4

CURRENT CLINICAL TOPICS IN INFECTIOUS DISEASES

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Contents

Diagnosis and management of septic arthritis

NEAL H. STEIGBIGEL

It appears that the overall incidence of acute nongonococcal septic arthritis has remained unchanged during the era of antibiotics, although detailed statistics are not available (1,2). This condition may affect all ages but is now particularly encountered in infants, children, and the elderly (2,3). It may be associated with significant mortality or serious permanent sequelae, especially in infants, individuals with major underlying diseases, including chronic arthritis, and in those who are immunocompromised (2–5). In contrast, gonococcal arthritis has become more common over the past 20 years, is encountered primarily in sexually active adolescents and adults, especially women, and, with current antibiotic treatment, has a benign outcome in the majority of affected persons (6–10). Taken together, gonococcal and nongoncoccal septic arthritis represent the most common forms of acute arthritis noted in patients presenting at some hospitals (11).

An improved outcome in patients with nongonococcal septic arthritis depends on early diagnosis and prompt initiation of appropriate antimicrobial therapy, together with effective joint drainage (2–5,12,13). Therapy should be initiated before confirmation of etiology by culture becomes available. Diagnosis can usually be made early and appropriate therapy begun promptly following a careful consideration of the clinical setting together with examination of aspirated synovial fluid. In selected patients, additional diagnostic studies, some of which have become available recently, will provide additional help. The focus of this review will be on the diagnosis and management of patients with acute nongonococcal septic arthritis.

PATHOGENESIS AND PATHOPHYSIOLOGY

A consideration of some aspects of the pathogenesis and pathophysiology of septic arthritis is relevant to the rational management of patients with this condition.

Septic arthritis occasionally occurs as a result of inoculation of bacteria directly into the joint (by accidental trauma, injection of drugs, or surgery) or by extension of contiguous infection such as osteomyelitis. In the latter situation spread from

bone to synovium and then to the joint space is favored in early infancy and in the adult by the presence of vascular anastomoses between metaphysis and epiphysis and by a common blood supply of the epiphysis and the synovium. In later childhood these anastomoses are not present and the epiphyseal growth cartilage is usually an effective barrier to the spread of bone infection to the joint (14,15). When joint infection does occur in childhood as an extension of osteomyelitis, it often does so in the hip where the joint capsule extends beyond the epiphyseal cartilage and attaches to the periosteum of the metaphysis, allowing entry of organisms from a subperiosteal infection in that area (15).

Septic arthritis much more commonly is the result of joint invasion by bacteria directly from the bloodstream during bacteremia (12,13). Since bacteremia occurs much more frequently than septic arthritis, the joint must be able to resist penetration by most blood-borne bacteria. Histological evidence of synovitis, with or without the demonstrated presence of bacteria, is common in bacteremic states and may correlate with the frequent arthralgias reported by such patients (16). Synovitis or frank septic arthritis has been produced experimentally in association with bacteremic infection (17). The synovial membrane is able to limit and clear the blood-borne bacterial infection in the synovium in most instances, apparently by major phagocytic activity and intracellular killing by synovial cells (18). The development of frank septic arthritis from bacteremia therefore can be considered as related to the intensity and duration of the bacteremia as well as to the special virulence or adherence characteristics of the bacterial pathogen (7,17) and to the competence of the defen mechanisms of the host.

Since monarticular involvement occurs in most cases of nongonococcal septic arthritis associated with bacteremic infection, local host factors must be important in allowing for colonization of the involved joint. The presence of preexisting arthritis, especially rheumatoid arthritis, is a well-known predisposing factor (19–21). In addition to the unknown effects that the tissue damage of the rheumatoid joint would have on the pathogenesis of septic arthritis, other potentially relevant factors in patients with rheumatoid arthritis have been identified, including diminished chemotaxis (22) and phagocytosis (23) by neutrophils and decreased bactericidal activity of synovial fluid (24). The more common involvement of the large weight-bearing joints in septic arthritis may be related to the larger vascular bed of such joints which could deliver a greater bacterial load, as well as to the likelihood that these joints would be subject to greater trauma. It has been suggested that hematoma formation in traumatized joints may be a predisposing factor to the subsequent development of septic arthritis (25).

