associated with increased frequency of sequelae in some literature reports [152, 153], and it is known that *S. aureus* is more virulent in comparison to *H. influenzae* [3, 14].

Summary

Septic arthritis must be in the differential in any child presenting with joint inflammation, refusal to move a joint, and/or constitutional symptoms as a prompt diagnosis and treatment decreases associated morbidity. Physicians need to expedite a laboratory and radiological evaluation, drainage, and prompt antibiotic initiation for best patient outcomes.

References

1. Laine JC, Denning JR, Riccio AI, Jo C, Joglar JM, Wimberly RL. The use of ultrasound in the management of septic arthritis of the hip. J PediatrOrthop B. 2015;24(2):95–8.
2. Edwards MS, Baker CJ, Wagner ML, Taber LH, Barrett FF. An etiologic shift in infantile osteomyelitis: the emergence of the group B streptococcus. J Pediatr. 1978;93(4):578–83.
3. David K, Hong KG. Principles and practice of pediatric infectious diseases. In: Long SS, Prober CG, Fischer M, editors. Infectious and inflammatory arthritis. 5thed ed. Philadelphia: Elsevier Inc.; 2018. p. 487–93.

4. Brewer GF, Davis JR, Grossman M. Gonococcal arthritis in an adolescent girl. Am J Dis Child. 1971;122(3):253–4.
5. Goldenberg DL, Brandt KD, Cathcart ES, Cohen AS. Acute arthritis caused by gram-negative bacilli: a clinical characterization. Medicine (Baltimore). 1974;53(3):197–208.
6. Kleiman MB, Lamb GA. Gonococcal arthritis in a newborn infant. Pediatrics. 1973;52(2):285–7.
7. Asmar BI. Osteomyelitis in the neonate. Infect Dis Clin N Am. 1992;6(1):117–32.
8. Benjamin DK Jr, Stoll BJ, Fanaroff AA, McDonald SA, Oh W, Higgins RD, et al. Neonatal candidiasis among extremely low birth weight infants: risk factors, mortality rates, and neurodevelopmental outcomes at 18 to 22 months. Pediatrics. 2006;117(1):84–92.
9. Benjamin DK Jr, Stoll BJ, Gantz MG, Walsh MC, Sanchez PJ, Das A, et al. Neonatal candidiasis: epidemiology, risk factors, and clinical judgment. Pediatrics. 2010;126(4):e865–73.
10. Trofa D, Gacser A, Nosanchuk JD. Candida parapsilosis, an emerging fungal pathogen. ClinMicrobiol Rev. 2008;21(4):606–25.
11. Tindel JR, Crowder JG. Septic arthritis due to Pseudomonas aeruginosa. JAMA. 1971;218(4):559–61.
12. Roca RP, Yoshikawa TT. Primary skeletal infections in heroin users: a clinical characterization, diagnosis and therapy. ClinOrthopRelat Res. 1979;144:238–48.
13. Krogstad P. Feigin and Cherry's textbook of pediatric infectious diseases.Septic arthritis. 8th ed. Philadelphia: Elsevier, Inc; 2019. p. 529–34.
14. Barton LL, Dunkle LM, Habib FH. Septic arthritis in childhood.A 13-year review. Am J Dis Child. 1987;141(8):898–900.
15. MacNeil JR, Cohn AC, Farley M, Mair R, Baumbach J, Bennett N, et al. Current epidemiology and trends in invasive Haemophilus influenzae disease--United States, 1989–2008. Clin Infect Dis. 2011;53(12):1230–6.
16. Bowerman SG, Green NE, Mencio GA. Decline of bone and joint infections attributable to Haemophilus influenzae type b. ClinOrthopRelat Res. 1997;341:128–33.
17. Luhmann JD, Luhmann SJ. Etiology of septic arthritis in children: an update for the 1990s. PediatrEmerg Care. 1999;15(1):40–2.
