Disseminated gonococcal infection

The tenosynovitis-dermatitis and suppurative arthritis syndromes[1]

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Neisseria gonorrhoeae **causes disseminated gonococcal infection (DGI), the most common form of infectious arthritis seen in both community and major teaching hospitals. The epidemiology, bacteriology, pathology, clinical manifestations, diagnosis, recommended treatment, complications, and prevention of DGI of connective tissue and skin are reviewed. The evidence of the need for a classification of DGI that recognizes two separate patterns of disease as opposed to a continuum is discussed. A classification that recognizes two separate patterns of disease (a tenosynovitis-dermatitis and a suppurative arthritis) is used to analyze and compare data from an earlier published study with a more recent investigation. The results of this analysis demonstrate the utility of the classification. This classification, based on the presence or absence of a synovial effusion, aids in diagnosis, allows prediction of complications and length of hospitalization, and suggests when oral antibiotic regimens may be used.**

Index terms: Arthritis, infectious • *Neisseria gonorrhoeae*

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The clinical spectrum of infections caused by *Neisseria gonorrhoeae* extends from a minor mucosal infection, which may be asymptomatic, to a disseminated blood-borne infection involving skin, joints, and rarely meninges, heart, and bone. While host defenses are usually adequate to isolate *N gonorrhoeae* to mucosal surfaces, it has become apparent that characteristics of certain strains of *N gonorrhoeae*, such as surface membrane components, nutritional requirements, antibiotic sensitivity, and resistance to killing by normal human serum, are more likely to cause dissemi-

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nated gonococcal infection (DGI). Additionally, these characteristics appear to determine the clinical pattern of the DGI of skin and connective tissue. One pattern is a tenosynovitis-dermatitis and the other is a suppurative arthritis. These and other aspects of the DGI of skin and connective tissue are reviewed.

Host factors—epidemiology

Incidence

DGI is the most common form of infectious arthritis seen in both community and major teaching hospitals.[1,2] The incidence of DGI parallels the incidence of uncomplicated gonorrhea. In 1983, 900,435 cases (388/100,000) of uncomplicated gonorrhea were reported to the Centers for Disease Control.[3] It is estimated that there are an equal number of unreported symptomatic cases of gonorrhea. Additionally, there are unrecognized asymptomatic cases equal in numbers to the symptomatic cases. Of this total of approximately 4 million cases per year, DGI will develop in 0.1% to 0.3%.[4] If the total number of estimated symptomatic and asymptomatic cases of gonorrhea is used to calculate yearly incidence, the rate of DGI is 2.8/100,000. This incidence is approximately the same as that of primary and secondary syphilis. There has been only a slight decline in the reported incidence of gonorrhea since the highest incidence in the mid-1970s of 450/100,000. While host defenses usually prevent dissemination of infection, the stable large total number of cases of uncomplicated gonorrhea each year ensures a correspondingly high incidence of DGI.

Sex

Although slightly more males (60%) than females (40%) are reported to have uncomplicated gonorrhea, DGI is more likely to develop in three to five times more females.[1,2] The sex ratios have completely reversed since early reports of gonococcal arthritis by Keefer and Spink in 1937.[5] In that report, gonococcal arthritis was reported three times more frequently in the male than in the female.

Age

The age range of patients with DGI is similar to that of uncomplicated gonorrhea with 75% of cases in the 15- to 30-year age group.[3]

Psychosocial factors

The age-related incidence of gonorrhea is probably due to the increase in recent years in members of the 15- to 30-year-old group with multiple sexual partners. The heterosexual male incidence of gonorrhea is 20 times higher among those with five or more sexual partners compared to those with one[6]; homosexual men with multiple sexual partners are at increased risk of acquiring gonorrhea.[7]

Gonorrhea shows an intense concentration in central urban areas with concentric circles of diminishing incidence.[8] The central areas are characterized by high population density, low socioeconomic status, and a 20- to 40-fold increased risk of gonorrhea compared to other geographic areas. Asymptomatic infections maintain this increased risk. The prevalence of infections in central urban areas is as high as 20%.

Menstruation and pregnancy

Some studies show that women are more susceptible to DGI during the first week of menstruation, during pregnancy, and postpartum.[1,2,4] This increased risk is hypothesized to be related to local host factors, specifically that bacteremia is more likely to occur following menstruation when cervical pH is more conducive to gonococcal growth, peroxidase bactericidal activity of cervical mucus is lessened, and endocervical shedding of organisms is maximal.[7] The expression of transparent colony phenotype and certain cell wall proteins have been related to the menses.[10] These characteristics may be associated with more virulent strains that are able to disseminate.

Site of initial colonization

Pharyngeal colonization has been suggested to be associated with DGI more often than other primarily infected mucosal sites and has been proposed as a risk factor.[11] However, a recent prospective study found that only 5 of 49 patients with DGI had positive pharyngeal cultures.[1] This was not a significantly increased number as compared to other primary sites of infection. Thus, no primary site of infection has been proved to predispose to dissemination.

