Management of Septic Arthritis

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Abstract. Septic arthritis in children remains a serious disease with the potential for significant systemic and musculoskeletal morbidity. *Staphlococcus aureus* is the most common cause of bone and joint infections in all age groups. Microbial invasion of the synovial space occurs typically results from hematogenous seeding. Diagnosis in neonates and young infants can be difficult since the clinical signs are much less specific in these age groups. Early diagnosis by needle aspiration of the affected joint and prompt initiation of appropriate antimicrobial therapy in conjunction with drainage of the affected joint is critical to avoid destruction of the articular cartilage and prevent disability. Septic arthritis in infants and children should always be managed by a pediatrician in close consultation with an orthopedic surgeon. Empiric antibiotic regimens should always include adequate anti-staphylococcal coverage. Antibiotic treatment should be started with appropriate doses of intravenous antibiotics. Switch to oral antibiotic therapy can be made when patient demonstrates clinical improvement. A minimum of 3-4 weeks of therapy is recommended. Close follow-up is warranted to monitor the growth of the affected limb until skeletal maturity.
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Septic arthritis in children is a true medical emergency and poses a unique clinical challenge to the pediatrician, rheumatologist and orthopedic surgeon. The disease is more commonly seen in children than in adults. The term septic arthritis refers to microbial invasion of the joint space, not associated with contiguous osteomyelitis. Acute septic arthritis is bacterial regardless of age and also the most common form of infectious arthritis. Early diagnosis and subsequent appropriate medical and surgical intervention is imperative to avoid destruction of the articular cartilage and thus preventing permanent disability.

The authors review the pathogenesis, etiology, and clinical features of septic arthritis in children, and examine the current approaches to diagnosis and treatment of this condition.

PATHOGENESIS

Septic arthritis in childhood most frequently results from hematogenous spread of bacteria,[1] although infection can also occur due to local spread from a contiguous infection, and traumatic or surgical infection.[2] The pathogenesis of septic arthritis has been explored in various experimental models.[3] The synovial membrane is highly vascular and lacks a limiting basement membrane, allowing bacteria to seed the synovial space. The most common microorganism, *Staphylococcus aureus*, has been shown to bind to bone by expressing receptors (adhesins) for components of bone matrix (fibronectin, laminin, collagen, and bone sialoglycoprotein), the expression of collagen-bonding protein adhesin permits the attachment of the pathogen to cartilage.[4] Once the bacteria invade the synovial membrane, bacterial endotoxin stimulates the release of cytokines including tumor necrosis factor and interleukin-1. These cytokines in turn stimulate the release of proteolytic enzymes by synovial cells and chondrocytes, enhancing leukocyte migration. Neutrophil elastases augment destruction of the cartilage matrix within the joint. Pressure necrosis from accumulation of purulent synovial fluid further destroys synovium and cartilage.[1-3]

Septic arthritis can sometimes result from contiguous spread from adjacent osteomyelitis. In the newborn and young infant blood vessels connect the metaphysis and epiphysis, so it is common for pus from the metaphysis to enter the joint space.[5] The joint capsule of the hip and shoulder overlies the bony metaphysis of the femur and humerus, facilitating direct extension of bone infection into these joint spaces.

MICROBIOLOGY

The bacterial etiology of septic arthritis varies with age.[1,2,6,7] In neonates, *Staphylococcus aureus*, group B *Streptococcus* and gram negative enteric bacilli are usual pathogens.[5] Beyond the neonatal age group, *S. aureus* is

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the most common infecting organism in all age groups. In children 3 months to 5 years of age, *Haemophilus influenzae* type b remains an important cause of septic arthritis in resource poor countries which do not have a universal Hib vaccination program. Other important pathogens include *Group A streptococci, and Streptococcus pneumoniae. Neisseria gonorrhea* must be considered in neonates and sexually active adolescents. In the child with sickle cell anemia, in addition to *S. aurues, Salmonella spp.* frequently cause septic arthritis. Immunosuppresed patients are at high risk of being infected with gram negative bacteria. In chronic cases of septic arthritis, unusual pathogens such as mycobacteria and fungi should be considered. Other rare pathogens reported to cause septic arthritis include *Neisseria meningitidis, Salmonella spp.*, anaerobes, and *brucella. Kingella kingae* is a common cause of septic arthritis in children under age 5 in Israel.[8]

