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Humoral Immune Response to Gonococcal Infections

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The purpose of this paper is to review the recent advances in the knowledge of humoral immune responses to gonococcal infections in humans. The current knowledge of the molecular biology of *Neisseria gonorrhoeae*, including knowledge of antigen structure and mechanisms that yield antigenic heterogeneity, has outstripped the current knowledge of immune responses to the gonococcal antigens. Although it is clear that patients with uncomplicated infections develop increased levels of serum antigonococcal immunoglobulins, it is also evident that because of the new knowledge about antigenic heterogeneity, generalized interpretation of results from early studies often is not appropriate. Antibodies that are reactive with a given gonococcal antigen may not react at all with the same antigen from another strain of *N. gonorrhoeae*. Thus, in this review we emphasize data that have taken into account the antigenic heterogeneity or have included conserved antigens of the gonococcus.

SERUM ANTIBODY RESPONSE IN GONOCOCCAL INFECTION

Immunoglobulin Class

In the late 1960s, several studies of natural serum antibodies reactive with *N. gonorrhoeae* and other gram-negative organisms were reported (14–17). Indirect fluorescent-antibody assays were used and showed reactive immunoglobulin G (IgG) in adult sera and in umbilical-cord sera. Less IgM that was reactive and relatively little reactive IgA were found in the sera from adults. The IgG in immune sera could be distinguished from naturally occurring IgG antibodies by reaction with heat-labile gonococcal antigens (14). Similarly, 9 of 10 men with experimental gonococcal urethritis developed significant increases in reactive IgG levels in serum (15); fewer of the patients showed increased levels of reactive IgM or IgA. Serum IgA reactive with *N. gonorrhoeae* probably is secretory, implying that mucosal cells are the origin of the antibody (22).

IgG3 is the predominant IgG subclass reactive with a variety of gonococcal antigens, followed by IgG1 and IgG4 (34). There is minimal IgG2 reactive with gonococcal antigens following infection, suggesting that polysaccharides are not important in the immune response to gonorrhea.

Antigen Specificity

Antigenic heterogeneity is a major consideration when studying humoral immunity in gonococcal infection. Pili, protein II (PII), and lipooligosaccharide (LOS) are the most important antigens, quantitatively, in generating antibody responses in gonococcal infection. These three antigens shift from one antigenic form to another at a frequency of 1 in 10^3, or greater. Because of the rapid shifting from one antigenic form to another, nearly every strain of *N. gonorrhoeae* may be antigenically distinct. Indeed, it is possible that each gonococcus has the potential to be antigenically distinct from its neighbors. The molecular biology of pili (25a), protein I (PI) (28a), PII (42a), protein III (PIII) (7a), and H.8 (12a) is discussed elsewhere in this issue. Humoral immunity related to these antigens is discussed below.

Pili. Pili are the hairlike appendages that extend from the gonococcal celi surface and are thought to function in the attachment of gonococci to host cells. Soon after the description of gonococcal pili in 1971, it was noted that patients make antibodies against pili, as measured by using pili from a laboratory strain of *N. gonorrhoeae* as the test antigen (12). The observations were repeated by several investigators. One study noted that there were differences in the antibody levels between men and women, although there was some overlap; the antibody levels were related to the number of previous gonococcal infections, but, again, there was a great deal of overlap; and black Americans tended to have different levels from those of white Americans (20). Thus, gonococcal pili have not proven to be a useful reagent in development of a serological test to diagnose gonorrhea.

It is clear that patients make antibodies against the pili of the infecting gonococcal strain (36). In women, pili appeared to be the predominant antigen in the immune response. In men, there were higher levels of antibodies to other antigens than pili.

One consideration of humoral immunity to pili was that antibodies against pili blocked the pilus-mediated attachment to host cells (8, 59). A vaccine was developed by using pili from a laboratory strain of *N. gonorrhoeae* (8, 59), but a field trial of the vaccine showed it not to be efficacious (J. Boslego, R. Chung, J. Sadoff, D. McChesney, M. Piziak, J. Ciak, J. Brown, W. Caldwell, D. Berliner, G. Seitter, C. Brinton, and E. Tramont, Program Abstr. 24th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 294, 1984). Thus, although there is a strong humoral immune response to gonococcal pili, the antigenic heterogeneity of the pilin molecule makes development of a useful pilus vaccine difficult. Antibodies against synthetic peptides representing conserved regions of the pilin molecule appear to have biological activity in blocking the pilus-mediated attachment of gonococci to host cells (48); however, persons immunized with a gonococcal pilus vaccine lack antibodies against such synthetic peptides (R. Chung, C. Liu, J. Boslego, E. Tramont, S. Wood, and C. Brinton, Abstr. Annu. Meet. Am. Soc. Microbiol. 1986, B5, p. 25). To date, there are no data on the human immune response to immunization with synthetic peptides representing gonococcal antigens.