Asymptomatic infection

The association of asymptomatic mucosal infection with DGI has been found in most stud-

ies.[1,9,11] Additionally, local invasive complications such as pelvic inflammatory disease and epididymitis rarely occur simultaneously with DGI. The strain of *N gonorrhoeae* isolated from individuals with asymptomatic mucosal colonization and from DGI have similar nutritional requirements (auxotypes). The strain requires the nucleic acids arginine, hypoxanthine, and uracil (AHU auxotype) for growth. This strain appears to produce less attraction of inflammatory cells to the site of infection.[12,13] This nutritional requirement does not explain the virulence of the strain, but suggests that it has special but as yet unknown properties and may provide the basis for further epidemiologic study.

Complement deficiency

Hereditary deficiencies of complement factors are rare, but have been reported in association with recurrent infections of either *Neisseria meningitidis* or *N gonorrhoeae* and occasionally both organisms. A recent review of the 242 reported cases of complement component deficiency disclosed 11 patients who had 23 episodes of DGI.[14] Two of the 11 also had a history of infection with *N meningitidis*. The infections occurred predominantly in young black women (median age, 21 years) with deficiencies of one of the terminal pathway components (C5, C6, C7, C8). These components form the "membrane attack complex," which is important in cell membrane lysis.

Bacteriology

N gonorrhoeae is a gram-negative diplococcus whose only natural host is the human body. It has relatively fastidious requirements for in vitro culture and quickly perishes in an unprotected environment. Its transmission in humans usually requires direct exposure of infected secretions (mucus, semen) to mucous membranes of the pharynx, urogenital tract, or rectum. Characteristics of certain strains of *N gonorrhoeae* have been associated with DGI. These characteristics are surface membrane components, nutritional requirements, antibiotic sensitivity, and serum resistance.

Surface membrane components

The gonococcal surface membrane is complex and is similar to that of other gram-negative bacteria such as *Escherichia coli* and *Salmonella typhimurium*. Earlier studies of these organisms have led to an understanding of the similar gonococcal surface membrane. The pathophysiology of the surface membrane components (pili and a membrane composed of proteins, lipopolysaccharides [LPS], and phospholipids) are discussed.

Pili: Pili are proteinaceous "hairlike" surface projections of gonococci, which promote infectivity by facilitating the adherence of gonococci to muscosal surfaces and enabling resistance to phagocytosis by human polymorphonuclear neutrophil leukocytes (PMNs). The evidence of facilitated adherence of gonococci to mucosal surfaces is based on several observations. First, piliated gonococci are exclusively associated with two distinctive colonial morphologies on in vitro culture (colonial types 1 and 2). These colonies appear on culture of freshly isolated clinical specimens.[15–17] On repeated culture of these organisms in the laboratory, they lose their pili and assume a different appearance on the agar plate (colonial types 3 and 4). Colonial types 1 and 2 (with pili) are significantly more infective when inoculated into urethras of male volunteers. Second, pili adhere to the surfaces of human cells. Pili readily attached to human erythrocytes, spermatozoa, tissue culture cell lines of epithelial cells, and to fallopian tubes in organ culture. Radiolabeled pili attach to human oral and vaginal mucosal cells. Anti-pili antibodies in urogenital secretions inhibit the attachment of piliated gonococci to epithelial cells.[18]

Piliation is associated with resistance of virulent gonococci to phagocytosis by human PMNs. Colonial type 1 (piliated) gonococci attach to the PMN surface but are not ingested. Colonial type 3 (nonpiliated) are readily ingested after attachment.[18]

Pili are immunogenic and have determinants that are both type-specific (homologous) and cross-reactive (common). Like other gram-negative bacteria, gonococci have a remarkable antigenic diversity. Human anti-pili antisera prepared by systemic immunization detect 50% of the shared antigenicity between heterologous gonococcal strains. This lack of shared antigenicity has complicated development of an effective gonococcal pilus vaccine.

Membrane: Once gonococci adhere to the surface of epithelial cells utilizing their pili, they enter or are "interiorized" by the epithelial cells and are transported to the basal part of the epithelial cell. They then leave the surface epi-

thelial cell and are deposited on the lamina propria. In this way, the gonococci have evaded a major host defense—the mucosal epithelium. Since nonpiliated organisms are able to enter the epithelial cell, the most likely surface membrane component responsible for this is the outer membrane or cell wall of the gonococcus.[19] Like other gram-negative bacteria, the gonococcal outer membrane consists of an outer layer of lipopolysaccharide and an inner layer of phospholipid with the protein components of the membrane asymmetrically located.