CLINICAL FEATURES

Septic arthritis is usually accompanied by systemic manifestations including fever, malaise, poor appetite and irritability. The onset of septic arthritis is usually more acute than is the onset of osteomyelitis. In the infant or neonate, there may be fever, failure to feed, lethargy and pseudoparalysis of the extremity.[5] In the older child, the signs are more localized. Approximately 75% of cases of septic arthritis involve the joints of the lower extremities.[2,7] The knee is the most commonly involved site, followed by the hip and ankle, although the elbow, and shoulder may be often affected.[7] Thus, limp or refusal to walk is the most common clinical manifestation. If the joint of the arm is involved, there will be decreased mobility of the upper extremity. Physical examination of the infected joint will reveal local erythema, warmth, and swelling. Passive joint movement which stresses the joint capsule will illicit pain and the range of motion will be decreased. Joint dislocation may be observed. Smaller distal joints are less likely to be affected than are larger proximal ones. Over 90% of children have monoarticular joint infections.[2,7] However, certain infections with *N. gonorrhoea, N. meningitidis, Salmonella spp* and rarely *S. aureus* have been polyarticular.[2]

Neonatal septic arthritis represents a different spectrum of disease than does septic arthritis of childhood. Because of the unique nature of the vascular supply of the neonatal skeletal system, osteomyelitis and septic arthritis commonly occur concomitantly.[5] Infants with altered immune function, those undergoing invasive procedures or the presence of indwelling vascular lines remain at greatest risk.[9] A high index of suspicion for septic arthritis should be maintained in sick neonates since the signs and symptoms are subtle. Fever and other systemic signs of illness may be absent. The hip and the knee are the most commonly involved joints. Diminished movement of the affected limb, unrelated temporally to birth trauma, is a common clinical sign.[5] Infants with septic arthritis of the hip may be irritable when the hip is moved, especially during diaper changes. The affected hip is often held in a flexed, externally rotated and abducted position.

DIAGNOSTIC EVALUATION

Clinical suspicion of septic arthritis should lead to the examination of the joint fluid. Synovial fluid aspirated should be sent for Gram stain, aerobic and anaerobic bacterial cultures, and cell count with a leukocyte differential count. In addition to joint aspiration, a complete blood count, erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), blood culture, radiograph of the affected joint should be performed.

Joint Fluid Findings

The synovial fluid characteristics in various types of arthritis are depicted in Table 1. Synovial fluid in septic arthritis is typically turbid or grossly purulent. A synovial fluid white blood cell (WBC) count of greater than 50,000 cells/mm^3, with a predominance of polymorphonuclear neutrophils is strongly suggestive of septic arthritis even if the joint fluid culture is negative.[10] However, synovial fluid WBC count of greater than 50, 000/mm^3 can occur in juvenile rheumatoid arthritis, and counts less than 50, 000/mm^3 can occur in septic arthritis.[2] Synovial glucose may be low, protein and lactate elevated but these tests are not sensitive or specific to be generally used. The yield of organisms from joint fluid culture is about 50% to 60%.[6,7]

The WBC count may be elevated with a predominance of polymorphonuclear leukocytes.[6,7] Blood cultures are positive in 40% of patients with septic arthrtits.[2] Despite their limitations, the erythrocyte sedimentation rate (ESR) has been used as an adjunct to culture for the differential diagnosis of septic bone and joint infections and for monitoring response to treatment.[11] ESR is elevated in most patients with septic arthritis.[7,11] Likewise, levels of CRP often is increased in septic arthritis.[11] The ESR usually rises 3-5 days after initiation of therapy and then slowly returns to normal within about 4 weeks. In contrast, CRP peaks at day 2 of therapy and can normalize within 1 week in uncomplicated cases.