PI. PI is a major component of the gonococcal outer membrane and may have an important role in the pathogenesis of infection by insertion into the host cell membrane (7, 13). PI is antigenically conserved in each strain of *N. gonorrhoeae* but variable from one strain to another. There are two primary types, PIA and PIB, each having multiple serotypes (32, 33, 49). PIA strains are usually resistant to the bactericidal action of normal human serum, whereas PIB strains often are susceptible (29, 32).

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Patients with uncomplicated gonococcal genital infection, pelvic inflammatory disease, or disseminated infection have detectable serum antibodies reactive with PI (27, 28, 36). The anti-PI antibodies may be bactericidal for the gonococci (27). The antibody response to PI, however, is minimal when compared with the response to pili, PII, and LOS, especially given the large amount of PI in the gonococcal outer membrane.

PII. PIIs are variably expressed surface-exposed gonococcal proteins (3, 18, 56). At any one time a gonococcal strain may have no, one, two, or many PIIs in the outer membrane.

PII is one of the most important antigens in the humoral immune response to gonococcal infection in both men and women (36). Men and women infected with the same strain of *N. gonorrhoeae*, however, may have different immune responses to a specific PII or may develop antibodies to different PIIs (35). A biological role for anti-PII antibodies in gonococcal infection is undefined. One possible role is that by shifting expression of PII, gonococci may evade the immune system of the host.

PIII. PIII is a protein that is antigenically conserved in all gonococci. PIII is closely associated with PI in the outer membrane, but a specific function for PIII is not known.

Patients with gonococcal infection make small amounts of antibody to PIII (36). Whether there is any biological role for these antibodies in protection from infection is unknown. It has been demonstrated, however, that IgG reactive with PIII blocks the serum bactericidal action in disseminated gonococcal infection (47).

LOS. The LOS of gonococci is a relatively small form of bacterial endotoxin with molecular weights of 3,200 to 7,100 (24, 51). Each gonococcal strain can express several different antigenic forms of LOS at one time and can very rapidly switch from one antigenic form to another (38, 52). The LOS appears to be tightly associated with outer membrane proteins I and II (7, 26). Gonococcal LOS also has structures that are immunochemically similar to structures on human erythrocyte membranes (39). Because of its antigenic diversity and structure, association with outer membrane proteins, and endotoxic activity, gonococcal LOS has an important role in the immunology of gonorrhea.

Genital infection with *N. gonorrhoeae* elicits serum anti-LOS antibody directed against the LOS of the infecting strain (28, 36). Not all patients have serum antibody directed against the LOS present after subculture of the infecting strain, perhaps because of shifting of the antigenic forms of LOS on subculture. Patients do have more antibody against the LOS of their infecting strains than against the LOS of laboratory strains (1). Disseminated gonococcal infection elicits higher levels of anti-LOS antibody than genital infection does (37).

Antibody against LOS has several important functions in gonococcal infection. Antibody can activate complement through the classical or alternative complement pathways and can be chemotaxic for polymorphonuclear cells (19, 25). IgM and IgG directed against LOS can be bactericidal for gonococci; IgA can block the IgG-mediated bactericidal activity (2). Gonococci can express at least one antigenic form that confers resistance to the bactericidal action of normal human serum (50, 54); antibody to this form of LOS can be bactericidal, but that antibody is seldom present in human serum.

H.8. H.8 is a distinctive antigen common to the pathogenic neisseriae (23, 57). Patients with uncomplicated genital gonococcal infection, pelvic inflammatory disease, or disseminated infection make antibodies against H.8 (4, 5, 36). It is also evident that antibodies against H.8 do not protect the host from uncomplicated genital infections, since patients can have repeated infection when anti-H.8 antibodies are present.

IgA1 protease. The pathogenic *Neisseria* spp. produce extracellular IgA1 protease, which cleaves IgA1 and inactivates it (55). In preliminary observations it was found that only 8 of 48 patients with uncomplicated gonococcal infection, gonococcal pelvic inflammatory disease, or disseminated gonococcal infection developed antibodies reactive with gonococcal IgA1 protease; this incidence was no different than the one for uninfected controls (C. J. Lammel, M. S. Blake, W. D. Zollinger, E. W. Hook III, and G. F. Brooks, Program Abstr. 28th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 195, 1988). In contrast, the majority of patients with meningococcal disease or nasopharyngeal carriage had antibodies reactive with meningococcal IgA1 protease, and these antibodies were cross-reactive with the gonococcal IgA1 protease. Serum IgG reactive with meningococcal IgA1 protease inhibited the activity of both the meningococcal and gonococcal proteases.