The proteins of the membrane appear to be the activators of the host cell interiorization of gonococci. The proteins have been separated by physical chemical methods into three designated proteins. Protein I has the ability to form channels in lipid membranes. It has a similar amino acid sequence to *E coli* and *S typhimurium* proteins that create aqueous pores in cell membranes. Each particular strain of gonococcus expresses predominantly one type of protein I. This protein is a major antigen, which enables classification of a large number of strains into 16 specific serotypes. A limited number of strains as determined by these serotypes cause DGI. The group designated WI has comprised the majority of strains that cause DGI in several locations[1,20] and represents only a minority of the strains that cause DGI in other locations.[21]

Protein II appears to be involved in creating intercellular adhesions between neighboring gonococci, and causes the opaque appearance of colonies when grown in vitro. Colonies lacking protein II appear transparent. Strains with the transparent phenotype are more invasive, may be more resistant to the killing action of normal human serum, and more often isolated from disseminated sites of infection.[1] The phenotype of gonococci change from opaque to transparent during menses.[10] Thus, changes in the endometrium or cervix associated with pregnancy or menses may select strains of gonococci that are more virulent. This transformation to transparent colony type may, in part, account for the increased female incidence of DGI noted previously. Protein III appears to be linked within the outer membrane to a trimer (three molecules) of protein I.

Protein III appears to be identical in all strains of *N gonorrhoeae*.[19] It may serve primarily as a structural base for protein I as it is located on the pericytoplasmic (inner) aspect of the membrane. Its function in the pathogenesis of infection is unknown.

Nutritional requirements

Most gonococcal strains isolated in DGI have particular nutritional requirements or auxotype.[22,23] The growth medium requires the AHU auxotype. In one study, 58% of the gonococcal strains isolated in DGI had an AHU auxotype. In contrast, only 8% of the strains isolated in cases of uncomplicated gonorrhea had an AHU auxotype. These AHU gonococci seem to be less efficient in attracting inflammatory cells to the site of infection or colonization.[12,13] This lack of local inflammatory response probably best explains the observation mentioned previously that the primary sites of colonization in most DGI are asymptomatic.

Antibiotic sensitivity

Strains of gonococci that cause DGI have maintained an exquisite sensitivity to penicillin at present. Other strains that cause pelvic inflammatory disease for example require concentrations of penicillin three times higher than DGI strains to inhibit in vitro growth.[23] Cases of DGI caused by penicillinase-producing *N gonorrhoeae* (PPNG) have been reported, but appear to be rare even in areas with an increased incidence of uncomplicated gonorrhea caused by PPNG.[24,25]

Resistance to killing by normal human serum

Strains of *N gonorrhoeae* that cause uncomplicated gonorrhea are sensitive to the lytic and bactericidal action of serum antibody and complement. However, most strains that cause DGI are not killed by normal human serum.[26] This resistance to the usual killing ability of normal human serum may be achieved by recently identified naturally occurring human antibodies that bind to DGI strains of gonococci. These antibodies have been called "blocking antibodies" because they interfere with or block the normal antibody and complement-dependent lysis and killing of gonococci.[27,28] Protein I is most likely involved in binding this blocking antibody, but the exact outer membrane site of binding has not been demonstrated. The resistance to killing of DGI strains has clinical significance because these strains are more often isolated in patients with

Table 1. Bacteriologic properties of strains of *Neisseria gonorrhoeae* that disseminate

Surface membrane components
Pili are present on all pathogenic strains
Protein I of certain serotypes: coagglutination group WI
Transparent colonial phenotype
Nutritional requirements
AHU auxotype
Antibiotic sensitivity
Exquisitely sensitive to penicillin
Resistance to killing by normal human serum
The majority of strains isolated in DGI

AHU = arginine, hypoxanthine, uracil; DGI = disseminated gonococcal infection.

tenosynovitis-dermatitis (75%) than in patients with suppurative arthritis (47%).[1]

Interestingly, it has been found that the strains of *N gonorrhoeae* that infected patients with complement-component deficiencies were strains that were resistant to killing by normal human serum.[14] It might be assumed that complement-deficient patients would be most susceptible to those strains that were serum sensitive. The lack of a functioning terminal pathway should allow these serum-sensitive strains to avoid the lytic effect of the "membrane attack complex" and more easily disseminate. However, it has been demonstrated that serum-sensitive organisms are readily phagocytosed and killed by neutrophils in complement-deficient patients, while serum-resistant organisms are not efficiently ingested and killed in either normal or complement-deficient serum. These findings suggest that serum bactericidal activity of complement is not the only mechanism by which complement acts in defending the host against dissemination.

A summary of the bacteriologic properties of strains of *N gonorrhoeae* that disseminate is presented in *Table 1*.

Pathology

The pathology of septic arthritis of DGI is unlike other models caused by other organisms in which the majority of cultures of blood and synovial fluid are simultaneously positive.[29] In DGI, most blood and synovial fluid cultures are negative. When synovial fluid cultures are positive in DGI, the blood cultures are invariably negative.[1,30–32] Cultures of the skin lesions of DGI are rarely positive.[1,4,9,33] These findings and other evidence have led to speculation that some of the pathology seen in DGI may be due to immune-mediated or hypersensitivity phenomena caused by gonococcal antigens.