Imaging Findings

Plain radiography is not an effective tool for the early evaluation of septic arthritis.[12] Plain radiographs may be normal, or show periarticular soft tissue swelling and widening of the joint space owing to a large joint effusion. Sometimes capsular swelling is apparent with obliteration and displacement of the gluteal lines, and asymmetric fullness of the iliopsoas and obturator internus soft tissue planes.[12] Dislocation or subluxation of the femoral head may be seen, particularly in neonates. Subchondral bone erosions may be seen late in the course of the infection.[12] The appearance of sclerosis and decreased volume in the

proximal femoral epiphysis usually signifies the onset of avascular necrosis.[12] Ultrasound of the hips is the modality of choice in suspected septic arthritis involving the hip joint and may be useful in detecting early, less obvious joint fluid effusions.[13] If fluid is present, arthrocentesis can be performed and appropriate cultures can be obtained. Ultrasound-guided aspiration is an easy way to obtain fluid from the joint and have direct visualization of the fluid and needle during the procedure.[13] Scintigraphy is often employed to identify an associated metaphyseal osteomyelitis or vascular necrosis of the femoral head. Whole body bone scan is often preferred in young children even when symptoms appear very focal, because sometimes septic arthritis and osteomyelitis may be multifocal. In septic arthritis, the periarticular distribution of increased uptake is seen on both "blood-pool" and delayed images of the joint. There is symmetric uptake on both sides of the joint typical of septic arthritis.[2] Computed tomography (CT) and magnetic resonance imaging (MRI) are additional confirmatory studies; MRI is highly sensitive in early detection of joint fluid and is superior to CT in delineation of soft tissue structures.[14]

MANAGEMENT

Antimicrobial Therapy

Since selection of appropriate antibiotics is crucial in the therapy of septic arthritis,[6] identification of the causative microorganisms is extremely important. Every effort must be made to ensure that initial antibiotic therapy should be based on gram stain results of joint fluid or other sterile body fluid cultures. If no microoganisms are identified, empiric treatment should be initiated for the most likely the pathogens might be, considering the age and clinical picture of the patient (Table 2). This treatment may be changed based on the culture results and sensitivities of joint aspirates. Cases of both, septic arthritis and osteomyelitis, should be initially treated with high dose intravenous antibiotics in order to ensure an adequate serum concentrations to control the infection.

In neonatal septic arthritis when no bacteria are identified in gram stain, empiric treatment should be directed to *S. aureus*, Group B *Streptococci* and gram negative bacteria, especially *E. coli.* A beta-lactamase-resistant anti-staphylococcal penicillin, such as nafcillin or cloxacillin in combination with aminoglycoside or third generation cephalosporin, such as cefotaxime, provide an excellent coverage.[2,5]

The initial empiric antimicrobial therapy in cases of septic arthritis beyond the neonatal period should include adequate anti-staphylococcal coverage. Therefore, therapy must include an anti-staphylococcal agent either a beta-lactamase resistant penicillin (e.g., nafcillin or cloxacillin) or first generation cephalosporin (e.g. cefazolin) or clindamycin. In the first 5 years of life, in addition to *S. aureus*, empiric coverage for *H. influenzae* type b is also warranted and therefore cefuroxime or a combination of nafcillin or cloxacillin or clindamycin with ceftriaxone would be appropriate.[15] Similarly, if

Table 1. Synovial Fluid Findings in Arthritis*

Analysis	Normal	JRA	RA	SA
Color	yellow	yellow	yellow	serosanguineous
Clarity	clear	cloudy	opaque	turbid
Viscosity	very high	low	low	very low
WBC count	< 200	15–20 × 10^3	20–40 × 10^3	> 50,000
PMN (%)	< 25	60–75	50–75	> 75

*JRA = Juvenile rheumatoid arthritis; RA = Reactive arthritis; SA = Septic arthritis; PMN = Polymorphonuclear cell