18. Ceroni D, Kampouroglou G, Valaikaite R, Anderson della Llana R, Salvo D. Osteoarticular infections in young children: what has changed over the last years? Swiss Med Wkly. 2014;144:w13971.
19. Yagupsky P. Kingella kingae: from medical rarity to an emerging paediatric pathogen. Lancet Infect Dis. 2004;4(6):358–67.
20. Kiang KM, Ogunmodede F, Juni BA, Boxrud DJ, Glennen A, Bartkus JM, et al. Outbreak of osteomyelitis/septic arthritis caused by Kingella kingae among child care center attendees. Pediatrics. 2005;116(2):e206–13.
21. Moylett EH, Rossmann SN, Epps HR, Demmler GJ. Importance of Kingella kingae as a pediatric pathogen in the United States. Pediatr Infect Dis J. 2000;19(3):263–5.
22. Moumile K, Merckx J, Glorion C, Pouliquen JC, Berche P, Ferroni A. Bacterial aetiology of acute osteoarticular infections in children. ActaPaediatr. 2005;94(4):419–22.
23. Yagupsky P, Bar-Ziv Y, Howard CB, Dagan R. Epidemiology, etiology, and clinical features of septic arthritis in children younger than 24 months. Arch PediatrAdolesc Med. 1995;149(5):537–40.
24. Ceroni D, Cherkaoui A, Ferey S, Kaelin A, Schrenzel J. Kingella kingae osteoarticular infections in young children: clinical features and contribution of a new specific real-time PCR assay to the diagnosis. J PediatrOrthop. 2010;30(3):301–4.
25. Kimberlin DW. In: Brady MT, Jackson MA, Long SS, editors. *Kingella kingae* infections.Red Book 2018–2021 report of the committee on infectious diseases. 31 sted ed. Itasca, IL: American Academy of Pediatrics; 2018. p. 497–8.
26. Balakumar B, Gangadharan S, Ponmudi N, Kumar S, Prakash JJ, Palocaren T. Atypical osteomyelitis and concurrent septic arthritis due to Salmonella in immunocompetent children. J ClinOrthop Trauma. 2017;8(3):293–7.
27. Martin CM, Merrill RH, Barrett O Jr. Arthritis due to Serratia. J Bone Joint Surg Am. 1970;52(7):1450–2.
28. Kimberlin DW. In: Brady MT, Jackson MA, Long SS, editors. Bite wounds.Red Book 2018–2021 report of the committee on infectious diseases. Itasca, IL: American Academy of Pediatrics; 2018. p. 189–95.
29. Kimberlin DW. In: Brady MT, Jackson MA, Long SS, editors. Rat-Bite fever.Red Book 2018–2021 report of the committee on infectious diseases. Itasca, IL: American Academy of Pediatrics; 2018. p. 680–2.
30. Gomez-Reino JJ, Shah M, Gorevic P, Lusskin R. Pasteurellamultocida arthritis.Case report. J Bone Joint Surg Am. 1980;62(7):1212–3.
31. Norenberg DD, Bigley DV, Virata RL, Liang GC. Corynebacterium pyogenes septic arthritis with plasma cell synovial infiltrate and monoclonal gammopathy. Arch Intern Med. 1978;138(5):810–1.
32. Yocum RC, McArthur J, Petty BG, Diehl AM, Moench TR. Septic arthritis caused by Propionibacterium acnes. JAMA. 1982;248(14):1740–1.
33. Blair JE. State-of-the-art treatment of coccidioidomycosis skeletal infections. Ann N Y AcadSci. 2007;1111:422–33.
34. Darouiche RO, Cadle RM, Zenon GJ, Weinert MF, Hamill RJ, Lidsky MD. Articular histoplasmosis. J Rheumatol. 1992;19(12):1991–3.
35. Stead KJ, Klugman KP, Painter ML, Koornhof HJ. Septic arthritis due to Cryptococcus neoformans. J Infect. 1988;17(2):139–45.