Dermatitis

It has been postulated that skin lesions of DGI are due to direct tissue invasion and secondary inflammation by *N gonorrhoeae*.[32] However, cultures of skin lesions are rarely positive.[1,4,9,33] Although this might be due to the small number of gonococci in the lesions or their fastidious growth requirements,[22] evidence suggests that the skin lesions may be due to immune or hypersensitivity phenomena. Gonococcal antigens were found by immunofluorescent staining techniques in 14 of 16 sterile skin lesions[33] and histopathological descriptions of the skin lesions frequently disclose a polymorphonuclear vasculitis similar to a Schwartzman reaction. Other forms of noninfectious dermatitis such as urticaria erythema multiforme, and erythema nodosum have also been described.[1,33]

Tenosynovitis

Tenosynovitis and transient arthralgias, the most common clinical manifestations of DGI, closely resemble the symptoms in the immune complex arthritis of hepatitis B or serum sickness. These symptoms are not present in the typical purulent bacterial arthritis such as that produced by *Staphylococcus aureus*.[34] Circulating immune complexes have been identified in DGI, but unlike other immune complex diseases, the immune complex levels do not drop after successful treatment for DGI.[35,36]

Suppurative arthritis

The pathophysiology of suppurative arthritis of DGI had been considered to be similar to that of staphylococcal arthritis with usually purulent synovial fluid and recovery of viable organisms on culture. However, more than half of the synovial fluid cultures for *N gonorrhoeae* are negative and simultaneous blood cultures are invariably negative, unlike staphylococcal arthritis in which most synovial fluid cultures are positive and organisms can simultaneously be cultured from blood. Unlike other forms of purulent bacterial arthritis, suppurative arthritis of DGI rarely leads to significant joint destruction, even if unrecognized early and treatment is delayed. There is good evidence that the suppurative arthritis of DGI was often self-limited and resolved spontaneously in the preantibiotic era.[37] The pathological changes in the joint space and synovial tissue are usually limited to production of a purulent synovial fluid (average leukocytosis, white blood cell (WBC) count, 60,000 μL) and mild synovial inflammation. Circulating immune complexes in DGI may play a part in the pathogenesis of suppurative arthritis. One study found circulating immune complexes, using the Clq binding technique in 11 of 12 patients with DGI and speculated that these immune complexes might produce an initial sterile synovitis that could later promote the entry of gonococci into the synovial space.[38] Other investigators have recently developed an experimental model of suppurative arthritis in rabbits.[39] The intra-articular injection of *N gonorrhoeae* resulted in a suppurative arthritis identical to that following injection of *S aureus, E coli* and group A β-hemolytic streptococcus. Unlike the other bacteria, *N gonorrhoeae* could not be cultured from synovial fluid only two hours after the injection of a large number of organisms. The other bacteria could be cultured days to weeks after a single inoculation of organisms.[39] Additional experiments in which killed *N gonorrhoeae* or lipopolysaccharide antigen were injected resulted in histologic changes identical to those caused by live organisms. This model demonstrates one of the peculiar properties of the suppurative arthritis of DGI: the inability to culture organisms from synovial fluid. Thus, the suppurative arthritis of DGI may occur as the result of either the direct toxic effect of the live gonococcus, surface membrane antigens, immune complexes, or a combination of these effects.

Clinical manifestations

The clinical manifestations of DGI in the antibiotic era have been reported in many series during the past two decades.[1,2,4,9,30,31,40–45] These series come from large urban teaching hospitals, and, in this setting, DGI is the most common cause (40% to 52%) of infectious arthritis.[2,4] While there is agreement on most of the clinical features of DGI, there has been a continuing controversy regarding their pattern and sequence of development. The mutually exclusive nature of blood and synovial fluid cultures in DGI has offered an attractive scheme for classification of patients. However, unlike the models of staphylococcal or streptococcal infectious arthritis, only the minority of patients with DGI have either a positive blood (18% to 26%) or synovial fluid (20% to 29%) culture.[1,30,40,41] Most DGI patients cannot be classified on the basis of "proved" systemic cultures and are in a "transitional" or "indeterminant" category. They have been classified with schemes combining the results of positive cultures from primary mucosal sites and various clinical aspects of DGI.

Populations at risk

Women: Women aged 15 to 30 years (mean age, 23 years) account for 57% to 97% (mean, 78%) of persons with DGI. Onset of last menses of less than one week, pregnancy, and the postpartum period have been reported to be associated with DGI; however, only two studies in the past two decades have reported significance of frequencies of these conditions associated with DGI.[9,41] The chances of a woman being in the week interval following onset of menstruation at a given time is 25%. Two other studies[1,40] reported only 20% of patients with DGI who were in this interval, which is not significant. The incidence of pregnancy has been reported as 20% to 27% in series of patients with DGI in the 1960s[9,29–31] and has decreased to 11% to 15% in the 1970s.[1,2,4] Considering age, declining birth rate, and socioeconomic status, the incidence of pregnancy in patients with DGI may not be significant.