MIRP. The pathogenic *Neisseria* spp. make several iron-regulated proteins under conditions of limited iron such as those that exist in the human host. One of these proteins, major iron-regulated protein (MIRP), is conserved among the pathogenic *Neisseria* spp. Patients with uncomplicated gonococcal infection, pelvic inflammatory disease, or disseminated infection had serum antibodies reactive with MIRP and showed moderate to high levels of reactive IgG and IgM and low levels of reactive IgA (21, 43). Reactive immunoglobulin levels were higher in patients with previous gonococcal infections and also increased when repeated infections occurred during the study. The results indicate that the iron-regulated protein is expressed in vivo. Patients with anti-MIRP serum immunoglobulins had repeated uncomplicated genital infections, and, hence, the serum antibodies were not protective for genital infection. A possible role for anti-MIRP antibodies in modifying or preventing gonococcal pelvic inflammatory disease is unknown.

Others. Several other antigens may be important in the humoral immune response to gonococcal infection. The outer membrane protein-macromolecular complex participates in the bactericidal activity of immune rabbit serum. We are not aware of published data on the human immune response to this complex. Patients with gonococcal infection make antibodies against proteins in the 46- to 48- and 54- to 58-kilodalton ranges and a variety of undefined higher-molecular-mass antigens (36); the role of antibodies against these antigens is undefined.

HUMAN MUCOSAL ANTIBODY RESPONSE IN GONOCOCCAL INFECTION

There are considerably fewer data on the genital antibody response in gonococcal infection than on the serum antibody response. This is particularly true with respect to specific gonococcal antigens.

Immunoglobulin Class

Studies of women have provided the most useful data on mucosal antibody response in gonococcal infection. Investigators commonly used fluorescent-antibody techniques and a laboratory strain of *N. gonorrhoeae* and looked for reactive IgA and IgG. In one study of six women with gonococcal cervicitis, the concentrations of vaginal-wash IgA were

higher than the concentrations in uninfected controls (44). The titers of antigonococcal IgA were high at the time of infection, often higher than in serum; after treatment, the IgA levels rapidly returned to normal (44, 60). One study of cervical secretions from 75 women with uncomplicated gonorrhea (UGC) showed antigonococcal IgG in 97% of the subjects, IgA in 95%, and IgM in 39%; antigonococcal IgG was found in the cervical secretions of 33% of 70 women who were not infected; no antigonococcal IgA and IgM were detected (42). Similar results showing the presence of more reactive IgG than IgA have been reported recently (28, 36). The predominant IgG subclass in vaginal secretions reactive with gonococcal antigens is IgG3 (34).

Men with UGC usually have urethral exudate antibodies reactive with gonococci. Antigonococcal IgA was found in exudates of 29 (83%) of 35 men with UGC (30); also, antigonococcal IgA was found in the exudates of 9 of 11 men with a first infection and 20 of 24 men with repeated UGC (31). Another study reported the presence of antigonococcal IgA in exudates from 98% of 132 men with UGC (41); reactive IgG and IgM were found in 90% and 49%, respectively. Of 100 men with nongonococcal urethritis or without urethritis, only one had antigonococcal IgA, but 26 had antigonococcal IgG. Following treatment, the levels of measurable antigonococcal IgA declined very rapidly; the IgG levels declined more slowly and could still be detected at 28 days after treatment.

Antigen Specificity

Study of the antigen specificity of antibodies in genital fluids has been difficult compared with analysis of antibody reactivity with whole gonococci.

Pili. Pili, along with PI and PII, are the predominant antigens in the genital immune response to genital gonococcal infection (28, 36).

In early gonococcal pilus vaccine studies it was found that vaginal fluid antibodies were reactive with pili, outer membranes, and LOS (60, 61). The pilus vaccine induced vaginal fluid antibodies that functioned to inhibit the pilus-mediated attachment of the homologous strain of *N. gonorrhoeae* (40, 58).

PI. PI is the primary antigen in both the genital IgG and IgA responses to gonococcal infection when tested with the infecting organisms of the patients (36). The genital anti-PI antibody level has not been quantitated, but it is qualitatively higher than the serum anti-PI antibody level.