Table 2. Empiric Antibiotic Treatment of Septic Arthritis in Children

Age group	Common Pathogen	Antibiotic Choice
Neonates	*Staphylococcus aureus* Group B *Streptococci* Gram-negative bacilli	Nafcillin + Cefotaxime or Gentamicin
Children ≤ 5 yr	*S. aureus* *Haemophilus influenzae* type b or Group A *Streptococci* *Streptococcus pneumoniae*	Nafcillin plus Cefotaxime or Cefuroxime
Children > 5 yr	*S. aureus*	Nafcillin or Cefazolin or Clindamycin
Adolescents	*S. aureus* *Neisseria gonorrhoeae*	Nafcillin or Cefazolin or Clindamycin Add Ceftriaxone

methicillin-resistant *S. aureus* or penicillin-resistant *Pneumococci* are suspected, vancomycin should be empirically started. Recent data from North America indicate that many strains of *S. aurues* acquired in the community are resistant to the usual anti-staphylococcal antibiotics such as cloxacillin and cefazolin but often susceptible to clindamycin.[16] In sexually active adolescents, the empiric coverage should include agents active against N. gonorrhoeae.[17] Broad-spectrum antibiotics are needed for patients with sickle cell disease, since coliform bacteria are common. In such cases, therapy must include third generation cephalosporin, such as ceftriaxone in addition to anti-staphylococcal drug such as nafcillin or cloxacillin or clindamycin. Immunocompromised hosts are at greater risk of being infected by unusual organisms and should be treated somewhat differently. Several combinations of two or three antibiotics are currently been recommended. Vancomycin with ceftazidime or ticarcilline-clavulanate with aminoglycosides is most frequently used.

When the specific bacteria is identified and antimicrobial susceptibilities become available, therapy should be adjusted appropriately (Table 3). If the organism was not isolated and the patient is clearly showing improvement, the empiric therapy initially selected should continue. Treatment should always be started by the intravenous route. During intravenous antimicrobial therapy of patients with septic arthritis antibiotic concentrations in synovial fluid usually are high enough to provide optimal inhibitory activity, and the need for monitoring of drug activity in the serum is rarely indicated. Compliance is critical when patient begins oral therapy. Also, about 5% of patients, for a variety of reasons do not absorb oral antibiotics efficiently and do not achieve adequate serum concentrations.[18] Therefore, when oral therapy is being considered, some experts advocate that serum antibiotic concentrations be monitored by drawing a blood specimen at the time of anticipated peak antibiotic activity (45-60 min after ingesting an oral suspension and 2-3 h after taking a tablet or capsule);[18] serum bactericidal titers with oral antibiotic should be at least 1:8 or greater for achieving adequate inhibitory concentrations of antibitocs.[19]

There is considerable experience in the sequential parenteral-oral regimen for antibiotic therapy for osteomyelitis and septic arthritis.[18,20-22] An excellent review article has been published describing guidelines for oral therapy, choice of antibiotics, dosing and monitoring.[22] Oral antibiotic therapy can be instituted only when patient's clinical condition has improved (resolution of fever, pain decreased, and mobility increased), and strict compliance and close monitoring are ensured.[2, 15, 20-22] For oral therapy, a dosage 2 to 3 times that used for mild infections should be used to achieve high synovial fluid-serum ratios (Table 4).[18,22] Beside the convenience to patients and families, the oral route decreases the risk of complications of long-term intravenous therapy. In monitoring response to therapy, in addition to clinical

Table 4. Antibiotic Dosages For Treating Septic Arthritis in Children Intravenous Route

Antibiotic	Dose (mg/kg/day)	Doses/day
Nafcillin or Cloxacillin	100	4
Cefazolin	100- 150	3-4
Clindamycin	30	3-4
Cefuroxime	100- 150	3
Ceftriaxone	50	1
Cefotaxime	100- 150	3-4
Gentamicin	5- 7.5	3
Vancomycin	40	3
Oral Route		
Cephalexin	100- 150	4
Clindamycin	30	3-4
Dicloxacillin	75- 100	4