Other populations: Patients with DGI usually reflect the racial makeup of the population that the hospital serves. In urban areas such as Cleveland,[40] Memphis,[41] and Philadelphia[30] more than 90% of the patients with DGI are black. In suburban Detroit[2] and Seattle,[43] most patients with DGI are white. Homosexual men have a higher

reported incidence of uncomplicated gonorrhea, but the only study of DGI that reported results of sexual orientation found 2 of 14 males were homosexual.[1] This probably does not exceed the number expected by chance alone. Likewise, intravenous drug abuse, alcoholism, corticosteroid use, and diabetes mellitus have been associated with DGI, but there is no evidence that the association is anything but coincidental.

Presenting symptoms

Most patients with DGI present within three to five days of onset of symptoms with acute polyarthralgias as the most common symptom; 60% of patients have polyarthralgias and 40% have a monoarthralgia. Half of the patients with polyarthralgias have two or three painful joints and half have four or more painful joints.[1,40,41] Only a quarter of patients mention skin lesions at presentation.[41] Most patients (60% to 90%) do not report any genitourinary symptoms.[1,9,40]

Presenting signs

Skin lesions: On examination 47% to 80% of patients with DGI have typical skin lesions, which are initially tiny pink or red macules that blanch with pressure. They vary from 1 to 20 mm in diameter. They progress to papular, vesicular, petechial, and pustular stages with or without a necrotic center and usually have a hemorrhagic base. Pustules may rupture to form shallow ulcers. Infrequently, large bullae may occur. Initially the lesions are painless, nonpruritic, and usually appear during the first few days of infection. They occur in small numbers and are unevenly distributed on the trunk and extremities, including the palmar and plantar surfaces. The most common site is the distal portion of the extremities near the periarticular region. The face, scalp, and oral mucosa are usually not involved. Lesions are often seen in various stages of development and resolve within four to five days, usually without scarring.[46]

Tenosynovitis and arthritis: The connective tissue manifestations of DGI include both tenosynovitis and suppurative arthritis. Clinical criteria differentiating these two entities are not clear in most large case studies we reviewed. Admittedly, tenosynovitis of DGI is transitory and migratory, making a standardized assessment difficult. In some circumstances, distinguishing tenosynovitis from suppurative arthritis may be impossible without a diagnostic aspiration performed by an experienced clinician. Because of the difficulty in assessing tenosynovitis, few reports have given more than descriptive details. There is agreement that the hand and fingers are involved in half of the patients with tenosynovitis. Tenosynovitis involves the wrist in a quarter of patients; the ankle and knee in less, and the foot, elbow, and shoulder in even less.[2,30] Suppurative arthritis in DGI can be demonstrated by a large suppurative effusion (WBC, 30,000 to 80,000/μL) most often of the knee. Suppurative arthritis less often involves the wrist, ankle, and elbow and rarely the hip and shoulder.[2,4,30,40]

Mucosal signs: Although the primary mucosal infection in DGI is usually asymptomatic, a quarter to a half of patients in whom the urethra and cervix are examined have genitourinary signs of the primary infection. Infections of the rectum and pharynx are usually asymptomatic and are not detectable on clinical examination.[1,40]

Systemic signs: Most DGI patients have no fever or chills. If present, fever is rarely greater than 39 °C. This is in marked contrast to other bacterial arthritides.[1,2,4,31,40]

Laboratory findings

Sites of positive culture: Positive culture for infection of systemic sites in DGI is found in 18% to 26% of synovial fluid and 20% to 29% of blood cultures.[1,40,41] Primary mucosal infection is most frequently documented by genitourinary cultures. Cervical cultures in women with DGI are positive in 82% to 90% of cases. Urethral cultures in males with DGI are positive in approximately 50% to 60%.[1,30,44] Pharyngeal cultures are positive in 10% to 20% of cases and rectal cultures in 15%.[1,30] Aside from blood and synovial fluid cultures, there do not appear to be other mutually exclusive sites.

Peripheral blood findings: Mean peripheral blood leukocyte counts in most large series of patients are 11,000 to 12,000/μL and usually do not exceed 20,000/μL.[1,9,40,42] Erythrocyte sedimentation rates (ESR) are increased above 50 mm/hr in approximately half of patients with DGI.[1] Anemia when present is usually not related to DGI. One case of acute transient hemolysis has been noted.[9] Transient elevations of serum glutamic oxaloacetic transaminase (SGOT) although usually mild, have been noted in as many as a quarter of patients with DGI.[1,9] Such elevations have been noted in bacteremia caused by a variety of bacteria.[47]

Total hemolytic complement (CH50) is normal or elevated in almost all patients with DGI. Patients rarely have decreased activity of the "membrane attack complex," C6–8, and decreased levels of multiple components as in systemic lupus erythematosus or other consumption disorders.[1,4,14] A complement deficiency should be suspected if a patient has recurrent DGI, a history of prior *N meningitidis* infection, or a family history of such infections. The diagnosis of complement deficiency is most easily established by performing a CH50 study. If this activity is significantly depressed, further testing using assays for the individual complement components is needed to establish the specific component deficiency.

