Gonococcal Arthritis
(Disseminated Gonococcal Infection)

Peter A. Rice, MD

Division of Infectious Diseases and Immunology, University of Massachusetts Medical School, Lazare Research Building (LRB), Room 321, 364 Plantation Street, Worcester, MA 01605, USA

Neisseria gonorrhoeae was once the most common cause of septic arthritis in the United States, but the prevalence of gonorrhea has plummeted in the United States since the onset of the AIDS epidemic. Gonorrhea may be poised to become more troublesome, because gonococcal resistance to fluoroquinolones and other antibiotics is increasing, and many contemporary physicians are unfamiliar with the musculoskeletal manifestations of gonococcal infection. Gonorrhea generally causes either a suppurative arthritis resembling septic arthritis caused by other bacteria, or a distinct syndrome of disseminated gonococcal infection, with tenosynovitis, skin lesions, and polyarthralgias, rather than frank arthritis.

Etiology and pathogenesis

Neisseria gonorrhoeae is the most common sexually transmitted bacterium causing infective arthritis. During the 1970s and 1980s, it was also the most common cause of infective arthritis in the United States [1–4]. Septic arthritis caused by N gonorrhoeae is usually monoarticular or pauciarticular, and is often associated with positive synovial fluid cultures. By contrast, in the overtly bacteremic form of the disease, suppurative arthritis almost never occurs. Instead, gonococemia is usually associated with polyarthralgias and skin lesions, and may be more deserving of the term “disseminated gonococcal infection” (DGI).

An immunologic basis has been postulated for the polyarthralgias and skin lesions of DGI [5,6], but DGI may result directly from synovial and periarticular infection. Gonococcal bacteremia is commonly documented in

This work was supported by grant No. AI 032725 from the National Institutes of Health.

E-mail address: peter.rice@umassmed.edu
this form of the disease with positive blood cultures in up to 50% of DGI patients with tenosynovitis and polyarthralgias, suggesting that the synovium and periarticular tissues are seeded early in the disease [1,4,7–10]. The skin and visceral lesions of DGI may also represent localized infection [4,5,10–13]. *N gonorrhoeae* can sometimes be identified microscopically or by immunochemical methods in apparently sterile joint fluids, periarticular tissues, or in skin lesions of patients with DGI [12,13]. The rapid improvement of polyarthralgias with appropriate antimicrobial therapy, usually within 48 hours, is consistent with a direct therapeutic effect against *N gonorrhoeae*, and is indirect diagnostic evidence of DGI [4,7,8,10,14–17].

Other evidence militates against an immunologic basis for most cases of DGI. Attempts to identify circulating immune complexes in patients with DGI have yielded conflicting results. Reduction of complement to abnormal levels is uncommon, although mild falls in complement often occur, presumably caused by consumption [4,18,19]. Nonetheless, the question of pathogenesis is still not resolved, and immune complex deposition or other immunologic mechanisms may play a role in individual patients. For example, the later entry of circulating gonococci into the joint space later may be facilitated by immune complex synovitis early in the course of DGI [20]. It is also possible that gonococcal cell wall constituents, such as lipo-oligosaccharide or peptidoglycan fragments, circulate from the site of mucosal infection to initiate arthritis in the absence of viable gonococci [21].

The lower incidence of DGI is caused by a lower prevalence of gonococcal strains able to enter the bloodstream and survive, going on to seed joint, tendon sheath, skin, and other tissues. DGI strains may have special growth requirements, particularly the arginine, hypoxanthine, and uracil auxotype, that make them fastidious and more difficult to isolate [22]. These strains often belong to the porin 1A serotype [23]. Porin is the most abundant gonococcal surface protein, accounting for more than 50% of outer membrane protein. Porins are aqueous anion channels penetrating an otherwise hydrophobic outer membrane. DGI strains resist the bactericidal action of human serum [24], and generally do not cause genital inflammation, probably because of limited generation of chemotactic factors. These characteristics are related to the ability of porin 1A strains to bind to complement down-regulatory molecules, such as factor H and C4 binding protein [25,26], diminishing the local inflammatory response. Porin is an immunologic target of bactericidal and opsonophagocytic antibodies that arise after infection, or immunization with porin-containing vaccine candidates [27,28]. The critical role of humoral immunity is illustrated by the high rate of recurrent bacteremic gonococcal infection in patients with deficiencies of terminal complement components (C5-9) [29–31]. Up to 13% of patients with DGI have complement deficiencies [4], and persons with more than one episode of DGI should be screened with an assay for total hemolytic complement activity.
Epidemiology