PII. PII, along with PI and pili, is a major antigen in the female genital antibody response to gonococcal infection (36). We are not aware of any data on the genital anti-PII antibody response in men with gonorrhea. Whether the genital antibodies have a protective role in preventing or modifying gonococcal endocervical or urethral infection is unknown.

PIII. There is minimal if any measurable genital antibody response to PIII (36).

LOS. Although patients with genital infection make antibodies directed against gonococcal LOS, these antibodies are not as prominent in the immune response as are antibodies against PI, PII, and pili (28, 36).

H.8. One study in which vaginal fluid antibodies were studied for reactivity to a broad spectrum of gonococcal antigens did not demonstrate a genital antibody response to H.8 or to the broad band of reactivity that represents H.8 (36).

IgA1 Protease. Split products of IgA1 have been found in the genital secretions of women with gonorrhea, indicating that the gonococcal IgA1 protease is present and active during genital infection (6). To date, however, the enzyme has not been detected in genital secretions when a monoclonal antibody probe has been used; also, antibodies against IgA1 protease have not been found in genital secretions of women with gonorrhea (C. J. Lammel, M. S. Blake, and G. F. Brooks, unpublished observations).

MIRP. The reactive IgA and IgG levels in vaginal fluid were higher for pelvic inflammatory disease patients with no prior infections than for those with at least one prior infection (43). In contrast, the reactive IgA and IgG levels in vaginal fluid of UGC patients were higher for patients with prior infections than for those with no prior infections.

FUNCTIONAL IMMUNITY IN GONOCOCCAL INFECTION

Bactericidal and Phagocytic Systems

Extensive studies have been done on bactericidal and phagocytic systems in the immune response to gonococcal infection. Limited space precludes thorough review of the subject, and the reader is referred to other articles in this volume for additional information.

Gonococci isolated from patients with disseminated infection are resistant to the bactericidal action of most normal human sera and convalescent-phase sera (10, 53). This resistance is by virtue of blocking antibody directed against PIII and possibly other outer membrane antigens (7a, 47). Patients with a deficiency of one of the late-acting complement components also are at high risk for disseminated neisserial infection because their antibody-complement-mediated bactericidal systems are not functional (45). Antibodies also are opsonic for gonococci (10). A protective role for opsonization and phagocytosis is, however, not clear, because patients with late-acting complement component deficiency may have functional opsonization and phagocytosis and still have bacteremia.

The amount of complement present in the female genital tract is small (46) and probably will not allow complement-mediated bactericidal and opsonic systems to function there. Examination of a Gram stain of a genital exudate sample from an infected patient shows that gonococcal association with polymorphonuclear cells is important in the disease process. It is, however, not clear that the gonococcus-polymorphonuclear cell association in the genital tract is antibody mediated. Some PIIs mediate attachment of gonococci to polymorphonuclear cells, but it is not known whether human antibody can modify this process.

Preventing Attachment to Mucosal Cells

The pilus vaccine studies have provided evidence that anti-pilus antibody can prevent the attachment of homologous gonococci to mucosal cells (8, 59). The antigenic heterogeneity of gonococcal pili, however, may preclude a more broad-spectrum antibody-mediated prevention of gonococcal attachment to mucosal cells.

A monoclonal antibody directed against a PII can partially prevent PII-mediated attachment to eucaryotic cells. There are no data on the function of human anti-PII antibodies in modifying the PII-mediated attachment process, nor are there any data about human antibodies, other than anti-pilus antibodies, that modify attachment.

FURTHER QUESTIONS AND CONSIDERATIONS ABOUT IMMUNITY IN GONOCOCCAL INFECTION

Prevention of genital gonococcal infection and especially the major complication of pelvic inflammatory disease is an important objective. To date, however, there are no data on the humoral immune response to indicate that prevention of infection is likely.

Many studies have been oriented toward examination of antibody-complement-mediated bactericidal systems, but it is clear that the presence of serum bactericidal activity does not prevent uncomplicated gonococcal infection (9). It is not known whether the presence of serum antibody and bactericidal activity prevents or modifies gonococcal pelvic inflammatory disease.

Sera of patients may have high levels of antibody against pili, PI, PII, LOS, H.8, MIRP, and a variety of other gonococcal antigens. The patients also may have repeated uncomplicated genital gonococcal infection when these antibodies are present. It is, however, not known whether the presence of these antibodies prevents or modifies gonococcal pelvic inflammatory disease. Only one set of data from a small number of patients indicates that women do not have repeated gonococcal pelvic inflammatory disease with gonococci of the same PI type that caused their first infection (11).

There is insufficient understanding of genital antibody function in gonococcal infection to determine whether the antibody plays a role in modifying or preventing initial or repeated infection.

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