Table 3. Specific Antibiotic Treatment of Septic Arthritis in Children

Microorganisms Isolated	Treatment of Choice	Alternatives
Staphylococcus aureus	Nafcillin or Cloxacillin	Cefazolin, Clindamycin, Vancomycin*
H. influenzae type b	Cefuroxime or Ceftriaxone	Chloramphenicol
Group B *Streptococci*	Peniclin G or Ampicillin plus Gentamicin	
Group A *Streptococcus*	Penicillin G or Ampicillin	Clindamycin
Streptococcus *pneumoniae*	Ceftriaxone or Clindamycin	Penicillin G or Ampicillin for susceptible strains Vancomycin*
Enteric gram-negative rods	Gentamicin or Ceftriaxone	Piperacillin
Pseudomonas aeruginosa	Ceftazidime or Ticarcillin plus Gentamicin	
Neisseria Gonorrhoeae	Ceftriaxone	Penicillin G for susceptible strains
Salmonella species	Ceftriaxone	Chloramphenicol
Anaerobes	Penicillin, Clindamycin	Metronidazole

*Vancomycin is recommended for methicillin-resistant *S. aureus* and penicillin-resistant pneumococci

improvement, acute phase reactants including ESR and CRP is helpful.[11] The appropriate duration of therapy for septic arthritis is still controversial and depends on the infecting pathogen, the joint involved and the host.[15] However, it is advised to treat for 3 to 4 weeks in uncomplicated cases.[2,15] Longer duration of therapy (e.g. 4 weeks) may be necessary for septic arthritis of the hip or shoulder and/or is caused by S. aureus or Gram-negative bacteria when compared to infection of a small to medium joint such as the knee caused by S. pneumoniae, H. influenza or Neisseria spp (e.g, 2-3 weeks).[2,15] A minimum of 7 days therapy is recommended for gonococcal tennosynovitis.[17]

Intra-articular injections of antibiotics are not recommended because of excellent penetration of most antibiotics into synovial space. Furthermore, infusion of certain antimicrobial agents may trigger synovial inflammatory response.[15]

Surgical Therapy

Septic arthritis in infants and children should always be managed by a pediatrician in close consultation with an orthopedic surgeon. In septic arthritis of the hip (or shoulder) joint, open surgical drainage should be performed immediately. In the treatment of septic arthritis of joint other than the hip, open surgical drainage is not necessary and therapy can be individualized. However, prompt aspiration of the joint should be performed to decompress the joint and also to obtain synovial fluid for analysis and culture. Joint drainage and irrigation is an important part of the management of septic arthritis. This can be accomplished by repeated closed needle aspiration or drain placement. Although no prospective, randomized study has been conducted to evaluate any surgical procedure, repeated needle aspiration of the infected joint has been associated with a successful outcome and early identification of the causative microorganism. Following daily joint aspiration, if fluid is still accumulating after 4 to 5 days, open surgical drainage is recommended. It is being advised that during arthrotomy the joint should to be flushed with sterile saline solution. In summary, the well established indications for open surgical drainage in children with septic arthritis based include: (1) hip or shoulder joint disease; (2) the presence of large amounts of pus, fibrin, debris or loculation within the joint space; (3) concomitant osteomyelitis; (4) if no clinical improvement noted within 5-7 days of repeated aspirations.[15] Other experts advocate that surgical drainage should be performed on any infant or young child with septic arthritis, since needle aspiration has shown inferior outcome in very young children.

PROGNOSIS

Sequelae of septic arthritis in children are not uncommon and include cartilage damage, stiff joint with poor mobility, abnormal bone growth if the epiphysis is involved, unstable joint and joint dislocation.[2,7] Predictors of poor outcome with septic arthritis include infection in the hip and shoulder, associated adjacent osteomyelitis, infection with S. aureus, young age (e.g < 6-12 months, neonate), a delay of 4 days or more before decompression and antibiotic therapy, and prolonged time to sterilization of synovial fluid.[2,7]

CONCLUSION

Because of its seriousness, septic arthritis should be considered early in the differential diagnosis of any child presenting with joint inflammation. Physicians who care for children should be aware of the early signs and symptoms of septic arthritis and be aggressive about establishing the diagnosis so that treatment is not delayed. Early orthopedic consultation and a low threshold for performing arthrocentesis are prudent. Prolonged and appropriate antimicrobial therapy is warranted to achieve optimal results.

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