The acute inflammation which rapidly follows bacterial invasion of the synovium and joint space involves a complex series of interactions between bacterial components (exotoxins, endotoxin, enzymes, peptidoglycan of cell wall) and host systems (12,13,25a,26). Complement activation with resulting release of histamine and stimulation of chemotaxis and phagocytosis may take place with or without the presence of immune complexes in the joint. Joint damage due to cartilage destruction may rapidly follow establishment of infection (13,27). Increased intraarticular pressure, ischemia, and the activation or release of chondrolytic enzymes from

plasma, lysosomes of polymorphonuclear leukocytes, or synovial cells probably contribute to joint destruction (28–31).

DIAGNOSIS

The early diagnosis of septic arthritis can usually be made by combining a careful consideration of the clinical setting with appropriate examination of aspirated synovial fluid. In selected patients, additional diagnostic studies may provide further guidance. Such an approach will also suggest a likely group of bacterial pathogens for the patient under consideration so that appropriate antimicrobial therapy can be started prior to the availability of culture results.

Clinical setting

Clinical onset, symptoms, and signs of septic arthritis and distribution of joints involved The classic presentation is found in many patients with septic arthritis: an onset over several days of warmth, pain, and swelling in a single joint, or less often in multiple joints, associated with fever and sometimes with chills, as well as tenderness and limitation of range of motion of the joint on physical examination (4,12,13,31a). In some recently reported series these findings were present in almost all patients (4). However, in recent years a more atypical presentation has been noted frequently (2,3,32,33). Fever is variably present (in 40 to 90 percent of patients) (3,4,32) and, when present, is often low grade in intensity or transient (2,4,11). Rosenthal et al. (3) noted the presence of pain in only 48 of 71 individuals with septic arthritis. Substantial limitation of the range of motion of the joint (with or without pain) is the most consistently recorded sign (31a) and one that may help to differentiate infection in the joint per se from cellulitis or bursitis. When tenderness is present, it is often diffuse in its periarticular location in contrast to the "point" tenderness often noted in acute osteomyelitis. Although the clinical onset of septic arthritis often evolves over several days, the diagnosis in the average patient is often not made until symptoms have been present for 1 to 2 weeks (2,3); longer delay is common in patients with infected prosthetic joints or in those with rheumatoid arthritis with septic arthritis (3,33).

An atypical presentation occurs frequently in neonates and in patients with underlying chronic arthritis, drug users, and those who are immunocompromised (see predisposing factors below). Septic arthritis of the deeply situated joints such as the hip, shoulder, spine, or sacroiliac joint is often manifest by less obvious and poorly localized signs of inflammation (12). Sepsis in the hip in adults usually presents with hip pain and fever (34). The thigh is usually held in a position of flexion, adduction, and internal rotation and is severely limited in range of motion by pain. However, pain may be in the groin, lateral upper thigh, or buttocks or referred to the knee (12,35). Infection usually reaches the hip by the hematogenous route (34), but occasionally there may be direct penetration (36) or extension by contiguity from an intraabdominal focus by way of the retroperitoneum, along the iliopsoas muscle to the capsule of the hip joint (34,37). In the latter situation the pathogens

are usually polymicrobial and may involve species of Enterobacteriaceae and anaerobes. Hip involvement in infancy is discussed below in the context of that age group.