Classification of patients with DGI

Classification of patients with DGI simplifies diagnosis of DGI, which may be obscured because of its varied presentation. Previous classification schemes separated patients with positive blood cultures from those with positive synovial fluid cultures. Patients with positive synovial fluid cultures normally had suppurative arthritis. Unfortunately, most of the patients remained unclassified. Further classification relied on clinical signs, many of which are brief and subtle, thus subject to various interpretations. Some investigators proposed a continuous (sequential) process of initial bacteremia (positive blood cultures, higher temperature, chills, tenosynovitis, and skin lesions) followed later, if untreated, by a joint-localized stage (positive synovial fluid culture, suppurative arthritis).[9,40] However, the utility and accuracy of this scheme was disputed by others who found similar clinical features in both of the proposed stages and found no significant difference in the time between initial symptoms and later clinical signs or positive cultures.[1,30,31]

Recently O'Brien et al[1] have suggested a classification scheme based on the presence or absence of a joint effusion. Patients with typical skin lesions and/or tenosynovitis and no joint effusions were placed in group 1. Aspiration was attempted in patients with questionable joint effusion, but no fluid was obtained in any of these. Patients with joint effusions who had suppurative arthritis as demonstrated by purulent synovial fluid on arthrocentesis were placed in group 2. This scheme has an immediate advantage of classifying patients from the time of first presentation on the basis of a single characteristic: the presence or absence of purulent synovial effusion. The findings of this study from 1975 to 1982 are compared to those of Keiser et al[40] from 1963 to 1967. While the earlier study classified patients on the basis of the presence or absence of synovial fluid (*Table 2*), Keiser et al recorded "number of joints involved" and a positive or negative "joint fluid culture." To compare the two studies, it was assumed that if synovial fluid was not cultured it was not obtained and that in the absence of joint fluid, the joint involvement was tenosynovitis rather than suppurative arthritis. It was assumed that "involved" meant symptomatic. The data regarding presenting symptoms and signs shows that more group 1 patients have skin lesions and tenosynovitis than group 2 patients. Additionally, 18 of 19 positive blood cultures occur in group 1. The data of Keiser et al but not that of O'Brien et al indicated that polyarticular symptoms and fever and chills occur more often in group 1 patients and that a monoarthritis occurs more often in group 2 patients. The duration of symptoms before hospitalization is nearly the same except that the Keiser et al group 1 patients were admitted 9.5 days after admission. This mean number was influenced by 3 patients who presented more than 25 days after onset of symptoms. The mean time after omitting these 3 patients was 2.6 days. In the original analysis, Keiser et al found the mean time of positive blood culture to be 1.5 days after onset of symptoms. This was based on 6 patients with positive blood cultures. Similar data showing a shorter duration of symptoms before positive blood cultures than before synovial cultures has been reported[48] but disputed by others.[1,30,31] O'Brien et al found no difference between the duration of symptoms before hospitalization in group 1 and group 2. The duration for both groups was four days. The data of other studies does not allow reanalysis. Additional information suggesting that different strains (as reflected by variation in resistance to killing by normal human sera) may produce different clinical manifestations is presented in the data of O'Brien et al in *Table 2*. There is a difference in resistance to normal serum with 18/24 (75%) of strains isolated in group 1 and 9/19 (47%) in group 2. O'Brien et al found that the duration of hospitalization for patients was four days for group 1 and seven days for group 2.

Thus, grouping patients with no synovial effusion (group 1) includes patients with positive

Table 2. Clinical and laboratory features of patients with disseminated gonococcal infection

	Group 1 (Tenosynovitis/Skin Lesions)		Group 2 (Suppurative Arthritis)	
	Keiser et al[40]	O'Brien et al[1]	Keiser et al[40]	O'Brien et al[1]
No. of patients	16	30	14	19
Sex	15-F, 1-M	23-F, 7-M	14-F, 0-M	12-F, 7-M
Presenting symptoms				
Monoarticular	0 (0%)	7 (23%)	6 (43%)	5 (26%)
Polyarticular	16 (100%)	18 (60%)	8 (57%)	13 (68%)
Presenting signs				
Fever/chills	12 (75%)	15 (50%)	6 (43%)	6 (32%)
Tenosynovitis (polyarthritis)	16 (100%)	26 (87%)	7 (50%)	4 (21%)
Skin lesions	10 (63%)	27 (90%)	4 (29%)	8 (42%)
Cultures positive				
Blood	5 (31%)	13 (43%)	1 (7%)	0 (0%)
Synovial fluid	0 (0%)	0 (0%)	8 (57%)	9 (47%)
Blood and synovial fluid	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Duration of symptoms before admission (days)	9.5 2.6*	4	5.2	4
Length of hospitalization (days)	ND	4	ND	7
No. of strains resistant to normal human serum	ND	18/24 (75%)	ND	9/19 (47%)

*Average duration of symptoms if 3 patients are excluded who presented >25 days after onset of symptoms.
ND = no data.

blood cultures, who more frequently have clinical signs of tenosynovitis, skin lesions, and infection with serum-resistant organisms. Group 1 patients are also likely to be hospitalized for shorter periods. Patients with a suppurative synovial effusion (group 2) less often have tenosynovitis, skin lesions, rarely have positive blood cultures, and more often are infected with serum-sensitive organisms. Although a larger series would be necessary to confirm the significance of these data, this scheme enables immediate classification of all patients on a single relatively objective criteria. This aids in subsequent formulation of differential diagnosis, selection of treatment, and predicting prognosis.