36. Bayer AS, Scott VJ, Guze LB. Fungal arthritis.III. Sporotrichal arthritis. Semin Arthritis Rheum. 1979;9(1):66–74.
37. Riise OR, Handeland KS, Cvancarova M, Wathne KO, Nakstad B, Abrahamsen TG, et al. Incidence and characteristics of arthritis in Norwegian children: a population-based study. Pediatrics. 2008;121(2):e299–306.
38. Kang SN, Sanghera T, Mangwani J, Paterson JM, Ramachandran M. The management of septic arthritis in children: systematic review of the English language literature. J Bone Joint Surg Br. 2009;91(9):1127–33.
39. Nade S, Robertson FW, Taylor TK. Antibiotics in the treatment of acute osteomyelitis and acute septic arthritis in children. Med J Aust. 1974;2(19):703–5.
40. Welkon CJ, Long SS, Fisher MC, Alburger PD. Pyogenic arthritis in infants and children: a review of 95 cases. Pediatr Infect Dis. 1986;5(6):669–76.
41. Griffin PP. Bone and joint infections in children. PediatrClin N Am. 1967;14(3):533–48.
42. Morrey BF, Bianco AJ Jr, Rhodes KH. Septic arthritis in children. OrthopClin North Am. 1975;6(4):923–34.
43. Masson AT, Gudnason T, Jonmundsson GK, Erlendsdottir H, Kristinsson KG, Kristjansson M, et al. Bacterial osteomyelitis and arthritis in Icelandic children 1996–2005. Laeknabladid. 2011;97(2):91–6.
44. Shetty AK, Gedalia A. Septic arthritis in children. Rheum Dis Clin N Am. 1998;24(2):287–304.
45. Nelson JD, Koontz WC. Septic arthritis in infants and children: a review of 117 cases. Pediatrics. 1966;38(6):966–71.
46. Borella L, Goobar JE, Summitt RL, Clark GM. Septic arthritis in childhood. J Pediatr. 1963;62:742–7.
47. Yagupsky P, Dagan R, Howard CB, Einhorn M, Kassis I, Simu A. Clinical features and epidemiology of invasive Kingella kingae infections in southern Israel. Pediatrics. 1993;92(6):800–4.
48. Wiley JJ, Fraser GA. Septic arthritis in childhood. Can J Surg. 1979;22(4):326–30.
49. Dubnov-Raz G, Ephros M, Garty BZ, Schlesinger Y, Maayan-Metzger A, Hasson J, et al. Invasive pediatric Kingella kingae

infections: a nationwide collaborative study. Pediatr Infect Dis J. 2010;29(7):639–43.
50. Bidet P, Collin E, Basmaci R, Courroux C, Prisse V, Dufour V, et al. Investigation of an outbreak of osteoarticular infections caused by Kingella kingae in a childcare center using molecular techniques. Pediatr Infect Dis J. 2013;32(5):558–60.
51. Centers for Disease C, Prevention. Osteomyelitis/septic arthritis caused by Kingella kingae among day care attendees--Minnesota, 2003. MMWR Morb Mortal Wkly Rep. 2004;53(11):241–3.
52. Carrillo-Marquez MA, Hulten KG, Hammerman W, Mason EO, Kaplan SL. USA300 is the predominant genotype causing Staphylococcus aureus septic arthritis in children. Pediatr Infect Dis J. 2009;28(12):1076–80.
53. Gafur OA, Copley LA, Hollmig ST, Browne RH, Thornton LA, Crawford SE. The impact of the current epidemiology of pediatric musculoskeletal infection on evaluation and treatment guidelines. J PediatrOrthop. 2008;28(7):777–85.
54. Peltola H, Paakkonen M, Kallio P, Kallio MJ, Group O-SS. Clindamycin vs. first-generation cephalosporins for acute osteoarticular infections of childhood--a prospective quasi-randomized controlled trial. ClinMicrobiol Infect. 2012;18(6):582–9.