The risk of DGI with gonorrhea infection was 0.5% to 3% in the 1970s, depending largely on the regional prevalence of specific strains of *N. gonorrhoeae* [4,10,11]. These strains were then endemic in the Northwestern United States, where DGI occurred in up to 3% of patients with gonorrhea [32]. Current rates of DGI are low because of declines in the prevalence of these strains, and an overall drop in gonorrhea prevalence since the early 1980s. In the preantibiotic era, DGI was reported primarily in men [33], but studies in the 1960s and 1970s reported a female predominance of 78% to 97% [1,4,7–10,32,34]. Menstruation is a major risk factor for dissemination. In about half of affected women, symptoms of DGI begin within 7 days after the onset of menses. Hormonal factors and the more alkaline pH of genital secretions during menses may facilitate growth of *N. gonorrhoeae*. The phenotypes of gonococci expressed during menses may be more likely to disseminate. Dissemination of *N. gonorrhoeae* from a rectal source is uncommon in homosexual men, because these strains express phenotypes that are unlikely to disseminate [35].

Clinical and laboratory features

The clinical manifestations of DGI and gonococcal arthritis have sometimes been classified into two stages: a bacteremic stage, or a joint-localized stage with suppurative arthritis. An obvious progression from the bacteremic to the joint-localized stage usually is not evident [4]. Patients in the bacteremic stage have higher fever, often accompanied by rigors. Polyarthralgias are common during gonococcal bacteremia, and may occur in conjunction with tenosynovitis and skin lesions. Painful joints often include the knees, elbows, and the more distal joints; the axial skeleton is generally spared. Skin lesions are seen in about 75% of patients with bacteremia, although they usually are painless and patients may be unaware of their presence. They typically number between 5 and 40, appearing on the extremities and sometimes on the trunk, but rarely on the face. Papules or small macules are the most common lesions, followed by pustules, often with a hemorrhagic component. A wide variety of skin lesions are associated with DGI (Fig. 1), including vesicles and bullae, and immunologic lesions, such as erythema nodosum, erythema multiforme, and urticaria. *N. gonorrhoeae* usually cannot be cultured from skin lesions by culture, and lesions may sometimes appear after appropriate antibiotic therapy has been started.

In the preantibiotic era, overt arthritis, confirmed by joint aspiration, was often reported; tenosynovitis was reported less frequently [32]. In more recent series of DGI, however, tenosynovitis was present in 67% to 68%, polyarthralgias in 52%, and monoarthritis in 42% to 48% [4,32]. The variable descriptions of these musculoskeletal manifestations may relate to...
different definitions of arthritis and tenosynovitis in different series. For example, a common criterion for arthritis requires the demonstration of purulent synovial fluid having greater than 25,000 leukocytes/mm³. Using this definition, frank arthritis may be less common than tenosynovitis accompanied by arthralgias [4]. It is unclear whether the increased reporting of tenosynovitis is related to a true change in the clinical manifestations, or whether it is simply resulting from increased recognition of tenosynovitis, instead of classifying all periarticular inflammation as arthritis. Tenosynovitis usually involves multiple sites, especially wrists, fingers, toes, and ankles. The differential diagnosis of the bacteremic stage of DGI includes reactive arthritis; acute rheumatoid arthritis; sarcoidosis; erythema nodosum; drug-induced arthritis; and viral infections (eg, hepatitis B and acute HIV infection). The distribution of joint symptoms in reactive arthritis, perhaps the most common differential diagnosis, differs from DGI (Fig. 2), as do the skin and genital manifestations [36,37].

Suppurative gonococcal arthritis usually involves one or two joints. The knees, wrists, ankles, and elbows are involved in decreasing order of frequency. The occurrence of arthritis in the absence of signs and symptoms of the bacteremic stage has led to the suggestion that these are separate
syndromes. Most patients who develop gonococcal suppurative arthritis do so without prior polyarthralgias or skin lesions. In the absence of symptomatic genital infection, this disease cannot be distinguished from septic arthritis caused by other pathogens. Other joints, such as the sternoclavicular and temporomandibular joints, and the small joints of the feet are occasionally involved. Rarely, direct extension of an infection from the small joints of the hand to adjacent phalanges results in osteomyelitis [14]. The synovial fluid leukocyte count in suppurative arthritis ranges between 40,000 and 60,000 cells/mm³ (with greater than 80% polymorphonuclear leukocytes) in most series reporting synovial fluid analyses. Mean synovial fluid leukocyte counts in gonococcal suppurative arthritis are similar to those in staphylococcal and other types of nongonococcal bacterial arthritis [38]. Synovial fluid analysis and tests for N gonorrhoeae (ideally, both culture and DNA amplification) are important in identifying patients with crystal-induced arthritis and gonococcal septic arthritis. Other forms of septic arthritis should also be sought routinely with specific tests for pyogenic and other bacteria. Synovial fluid leukocyte counts are useful in establishing the presence of inflammation, but not in establishing its cause. Protein, glucose, and complement levels provide nonspecific but sometimes useful information.