Recent reports have detailed the clinical picture of pyogenic sacroiliitis in children and adults and have noted its occurrence particularly in children between the ages of 7 and 14, in adults with a history of illicit drug abuse, and in pregnancy (38–41). Onset may be rapid, but more commonly it is relatively slow and progressive over a period of weeks; most patients have fever. Involvement of the sacroiliac joint is almost always unilateral and is usually the result of bacteremia from a distant focus. In children *Staphylococcus aureus* has been isolated from the joint or blood in 90 percent of cases (40), while in drug addicts a variety of gram-negative bacilli, including *Pseudomonas* species or *Staph. aureus*, have been isolated (39,41). Patients with this syndrome complain of poorly localized pain in the buttock, low back, hip, lower abdomen, thigh, or calf; they may have difficulty in walking and pain may reflect sciatic radiation. Physical examination often shows spasm of the gluteal muscles, and in adults tenderness on palpation of the sacroiliac joint is noted regularly (39). Abdominal pain and tenderness on deep palpation of the lower abdomen and on rectal examination sometimes erroneously suggest the presence of an acute abdomen (38). On rare occasions, the infection of the sacroiliac joint may be the result of extension of an intraabdominal infection, or infection may extend from the joint into the retroperitoneum, pelvis, or thigh (39). Slow and gentle manipulation of the hip can usually demonstrate full range of motion of that joint and thereby differentiate the condition from that of a septic hip (39,40). Examination can further localize the problem by painful stressing of the sacroiliac joint through several maneuvers: (1) Pain on pelvic compression is produced by applying pressure to the superior iliac crest with the patient lying on his side: (2) Pain and limitation of movement is produced by hyperextension of the hip and lower extremity (Gaenslen maneuver). This maneuver may also be positive with a herniated nucleus of an intervertebral disc. (3) In the FABERE maneuver pain and limitation of motion is found by briskly flexing, abducting, and externally rotating the hip, which is accomplished by placing the ipsilateral lateral malleolus on the opposite knee while the patient is in the supine position (38–40). When the last maneuver is performed slowly, the patient with sacroiliac involvement will usually show full range of motion. Finally, recent studies have demonstrated the value of radionuclide scintiscans as well as aspiration of the sacroiliac joint under fluoroscopic control for early diagnosis (see laboratory studies below) (39–41).

Pustular skin lesions similar to those commonly observed in disseminated gonococcemia have been described in patients with meningococcal arthritis (42,43) and in occasional patients with septic arthritis due to group A streptococci (4) and *Haemophilus influenzae* (11,44). Tenosynovitis is observed commonly in patients with the gonococcal dermatitis-arthritis syndome, but is rare in patients with other forms of septic arthritis (8,45).

Nongonococcal septic arthritis usually affects one joint, most commonly the knee (Table 1). Involvement of the knee, hip, ankle, or elbow accounts for 90 percent of cases in children (46). In adults, septic arthritis of the shoulder and sternoclavicular joints occurs with substantial frequency in comparison with children. Polyarticular nongonococcal infection occurs in 10 to 20 percent of adults and chil-

Table 1 Joints affected by nongonococcal septic arthritis

	Knee	*Hip*	*Ankle*	*Elbow*	*Shoulder*	*Wrist*	*Sterno-clavicular*	*Sacro-iliac*	*Other*	*Total no. of joints affected*
Age under 15 years*	123 (37)	96 (29)	48 (14)	38 (11)	12 (4)	12 (4)	1	—	4	334
Age over 15 years†	187 (46)	82 (20)	24 (6)	19 (5)	40 (10)	25 (6)	15 (4)	4	8	404

*From Reference 2, 3, 46.

†From References 1–3, 10, 11.

NOTE: Number in parentheses represents the percentage of total joints affected.

dren with septic arthritis (1–4,10,11,46). In contrast, more than one joint is involved in the majority of patients with gonococcal arthritis (8).

Age factors and predisposing conditions in relationship to the likely bacterial etiology of septic arthritis Since most cases of septic arthritis result from bacteremia, it is not surprising that the organisms frequently responsible for joint sepsis are those which commonly cause bacteremia in particular age groups (Table 2) or in patient populations (Table 3). However, some species such as *Staph. aureus* or *Neisseria gonorrhoeae* may have a particular avidity for the synovium, out of proportion to their frequency in causing bacteremia. Particular adherence or virulence characteristics for the synovium have not been defined. In contrast, bacteremia due to Enterobacteriaceae is common, and yet septic arthritis with these organisms is uncommon except in neonates, those with underlying chronic arthritis, or those who are immunocompromised (4).