55. Perlman MH, Patzakis MJ, Kumar PJ, Holtom P. The incidence of joint involvement with adjacent osteomyelitis in pediatric patients. J PediatrOrthop. 2000;20(1):40–3.
56. Goldenberg DL, Reed JI. Bacterial arthritis. N Engl J Med. 1985;312(12):764–71.
57. Silveira LH, Cuellar ML, Citera G, Cabrera GE, Scopelitis E, Espinoza LR. Candida arthritis. Rheum Dis Clin N Am. 1993;19(2):427–37.
58. Ogden JA. Pediatric osteomyelitis and septic arthritis: the pathology of neonatal disease. Yale J Biol Med. 1979;52(5):423–48.
59. Armstrong RW, Bolding F, Joseph R. Septic arthritis following arthroscopy: clinical syndromes and analysis of risk factors.1992/01/01 ed1992.p. 213–23.
60. Ashraf A, Luo TD, Christophersen C, Hunter LR, Dahm DL, McIntosh AL. Acute and subacute complications of pediatric and adolescent knee arthroscopy. Arthroscopy. 2014;30(6):710–4.
61. Hagino T, Ochiai S, Watanabe Y, Senga S, Wako M, Ando T, et al. Complications after arthroscopic knee surgery. Arch Orthop Trauma Surg. 2014;134(11):1561–4.
62. Tarkowski A. Infection and musculoskeletal conditions: infectious arthritis. Best Pract Res ClinRheumatol. 2006;20(6):1029–44.
63. Herrmann M, Vaudaux PE, Pittet D, Auckenthaler R, Lew PD, Schumacher-Perdreau F, et al. Fibronectin, fibrinogen, and laminin act as mediators of adherence of clinical staphylococcal isolates to foreign material. J Infect Dis. 1988;158(4):693–701.
64. Shirtliff ME, Mader JT. Acute septic arthritis. ClinMicrobiol Rev. 2002;15(4):527–44.
65. Darouiche RO, Landon GC, Patti JM, Nguyen LL, Fernau RC, McDevitt D, et al. Role of Staphylococcus aureus surface adhesins in orthopaedic device infections: are results model-dependent? J Med Microbiol. 1997;46(1):75–9.
66. Switalski LM, Patti JM, Butcher W, Gristina AG, Speziale P, Hook M. A collagen receptor on Staphylococcus aureus strains isolated from patients with septic arthritis mediates adhesion to cartilage. MolMicrobiol. 1993;7(1):99–107.
67. Tong SY, Davis JS, Eichenberger E, Holland TL, Fowler VG Jr. Staphylococcus aureus infections: epidemiology, pathophysiology, clinical manifestations, and management. ClinMicrobiol Rev. 2015;28(3):603–61.
68. Fischer B, Vaudaux P, Magnin M, el Mestikawy Y, Proctor RA, Lew DP, et al. Novel animal model for studying the molecular mechanisms of bacterial adhesion to bone-implanted metallic devices: role of fibronectin in Staphylococcus aureus adhesion. J Orthop Res. 1996;14(6):914–20.
69. Gjertsson I, Jonsson IM, Peschel A, Tarkowski A, Lindholm C. Formylated peptides are important virulence factors in Staphylococcus aureus arthritis in mice. J Infect Dis. 2012;205(2):305–11.
70. Colavite-Machado PM, Ishikawa LL, Franca TG, Zorzella-Pezavento SF, da Rosa LC, Chiuso-Minicucci F, et al. Differential arthritogenicity of Staphylococcus aureus strains isolated from biological samples. BMC Infect Dis. 2013;13:400.
71. Mader JT, Shirtliff M, Calhoun JH. The host and the skeletal infection: classification and pathogenesis of acute bacterial bone and joint sepsis. Baillieres Best Pract Res ClinRheumatol. 1999;13(1):1–20.