Fig. 2. Distribution of joints with arthritis in 102 patients with disseminated gonococcal infection and 173 patients with Reiter’s syndrome. *Sternal includes the sternoclavicular joints. †SI denotes the sacroiliac joint. (From Kousa M, Saikku P, Richmond S, et al. Frequent association of chlamydial infection with Reiter’s syndrome. Sex Transm Dis 1978;5:57–61; with permission.)
Gonococcal endocarditis, although rare today [39,40], was relatively common in the preantibiotic era, causing about one quarter of reported cases of endocarditis [41,42]. Central nervous system infections including meningitis [43] and epidural abscess [44] occur rarely.

Although most patients with DGI have fever and many have shaking chills, up to 40% are afebrile [4]. Most DGI patients deny local genitourinary, rectal, or pharyngeal symptoms, despite the fact that genital, anorectal, or pharyngeal gonococcal infection can be identified in 70% to 80% of patients with DGI or in their sex partners. All potential mucosal sites of infection should be tested for gonococcal infection, regardless of the presence or absence of local symptoms. In a series from Seattle, *N gonorrhoeae* was identified by culture or by antigen detection using a direct fluorescent antibody test on blood, synovial fluid, or skin lesions in 52 (51%) of 102 subjects with DGI [1]; in Boston 23 (47%) of 49 patients were so identified [4]. Recent sex partners should also be examined. DGI is sometimes confirmed bacteriologically only by detection of gonorrhea in a partner [1,45]. Similarly, *Chlamydia trachomatis* should be sought in DGI patients and their sex partners.

**Management**

Hospitalization is indicated if the diagnosis of DGI is unclear, if the patient has frank suppurative arthritis, or if the patient cannot be relied on to comply with treatment. DGI may require higher dosages of antibiotics and longer durations of therapy. Ceftriaxone, 1 g intravenously given daily, is the mainstay of antibiotic therapy for DGI. Cefotaxime or ceftizoxime, 1 g intravenously every 8 hours, can be substituted as an initial regimen. A diagnostic test for *C trachomatis* should also be performed on genital secretions or urine. The initial regimens for DGI should be continued for 24 to 48 hours after clinical improvement begins. Thereafter, therapy may be switched to a fluoroquinolone (eg, levofloxacin, 500 mg orally daily), used as continuation therapy to complete a full week of antimicrobial therapy [46]. Levofloxacin also treats possible co-infection with *C trachomatis*. Because of developing resistance, fluoroquinolones are no longer recommended for the treatment of gonorrhea in men who have sex with men, or for gonorrhea acquired in California, Hawaii, Asia, and the Pacific Islands [47]. Clinicians in other areas need to monitor local resistance trends to fluoroquinolones. Cefixime, 400 mg orally twice a day, can also be used as continuation therapy. Cefixime is currently available in the United States as a suspension; the tablet form has been subject to availability problems. Because cefixime does not effectively treat the possibility of *Chlamydia* co-infection, patients should receive either a single oral dose of azithromycin, 1 g, or doxycycline, 100 mg, twice daily for 1 week.

Closed drainage of purulent effusions should be performed once or twice, which is all that is usually necessary. Nonsteroidal anti-inflammatory drugs
may be indicated to alleviate pain, and are often useful to prevent recurrent joint effusions. Open drainage of suppurative joints is rarely necessary, but may be needed for joints that are difficult to drain percutaneously, such as the hip. All those who experience more than one episode of DGI should be evaluated for complement deficiency.

When the diagnosis is uncertain, a trial of antibiotic therapy may be warranted. Antibiotic-responsive, culture-negative acute arthritis in a sexually active young person often is caused by DGI. Blood cultures must be obtained before the therapeutic trial, not only to detect gonococcemia but also to help exclude other septic arthritides and infective endocarditis. Failure to respond to treatment necessitates evaluation either for other rheumatologic conditions, such as an acute presentation of a connective tissue disease, or another infection. If monoarticular supplicative arthritis persists during continued observation, synovial biopsy may be required to exclude tuberculosis, fungal infection, or a synovial tumor.

Summary

Septic arthritis caused by *N gonorrhoeae* is monoarticular or pauciarticular, and is more commonly associated with positive synovial fluid cultures and negative blood cultures. Gonococcal bacteremia is more likely to be associated with polyarthralgias and skin lesions. The diagnosis of gonococcal arthritis or DGI is also secure if a mucosal gonococcal infection is documented in the presence of a typical clinical syndrome that responds promptly to appropriate antimicrobial therapy. Hospitalization is indicated in patients with suppurative arthritis or when the diagnosis is in doubt. Initial treatment with ceftriaxone or another advanced-generation cephalosporin is warranted until signs and symptoms have improved; continuation of treatment for a total period of therapy of 1 week can be accomplished with a fluoroquinolone.

References