In the neonate septic arthritis occurs as a result of bacteremia often by extension of contiguous hematogenous osteomyelitis (difficult to recognize clinically) or occasionally as a consequence of femoral venipuncture (36,46–49). The bacterial pathogens noted frequently in recent reports are *Staph. aureus*, group B and other streptococci, and Enterobacteriaceae and less commonly *Pseudomonas aeruginosa*, *N. gonorrhoeae*, and *H. influenzae*. When *Staph. aureus* causes septic arthritis in the neonate, there is usually associated osteomyelitis (47). The neonate with septic arthritis is usually afebrile and suggests the presence of joint pathology by showing limited use of the involved extremity ("pseudoparesis"), crying on passive movement of the joint, and variable signs of joint inflammation. The hip, knee, or shoulder is most frequently affected and multiple joint involvement is common. When the hip is involved, it is often maintained in the "frog leg" position (flexed, abducted, and externally rotated) and there may be edema or swelling of the extremity, buttock, or genitalia on the involved side with asymmetrical thigh and buttock creases (50); abdominal distension sometimes suggests an intraabdominal problem. Rising intraarticular pressure distends the capsule of the hip joint and may even push the femoral head laterally and cause dislocation. The retinaculum blood vessels, which travel on the surface of the femoral neck and supply the epiphysis, are easily compressed by the increased intraarticular pressure. This often leads to epiphyseal damage or even to infarction of the femoral head if early and effective

Table 2 Bacteria which cause nongonococcal septic arthritis tabulated by age groups involved

	Under 2	*2–5*	*5–15*	*Under 15**	*Over 15*
Staph. aureus	6 (10)	15 (42)	30 (58)	107 (40)	198 (55)
Staph. epidermidis	2	2	1	10 (4)	9 (3)
Streptococci, excluding *Strep. pneumoniae*	6 (10)	8 (22)	12 (23)	43 (16)	49 (14)
Strep. pneumoniae	5 (8)	2	1	12 (5)	11 (3)
H. influenzae	33 (52)	4 (11)		63 (24)	2
Other gram-negative bacilli, including *P. aeruginosa*	8 (13)	3 (8)	6 (12)	23 (9)	81 (23)
P. aeruginosa	3	2	2	11	14
Others	2	2	2	8	8
Total	63	36	52	266	358
Reference†	46	33, 46	9, 33, 46	3, 4, 9, 25, 33, 46	1, 3, 4, 9, 11, 33

*Includes data from some studies which did not break down ages within the childhood group.

†Selected series published subsequent to 1969; some series exclude cases of septic arthritis related to penetrating trauma or surgery.

NOTE: Number of bacterial isolates; some patients had more than one isolate. Number in parentheses represents the percentage of isolates within each age group.

Table 3 Predisposing conditions for septic arthritis

Extraarticular site of infection, distant or contiguous
Infancy
Malignancy
Diabetes mellitus
Alcoholism
Immunosuppressive therapy
Chronic arthritis, especially rheumatoid arthritis
Prior joint trauma, joint surgery, intraarticular injection
Drug abuse
Presence of joint prosthesis
Hemoglobinopathy
Dog or cat bite or scratch

drainage is not instituted to decompress the joint space. Aspiration of the hip joint or even exploratory arthrotomy is required to substantiate the diagnosis.

Septic arthritis in the infant beyond the neonatal period is most often caused by *H. influenzae*, type B (especially between the ages of 4 months and 3 years), occasionally by streptococcal species or *Staph. aureus*, and rarely by *Neisseria menin-*

gitidis or other gram-negative bacilli (46). After the age of 3 years the vast majority of isolates from children with septic arthritis are staphylococcal or streptococcal species (46). *N. meningitidis* or gram-negative bacilli are occasionally involved, and *N. gonorrhoeae* has been reported in children in certain communities (46).

The gonococcus is now the most common single bacterial pathogen involved in septic arthritis in adolescents and adults, especially in young women who are sexually active (8,9). It accounted for 45 percent of 66 cases of acute septic arthritis reported in one series of proven cases (9). In recent reports staphylococci and streptococci were the most common causes of nongonococcal septic arthritis in adults; together they accounted for about 75 percent of bacterial isolates (Table 2). *Staph. aureus* accounted for 55 percent of nongonococcal bacterial isolates, while gram-negative bacilli, other than *H. influenzae*, accounted for 23 percent.