72. Roy S, Bhawan J. Ultrastructure of articular cartilage in pyogenic arthritis. Arch Pathol. 1975;99(1):44–7.
73. Dan M. Septic arthritis in young infants: clinical and microbiologic correlations and therapeutic implications. Rev Infect Dis. 1984;6(2):147–55.
74. Fox L, Sprunt K. Neonatal osteomyelitis. Pediatrics. 1978;62(4):535–42.
75. Howard JB, Highgenboten CL, Nelson JD. Residual effects of septic arthritis in infancy and childhood. JAMA. 1976;236(8):932–5.
76. Chacha PB. Suppurative arthritis of the hip joint in infancy.A persistent diagnostic problem and possible complication of femoral venipuncture. J Bone Joint Surg Am. 1971;53(3):538–44.
77. Bennett OM, Namnyak SS. Acute septic arthritis of the hip joint in infancy and childhood. ClinOrthopRelat Res. 1992;281:123–32.
78. Shetty AK, Gedalia A. Management of septic arthritis. Indian J Pediatr. 2004;71(9):819–24.
79. Eggink BH, Rowen JL. Primary osteomyelitis and suppurative arthritis caused by coagulase-negative staphylococci in a preterm neonate. Pediatr Infect Dis J. 2003;22(6):572–3.
80. Healy CM, Palazzi DL, Edwards MS, Campbell JR, Baker CJ. Features of invasive staphylococcal disease in neonates. Pediatrics. 2004;114(4):953–61.
81. 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(4):411–3.
82. Del Beccaro MA, Champoux AN, Bockers T, Mendelman PM. Septic arthritis versus transient synovitis of the hip: the value of screening laboratory tests. Ann Emerg Med. 1992;21(12):1418–22.
83. Paakkonen M, Kallio MJ, Kallio PE, Peltola H. Sensitivity of erythrocyte sedimentation rate and C-reactive protein in childhood bone and joint infections. ClinOrthopRelat Res. 2010;468(3):861–6.
84. Yagupsky P, Dubnov-Raz G, Gene A, Ephros M, Israeli-Spanish Kingella kingae Research G. Differentiating Kingella kingae septic arthritis of the hip from transient synovitis in young children. J Pediatr. 2014;165(5):985–9 e1.
85. Tetzlaff TR, McCracken GH Jr, Nelson JD. Oral antibiotic therapy for skeletal infections of children.II. Therapy of osteomyelitis and suppurative arthritis. J Pediatr. 1978;92(3):485–90.
86. Levine MJ, McGuire KJ, McGowan KL, Flynn JM. Assessment of the test characteristics of C-reactive protein for septic arthritis in children. J PediatrOrthop. 2003;23(3):373–7.
87. Shen CJ, Wu MS, Lin KH, Lin WL, Chen HC, Wu JY, et al. The use of procalcitonin in the diagnosis of bone and joint infection: a systemic review and meta-analysis. Eur J ClinMicrobiol Infect Dis. 2013;32(6):807–14.
88. Jaye DL, Waites KB. Clinical applications of C-reactive protein in pediatrics. Pediatr Infect Dis J. 1997;16(8):735–46; quiz 46-7
89. Hedstrom SA. Immunoassay of acute phase reactants and Latex-CRP as activity tests in chronic staphylococcal osteomyelitis. Scand J Infect Dis. 1983;15(2):161–5.
90. Margaretten ME, Kohlwes J, Moore D, Bent S. Does this adult patient have septic arthritis? JAMA. 2007;297(13):1478–88.

91. Ross JJ. Septic arthritis. Infect Dis Clin N Am. 2005;19(4):799–817.
92. Baldassare AR, Chang F, Zuckner J. Markedly raised synovial fluid leucocyte counts not associated with infectious arthritis in children. Ann Rheum Dis. 1978;37(5):404–9.
93. Willis AA, Widmann RF, Flynn JM, Green DW, Onel KB. Lyme arthritis presenting as acute septic arthritis in children. J PediatrOrthop. 2003;23(1):114–8.