Diagnosis

The typical patient with DGI is a young woman between 15 and 30 years of age, usually seen in an urban hospital serving the lower socioeconomic class. DGI is the most common form of acute nontraumatic arthritis seen in this setting. The clinical diagnosis indicated from the signs just discussed can be confirmed by culture and response to appropriate treatment.

Culture technique

Multiple cultures must be obtained in suspected DGI. Since most blood and synovial fluid cultures are negative, all potential mucosal sites must routinely be cultured. Specimens from mucosal sites must be grown on a special medium that allows the growth of gonococci but contains antibiotics that inhibit the growth of other nonpathogenic bacteria (normal flora). Thayer-Martin agar is such a medium and should be used for urethral, cervical, rectal, and pharyngeal cultures. Skin cultures rarely show growth and should not routinely be obtained. The urethra should be cultured in women who have had a hysterectomy in which the cervix was removed. A chocolate agar medium should be used for synovial fluid cultures as it is not necessary to inhibit other bacteria. The antibiotics in Thayer-Martin medium may decrease yields of gonococci on synovial fluid culture. Either medium should

be warmed before inoculation. This may be done by placing the agar plate with the agar side next to the skin in a pocket or under the arm for 5 to 10 minutes. Several sets of aerobic-anaerobic blood cultures should be routinely obtained.

Indirect detection of gonococci

Until recently, Gram's stain has been the only routinely available test for quickly detecting gonococci in clinical specimens outside of research laboratories. Gram's stain has been used principally to identify gram-negative diplococci within PMNs in purulent urethral discharges from males. The sensitivity and specificity of diagnosing gonorrhea in the male when typical organisms are seen in a purulent urethral discharge is equal to that of a urethral culture. Gram's stain for other specimens such as cervical discharge and skin scrapings has little diagnostic utility. A recently available enzyme immunoassay method for detection of gonococcal antigen has been developed and studied. Unfortunately, it has no better sensitivity in detecting gonococci in purulent urethral discharges and has a better but not a clinically useful increase in sensitivity and specificity compared to Gram's stain of cervical discharge.[49]

Differential diagnosis

The typical case of DGI is not usually difficult to distinguish from other arthritides particularly if skin lesions are present. In the 15- to 30-year-old group, especially in males, it may be necessary to differentiate Reiter's syndrome from DGI. Distinguishing features of Reiter's syndrome are the usual absence of fever and chills and lower extremity predominance of arthritis and tenosynovitis (especially the heel) with little migratory tendency. The skin lesions of Reiter's syndrome are hyperkeratotic on the palms and soles, and the mucosal lesions are erosive. These skin and mucosal lesions are not seen in DGI. Conjunctivitis rarely occurs in DGI. Spondylitis and HLA-B27 tissue type are not associated with DGI.[50] Infectious arthritis caused by other bacteria is distinguished by more frequent involvement in males, sparing teenagers and young adults, frequent presentation as a monoarthritis affecting large joints of the lower extremity, absence of tenosynovitis and rash, and its predilection for compromised hosts and drug addicts using the intravenous route. Patients with other bacterial arthritis often have other nonvenereal sites of infection. Because of the declining incidence of acute rheumatic fever, it is not often considered in the diagnosis of a patient with migratory polyarthralgias. However, it can be distinguished in children and young women by its high temperature, specific skin lesions if present, and confirmatory laboratory findings. Neither acute rheumatic fever nor Reiter's syndrome respond to the antibiotic treatment for DGI.

Treatment

The treatment of DGI is relatively straightforward once the diagnosis is entertained and measures have been taken to confirm it. Response to treatment is rapid and complications are unusual. Hospitalization is usually indicated for patients who have purulent joint effusions (group 2) because frequent aspiration may be necessary to manage the effusion. Those with an uncertain diagnosis may be hospitalized for observation and/or presumptive therapy. Perhaps the most important assessment in determining treatment is patient compliance. Effective treatment regimens are available for outpatient treatment of tenosynovitis-dermatitis (group 1); however, if the patient is not compliant, complications may result, symptoms may continue, and the patient may remain a carrier of an invasive strain of *N gonorrhoeae*. If it is thought that the patient is not compliant, hospitalization is indicated. The Centers for Disease Control[51] recommended the following treatment schedules:

1. *Aqueous crystalline penicillin G* (10 million units, administered intravenously, per day) until improvement occurs, followed by amoxicillin (500 mg) or ampicillin (500 mg) by mouth, four times a day, to complete at least seven days of antibiotic treatment; or
2. *Amoxicillin* (3.0 g) or *ampicillin* (3.5 g) by mouth, each with probenecid (1.0 g) followed by amoxicillin (500 mg) or ampicillin (500 mg) by mouth, four times a day for at least seven days; or
3. *Tetracycline HCl* (500 mg) by mouth, four times a day, for at least seven days, but not for complicated gonococcal infections in pregnant women; or
4. *Cefoxitin* (1.0 g) or *cefotaxime* (500 mg) given four times a day, intravenously, for at least seven days—the treatment of choice for disseminated infections caused by penicillinase-producing *N gonorrhoeae* (PPNG); or

5. *Erythromycin* (500 mg) by mouth, four times a day for at least seven days.

Controlled studies with penicillin, ampicillin, amoxicillin,[43–45] erythromycin,[43,45] and tetracycline regimens have demonstrated all to be equally effective in compliant patients. Other studies have shown excellent response to intramuscular procaine penicillin G.[41,44]

Complications

Treatment is usually uncomplicated. Suppurative effusions may require repeated aspiration, but open drainage is rarely necessary. Destruction of cartilage and bone is rare. Length of hospitalization is approximately twice as long for suppurative arthritis (seven to eight days) as for tenosynovitis-dermatitis. Intraarticular injection of antibiotics is unnecessary. Meningitis and endocarditis are rare complications of DGI; they are treated with high-dose aqueous crystalline penicillin G. Optimal duration of therapy is unknown, but most authorities treat patients for a month. Penicillinase-producing *N gonorrhoeae* (PPNG) have rarely been reported to cause DGI. These cases have occurred only in areas where PPNG are endemic. Only seven cases of DGI caused by PPNG had been reported in the literature by early 1983.[24,25] Although strains that cause DGI are usually exquisitely sensitive to penicillin, all gonococcal cultures should be routinely checked for production of penicillinase. *Table 3* summarizes the major clinical characteristics of DGI.

Table 3. Major clinical aspects of disseminated gonococcal infection

Sex
Women affected three to five times more often than men
Asymptomatic
Mucosal sites of primary infection are usually asymptomatic, but cultures of one or more sites are usually positive
Antibiotic treatment
Effects rapid improvement
Two major patterns of disease
Tenosynovitis-dermatitis (group 1)
Tenosynovitis and/or typical skin lesions are present
Blood cultures are positive in <40%
May be treated with oral antibiotics on an ambulatory basis (if compliant patient)
Suppurative arthritis (group 2)
Purulent synovial fluid aspirated
Synovial fluid cultures are positive in <50%
Blood cultures negative
Persistent effusion treated with repeated aspiration
Hospitalization is recommended and is longer than other DGI patients

Prevention

Efforts to prevent both DGI and uncomplicated gonorrhea have been comparable. While the number of cases of uncomplicated gonorrhea stabilized in, and has decreased slightly since, the late 1970s, this probably represents the period when those of the "baby boom" generation were in their teens and twenties, their years of highest incidence of gonorrhea. The high incidence of asymptomatic infection makes detection ineffective without large scale screening of populations at risk. Resources are not available to undertake such a task and although screening of males with first-voided urine cultures is painless, compliance among women for screening of cervical cultures could be predicted to be poor. "Barrier" methods of contraception offer some protection from transmission of gonorrhea for both partners. Condoms offer protection to heterosexual and homosexual males with numerous sexual partners. Diaphragms and spermicidal preparations provide a degree of protection for women. An effective gonococcal vaccine, which would allow primary prevention of gonorrhea (prevention of new cases) and which could be offered to the populations at risk, has not yet been developed. Schoolnik et al[18] have shown that antisera directed at pili may block mucosal adherence and colonization by gonococci. For this reason, pili have been proposed as constituents of a gonococcal vaccine. However, gonococcal pili are antigenically heterogenous and the protection conferred by a vaccine composed of denatured pilus filaments from a single gonococcal strain appears to be strain specific. Yet, it has been found that there is a weak cross-reactivity between the antisera of pili of different strains. This suggests a common determinant. Characterization of such a common determinant might lead to a suitable immunogen for the development of a gonococcal vaccine.[52]

Summary

Bacteriologic properties of certain strains of *N gonorrhoeae* and the clinical aspects of DGI can be combined to describe two distinct types of

disease: one associated with a tenosynovitis-dermatitis and the other with a suppurative arthritis. This classification clarifies the diagnosis of DGI and indicates which patients might be considered for outpatient treatment and, if hospitalized, predicts length of stay. Previously published data were analyzed with this method of classification and its utility and validity were confirmed. A diagnosis of DGI can usually be made on clinical grounds. Treatment can be undertaken with rapid resolution of symptoms.

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