An increasing proportion of cases of septic arthritis in adults due to gram-negative bacilli has been observed in recent years (4,51,52). Most such patients have predisposing conditions known to be associated with gram-negative bacterial infection including parenteral drug abuse, malignancy, diabetes mellitus, therapy with immunosuppressive drugs, or hemoglobinopathy (4,51–53). *Escherichia coli* and *Proteus mirabilis*, often associated with urinary tract infections, are common pathogens in those patients who are not parenteral drug abusers (4,51), while *P. aeruginosa* and *Serratia* species are the gram-negative organisms commonly involved in septic arthritis in drug addicts (52,53). Occasional adult patients with similar predisposing factors other than parenteral drug abuse have been reported wth *H. influenzae*, type B septic arthritis (54); patients with myelogenous leukemia who developed septic arthritis due to *Aeromonas hydrophila* have been described (55). Septic arthritis associated with *Salmonella* species is often due to *S. choleraesuis* (56) and is only rarely associated with a hemoglobinopathy, although several patients with sickle cell disease and salmonella arthritis have been reported recently from Nigeria (57). Individuals, particularly those with rheumatoid arthritis, who sustain bites or scratches by dogs or cats may occasionally develop septic arthritis due to *Pasteurella multocida* (58,59). Septic arthritis may rarely be due to *Campylobacter fetus* (60) or *Yersinia enterocolitica* (61); joint disease associated with these organisms is more commonly a "reactive" nonseptic polyarthritis encountered particularly in individuals possessing the HLA-B27 histocompatibility antigen and following intestinal infection caused by these organisms (62,63). Although septic arthritis is rarely due to anaerobic organisms, it has been noted more commonly in recent years, especially following intraarticular injections of corticosteroids and in patients who are immunocompromised, have rheumatoid arthritis, or prosthetic joints and who often have an extraarticular focus of anaerobic infection (3,64). Involvement of the sternoclavicular and sacroiliac joints has been prominent when Bacteroides species are involved.

Polymicrobial involvement occurs in 5 to 15 percent of patients with septic arthritis (3,4) and is often associated with penetrating trauma or a polymicrobial extraarticular focus of infection, as within the abdomen, especially in an immunocompromised patient.

At least one of the predisposing factors for nongonococcal septic arthritis is involved in the majority of adults with this condition (3,4,11,32): the presence of an

extraarticular focus of infection. Such a focus should be expected, given the fact that the hematogenous route of joint infections is most common. The primary focus of infection should be vigorously sought since it will help one to suspect the likely bacterial etiology of the septic arthritis and to determine rational management. Sometimes the hint as to the primary focus comes from the type of bacteria isolated from the joint. Typical correlations include skin and soft tissue infections or acute endocarditis with *Staph. aureus*, urinary tract infections with *E. coli* and *Proteus* species, intraabdominal foci with polymicrobial isolates often including Enterobacteriaceae and anaerobes, and otitis media or upper respiratory infections in children with *H. influenzae*, type B. A primary focus of infection is clearly demonstrated in at least one-half of patients with septic arthritis (3,4). Bacteremia is documented in about 35 to 50 percent of patients with nongonococcal septic arthritis (2–4,11,46).