94. Shmerling RH, Delbanco TL, Tosteson AN, Trentham DE. Synovial fluid tests. What should be ordered? JAMA. 1990;264(8):1009–14.
95. Nelson JD. The bacterial etiology and antibiotic management of septic arthritis in infants and children. Pediatrics. 1972;50(3):437–40.
96. 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(4):214–9.
97. Ryan MJ, Kavanagh R, Wall PG, Hazleman BL. Bacterial joint infections in England and Wales: analysis of bacterial isolates over a four-year period. Br J Rheumatol. 1997;36(3):370–3.
98. Brennan MB, Hsu JL. Septic arthritis in the native joint. Curr Infect Dis Rep. 2012;14(5):558–65.
99. Yagupsky P, Press J. Use of the isolator 1.5 microbial tube for culture of synovial fluid from patients with septic arthritis. J ClinMicrobiol. 1997;35(9):2410–2.
100. Christopher A, Ohl DF. Mandell, Douglas, and Bennett's principles and practice of infectious diseases.Infectious arthritis of native joints. 5th ed. Philadelphia: Elsevier; 2015. p. 1302–17.
101. Yang S, Ramachandran P, Hardick A, Hsieh YH, Quianzon C, Kuroki M, et al. Rapid PCR-based diagnosis of septic arthritis by early Gram-type classification and pathogen identification. J ClinMicrobiol. 2008;46(4):1386–90.
102. Fenollar F, Levy PY, Raoult D. Usefulness of broad-range PCR for the diagnosis of osteoarticular infections. CurrOpinRheumatol. 2008;20(4):463–70.
103. Carter K, Doern C, Jo CH, Copley LA. The clinical usefulness of polymerase chain reaction as asupplemental diagnostic tool in the evaluation and the treatment of children with septic arthritis. J PediatrOrthop. 2016;36(2):167–72.
104. Borst A, Leverstein-Van Hall MA, Verhoef J, Fluit AC. Detection of Candida spp. in blood cultures using nucleic acid sequence-based amplification (NASBA). DiagnMicrobiol Infect Dis. 2001;39(3):155–60.
105. Brian T, Fisher PBS, Zaoutis TE. Textbook of pediatric infectious diseases. 8th ed. Philadelphia, PA: Elsevier; 2019. 16 p
106. Morel AS, Dubourg G, Prudent E, Edouard S, Gouriet F, Casalta JP, et al. Complementarity between targeted real-time specific PCR and conventional broad-range 16S rDNA PCR in the syndrome-driven diagnosis of infectious diseases. Eur J ClinMicrobiol Infect Dis. 2015;34(3):561–70.
107. Stahelin J, Goldenberger D, Gnehm HE, Altwegg M. Polymerase chain reaction diagnosis of Kingella kingae arthritis in a young child. Clin Infect Dis. 1998;27(5):1328–9.
108. Chometon S, Benito Y, Chaker M, Boisset S, Ploton C, Berard 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(5):377–81.
109. Edwards JE. Principles and practice of infectious diseases *Candida* species. 8th ed. Philadelphia, PA: Elsevier Saunders; 2015. p. 2879–94.
110. Yaman G, Akyar I, Can S. Evaluation of the MALDI TOF-MS method for identification of Candida strains isolated from blood cultures. DiagnMicrobiol Infect Dis. 2012;73(1):65–7.
111. Volberg FM, Sumner TE, Abramson JS, Winchester PH. Unreliability of radiographic diagnosis of septic hip in children. Pediatrics. 1984;74(1):118–20.
112. Mitchell M, Howard B, Haller J, Sartoris DJ, Resnick D. Septic arthritis. RadiolClin N Am. 1988;26(6):1295–313.
113. Mandell GA. Imaging in the diagnosis of musculoskeletal infections in children. CurrProblPediatr. 1996;26(7):218–37.
114. Myers MT, Thompson GH. Imaging the child with a limp. PediatrClin N Am. 1997;44(3):637–58.
115. 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(2):399–403.
116. Gordon JE, Huang M, Dobbs M, Luhmann SJ, Szymanski DA, Schoenecker PL. Causes of false-negative ultrasound scans in the diagnosis of septic arthritis of the hip in children. J PediatrOrthop. 2002;22(3):312–6.
117. Greenspan A, Tehranzadeh J. Imaging of infectious arthritis. RadiolClin N Am. 2001;39(2):267–76.
118. Coan MR, Demos TC, Lomasney L, Pangan A. Radiologic case study. Pyogenic left sacroiliac infection. Orthopedics. 2002;25(2).:122, 97–200
119. Akkasilpa S, Osiri M, Ukritchon S, Junsirimongkol B, Deesomchok U. Clinical features of septic arthritis of sternoclavicular joint. J Med AssocThail. 2001;84(1):63–8.
120. Vyskocil JJ, McIlroy MA, Brennan TA, Wilson FM. Pyogenic infection of the sacroiliac joint. Case reports and review of the literature. Medicine (Baltimore). 1991;70(3):188–97.
121. Ross JJ, Hu LT. Septic arthritis of the pubic symphysis: review of 100 cases. Medicine (Baltimore). 2003;82(5):340–5.
122. Poznanski AK, Conway JJ, Shkolnik A, Pachman LM. Radiological approaches in the evaluation of joint disease in children. Rheum Dis Clin N Am. 1987;13(1):57–73.
123. Lejman T, Strong M, Michno P, Hayman M. Septic arthritis of the shoulder during the first 18 months of life. J PediatrOrthop. 1995;15(2):172–5.
124. Ernat J, Riccio AI, Fitzpatrick K, Jo C, Wimberly RL. Osteomyelitis is commonly associated with septic arthritis of the shoulder in children. J PediatrOrthop. 2017;37(8):547–52.
125. Street M, Crawford H. Pediatric humeral osteomyelitis. J PediatrOrthop. 2015;35(6):628–33.
126. Belthur MV, Palazzi DL, Miller JA, Phillips WA, Weinberg J. A clinical analysis of shoulder and hip joint infections in children. J PediatrOrthop. 2009;29(7):828–33.
127. Buchmann RF, Jaramillo D. Imaging of articular disorders in children. RadiolClin N Am. 2004;42(1):151–68, vii
128. Learch TJ, Farooki S. Magnetic resonance imaging of septic arthritis. Clin Imaging. 2000;24(4):236–42.
129. Donatto KC. Orthopedic management of septic arthritis. Rheum Dis Clin N Am. 1998;24(2):275–86.
130. Stutz G, Kuster MS, Kleinstuck F, Gachter A. Arthroscopic management of septic arthritis: stages of infection and results. Knee Surg Sports TraumatolArthrosc. 2000;8(5):270–4.
131. Sammer DM, Shin AY. Comparison of arthroscopic and open treatment of septic arthritis of the wrist.Surgical technique. J Bone Joint Surg Am. 2010;(92 Suppl 1 Pt 1):107–13.
132. Green NE, Edwards K. Bone and joint infections in children. OrthopClin North Am. 1987;18(4):555–76.
133. Yuan HC, Wu KG, Chen CJ, Tang RB, Hwang BT. Characteristics and outcome of septic arthritis in children. J MicrobiolImmunol Infect. 2006;39(4):342–7.
134. Ho G Jr. How best to drain an infected joint. Will we ever know for certain? J Rheumatol. 1993;20(12):2001–3.
135. Mathews CJ, Kingsley G, Field M, Jones A, Weston VC, Phillips M, et al. Management of septic arthritis: a systematic review. Ann Rheum Dis. 2007;66(4):440–5.