The association of major underlying disease or the immunocompromised state with septic arthritis often presenting in an "atypical" manner has already been discussed. The pathogens involved in these patients are usually *Staph. aureus*, streptococcal species, or gram-negative bacilli (3,4,51–53). The predisposition of patients with chronic arthritis, especially rheumatoid arthritis, to develop septic arthritis deserves emphasis (3,4,19–21). They are often those with long-term severe rheumatoid disease; however, in recent reports only a small proportion were being treated with systemic or intraarticular injections of corticosteroids (21). Most important in considering the diagnosis of joint infection in such patients is the awareness that fever may be absent or low grade in these patients and that chills and leukocytosis are also often not present. Polyarticular infection is common. The diagnosis is often suggested only by the development of disproportionate swelling or pain in one or several joints. It is then essential to perform joint aspiration and synovial fluid examination of one or several joints. *Staph. aureus* is involved in about 80 percent of these patients (4), with streptococcal species or gram-negative bacilli in most of the others. Skin lesions, especially ulcerated subcutaneous nodules or decubiti, appear to be the primary focus for the infection in many. Diagnosis is often delayed for 1 to 2 weeks in such patients (33), mortality is strikingly high [23 percent in the review by Goldenberg et al. (4)], and complete recovery occurs in only about one-half of the survivors (4). Patients with other forms of chronic arthritis (4) including gout (65–67), pseudogout, osteoarthritis, systemic lupus erythematosus, and Charcot's arthropathy are also predisposed to septic arthritis, although the association has been reported less frequently than in patients with rheumatoid arthritis. It is of interest that 3 of the 12 cases of septic arthritis with gouty arthritis reviewed recently were associated with *Streptococcus pneumoniae* (65–67). Pneumococcal septic arthritis is also encountered occasionally in infants (46) and in patients with rheumatoid arthritis, alcoholism, immunoglobulin deficiencies, and pneumococcal endocarditis (68). The primary focus for the pneumococcal infection is inapparent in 40 percent of such patients.

Hematogenous pyogenic bone or joint infections have been well described in intravenous heroin users (52,53,69). A thorough review of the experience with 24 patients over a 10-year period in the Los Angeles area as well as that of 101 additional patients reported in the literature is provided by Roca and Yoshikawa (69).

About 25 percent of the patients claimed to have had no use of heroin for at least 4 months. The typical patients were young adults (average age: 32) and without any recognized major underlying illness. Types of infection were vertebral osteomyelitis, probably often with spinal joint involvement (53 percent); sternoclavicular infection, usually involving bones and joint (10 percent); pelvic girdle infection (12 percent), especially involving the sacroiliac joint; and septic arthritis of the joints of the extremites, especially the knee (7 percent), wrist (4 percent), and shoulder (3 percent). Gram-negative bacilli were the pathogens in 88 percent of these infections; the source was unknown, but it may have been in the drug administration equipment. *P. aeruginosa* accounted for 78 percent of isolates, *Klebsiella-Enterobacter-Serratia* group (most often *Serratia* spp.) for 12 percent and *Staph. aureus* for 9 percent. An "atypical" presentation was often described with progressive pain and stiffness noted in the involved area for days to months. Swelling of the joint was often noted with sternoclavicular involvement and was present with sepsis in the peripheral joints. With involvement of the axial skeleton or central joints, fever was often absent or low grade and leukocytosis was frequently not present.

About 1 to 2 percent of patients who have undergone total hip replacement with a prosthesis are subject to deep infection around the prosthesis when the procedure is performed in a regular operating room and prophylactic antibiotics are used (70,71). One-half of the infections are recognized early (within 1 month of surgery) (71a) and 24 percent after 1 year has passed (71). Symptoms and signs of early infection include persistent pain after surgery, or drainage from the hip. Fever is often absent. Organisms involved in these infections are *Staph. aureus* (28 percent), *Staph. epidermidis* (21 percent), facultative gram-negative bacilli (20 percent), and anaerobes (5 percent) (70). In most early cases implantation of organisms probably takes place at the time of surgery, but metastatic infection by the hematogenous route, especially from gram-negative rod urinary tract infection, also occurs. Infection of prosthetic knee joints occurs more frequently, possibly related to host factors or to the thin soft tissue cover of the knee (72).

Laboratory and other diagnostic studies

Aspiration of the joint When the clinical setting, as described above, suggests a reasonable possibility of septic arthritis, it is essential to promptly attempt an aspiration of joint fluid so that the early diagnosis can be confirmed and rational management planned. Effective and early drainage of the joint is also essential for adequate treatment (see below). Other diagnostic studies are generally less helpful, although some may prove very useful in selected patients.

Techniques for joint aspiration are well described (73) and, as expected, are usually done most safely and effectively by those experienced with the proper procedure. Strict asepsis should be emphasized; tincture of iodine for skin preparation is usually used, followed by removal of iodine with alcohol prior to needle penetration. Needle puncture into the joint should not be made through an area of infected skin or soft tissue. Aspiration of fluid should be made with a heparinized syringe to prevent clotting of fluid and erroneous cell counts. Needle size for larger joints