136. Petersen S, Knudsen FU, Andersen EA, Egeblad M. Acute haematogenous osteomyelitis and septic arthritis in childhood.A 10-year review and follow-up. ActaOrthopScand. 1980;51(3):451–7.

137. Samilson RL, Bersani FA, Watkins MB. Acute suppurative arthritis in infants and children; the importance of early diagnosis and surgical drainage. Pediatrics. 1958;21(5):798–804.
138. Goldenberg DL, Brandt KD, Cohen AS, Cathcart ES. Treatment of septic arthritis: comparison of needle aspiration and surgery as initial modes of joint drainage. Arthritis Rheum. 1975;18(1):83–90.
139. Agarwal A, Aggarwal AN. Bone and joint infections in children: septic arthritis. Indian J Pediatr. 2016;83(8):825–33.
140. Kimberlin DW, Brady MT, Jackson MA, Long SS, editors. Red Book 2018–2021 report of the committee on infectious diseases. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018. 18 p
141. Kaplan SL. Osteomyelitis in children. Infect Dis Clin N Am. 2005;19(4):787–97, vii
142. Ruiz J, Garcia-Robles A, Marques MR, Company MJ, Solana A, Poveda JL. Influence of pharmacokinetic/pharmacodynamic ratio on vancomycin treatment response in paediatric patients with Staphylococcus aureus bacteremia. Minerva Pediatr. 2018 https://doi.org/10.23736/S0026-4946.18.04978-2. PMID: 29651827. [Epub ahead of print].
143. Bradley JS, Kaplan SL, Tan TQ, Barson WJ, Arditi M, Schutze GE, et al. Pediatric pneumococcal bone and joint infections. The pediatric multicenter pneumococcal surveillance study group (PMPSSG). Pediatrics. 1998;102(6):1376–82.
144. Ali RA, Kaplan SL, Rosenfeld SB. Polyarticularseptic arthritis caused by Haemophilus influenzae Serotype f in an 8-month-old immunocompetentinfant: acase report and review of the literature. Case Rep Orthop. 2015;2015:163812.
145. Kim HK, Alman B, Cole WG. A shortened course of parenteral antibiotic therapy in the management of acute septic arthritis of the hip. J PediatrOrthop. 2000;20(1):44–7.
146. Kolyvas E, Ahronheim G, Marks MI, Gledhill R, Owen H, Rosenthall L. Oral antibiotic therapy of skeletal infections in children. Pediatrics. 1980;65(5):867–71.
147. Newton PO, Ballock RT, Bradley JS. Oral antibiotic therapy of bacterial arthritis. Pediatr Infect Dis J. 1999;18(12):1102–3.
148. Peltola H, Paakkonen M, Kallio P, Kallio MJ, Osteomyelitis-Septic Arthritis Study G. 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(9):1201–10.
149. Ward J, Cohen AS, Bauer W. The diagnosis and therapy of acute suppurative arthritis. Arthritis Rheum. 1960;3:522–35.
150. Ho G Jr, Su EY. Therapy for septic arthritis. JAMA. 1982;247(6):797–800.
151. Peltola H, Vahvanen V. A comparative study of osteomyelitis and purulent arthritis with special reference to aetiology and recovery. Infection. 1984;12(2):75–9.
152. Newman JH. Review of septic arthritis throughout the antibiotic era. Ann Rheum Dis. 1976;35(3):198–205.
153. Goldenberg DL, Cohen AS. Acute infectious arthritis.A review of patients with nongonococcal joint infections (with emphasis on therapy and prognosis). Am J Med. 1976;60(3):369–77.
154. Benjamin DK Jr, Poole C, Steinbach WJ, Rowen JL, Walsh TJ. Neonatal candidemia and end-organ damage: a critical appraisal of the literature using meta-analytic techniques. Pediatrics. 2003;112(3 Pt 1):634–40.
155. Shmerling RH. Synovial fluid analysis.A critical reappraisal. Rheum Dis Clin N Am. 1994;20(2):503–12.