

1004 PORIN Porin (previously designated protein I) is the most abundant gonococcal surface protein, accounting for >50% of the organism's total outer-membrane protein. Porin molecules exist as trimers that provide anion-transporting aqueous channels through the otherwise hydrophobic outer membrane. Porin exhibits stable interstrain antigenic variation and forms the basis for gonococcal serotyping. Two main serotypes have been identified: PorB.1A strains are often associated with disseminated gonococcal infection (DGI), whereas PorB.1B strains usually cause local genital infections only. DGI strains are generally resistant to the killing action of normal human serum and do not incite a significant local inflammatory response; therefore, they may not cause symptoms at genital sites. These characteristics may be related to the ability of PorB.1A strains to bind to complement-inhibitory molecules, resulting in a diminished inflammatory response. Porin can translocate to the cytoplasmic membrane of host cells—a process that could initiate gonococcal endocytosis and invasion.

OTHER OUTER-MEMBRANE PROTEINS Other notable outer-membrane proteins include H.8, a lipoprotein that is present in high concentration on the surface of all gonococcal strains and is an excellent target for antibody-based diagnostic testing. Transferrin-binding proteins (Tbp1 and Tbp2) and lactoferrin-binding protein are required for scavenging iron from transferrin and lactoferrin in vivo. Transferrin and iron have been shown to enhance the attachment of iron-deprived *N. gonorrhoeae* to human endometrial cells. IgA1 protease is produced by *N. gonorrhoeae* and may protect the organism from the action of mucosal IgA.

Lipooligosaccharide Gonococcal lipooligosaccharide (LOS) consists of a lipid A and a core oligosaccharide that lacks the repeating O-carbohydrate antigenic side chain seen in other gram-negative bacteria (Chap. 145e). Gonococcal LOS possesses marked endotoxic activity and contributes to the local cytotoxic effect in a fallopian tube model. LOS core sugars undergo a high degree of phase variation under different conditions of growth; this variation reflects genetic regulation and expression of glycotransferase genes that dictate the carbohydrate structure of LOS. These phenotypic changes may affect interactions of *N. gonorrhoeae* with elements of the humoral immune system (antibodies and complement) and may also influence direct binding of organisms to both professional phagocytes and nonprofessional phagocytes (epithelial cells). For example, gonococci that are sialylated at their LOS sites bind complement factor H and inhibit the alternative pathway of complement. LOS sialylation may also decrease nonopsonic Op-mediated association with neutrophils and inhibit the oxidative burst in PMNs. The binding of the unsialylated terminal lactosamine residue of LOS to an asialoglycoprotein receptor on male epithelial cells facilitates adherence and subsequent gonococcal invasion of these cells. Moreover, oligosaccharide structures in LOS can modulate host immune responses. For example, the terminal monosaccharide expressed by LOS determines the C-type lectin receptor on dendritic cells that is targeted by the bacteria. In turn, the specific C-type lectin receptor engaged influences whether a T_H1- or T_H2-type response is elicited; the latter response may be less favorable for clearance of gonococcal infection.

Host Factors In addition to gonococcal structures that interact with epithelial cells, host factors seem to be important in mediating entry of gonococci into nonphagocytic cells. Activation of phosphatidylcholine-specific phospholipase C and acidic sphingomyelinase by *N. gonorrhoeae*, which results in the release of diacylglycerol and ceramide, is a requirement for the entry of *N. gonorrhoeae* into epithelial cells. Ceramide accumulation within cells leads to apoptosis, which may disrupt epithelial integrity and facilitate entry of gonococci into subepithelial tissue. Release of chemotactic factors as a result of complement activation contributes to inflammation, as does the toxic effect of LOS in provoking the release of inflammatory cytokines.

The importance of humoral immunity in host defenses against neisserial infections is best illustrated by the predisposition of persons deficient in terminal complement components (C5 through C9) to recurrent bacteremic gonococcal infections and to recurrent meningococcal meningitis or meningococcemia. Gonococcal porin induces

T cell–proliferative responses in persons with urogenital gonococcal disease. A significant increase in porin-specific interleukin (IL) 4–producing CD4+ as well as CD8+ T lymphocytes is seen in individuals with mucosal gonococcal disease. A portion of these lymphocytes that show a porin-specific T_H2-type response could traffic to mucosal surfaces and play a role in immune protection against the disease. Few data clearly indicate that protective immunity is acquired from a previous gonococcal infection, although bactericidal and opsonophagocytic antibodies to porin and LOS may offer partial protection. On the other hand, women who are infected and acquire high levels of antibody to another outer-membrane protein, Rmp (reduction modifiable protein, formerly called protein III), may be especially likely to become reinfected with *N. gonorrhoeae* because Rmp antibodies block the effect of bactericidal antibodies to porin and LOS. Rmp shows little, if any, interstrain antigenic variation; therefore, Rmp antibodies potentially may block antibody-mediated killing of all gonococci. The mechanism of blocking has not been fully characterized, but Rmp antibodies may noncompetitively inhibit binding of porin and LOS antibodies because of the proximity of these structures in the gonococcal outer membrane. In male volunteers who have no history of gonorrhea, the net effect of these events may influence the outcome of experimental challenge with *N. gonorrhoeae*. Because Rmp bears extensive homology to enterobacterial OmpA and meningococcal class 4 proteins, it is possible that these blocking antibodies result from prior exposure to cross-reacting proteins from these species and also play a role in first-time infection with *N. gonorrhoeae*.

Gonococcal Resistance to Antimicrobial Agents It is no surprise that *N. gonorrhoeae*, with its remarkable capacity to alter its antigenic structure and adapt to changes in the microenvironment, has become resistant to numerous antibiotics. The first effective agents against gonorrhea were the sulfonamides, which were introduced in the 1930s and became ineffective within a decade. Penicillin was then used as the drug of choice for the treatment of gonorrhea. By 1965, 42% of gonococcal isolates had developed low-level resistance to penicillin G. Resistance due to the production of penicillinase arose later.



Gonococci become fully resistant to antibiotics either by chromosomal mutations or by acquisition of R factors (plasmids). Two types of chromosomal mutations have been described. The first type, which is drug specific, is a single-step mutation leading to high-level resistance. The second type involves mutations at several chromosomal loci that combine to determine the level as well as the pattern of resistance. Strains with mutations in chromosomal genes were first observed in the late 1950s. As recently as 2007, chromosomal mutations accounted for resistance to penicillin, tetracycline, or both in ~16% of strains surveyed in the United States.

β-Lactamase (penicillinase)–producing strains of *N. gonorrhoeae* (PPNG) carrying plasmids with the P_c determinant had rapidly spread worldwide by the early 1980s. *N. gonorrhoeae* strains with plasmid-borne tetracycline resistance (TRNG) can mobilize some β-lactamase plasmids, and PPNG and TRNG occur together, sometimes along with strains exhibiting chromosomally mediated resistance (CMRNG). Penicillin, ampicillin, and tetracycline are no longer reliable for the treatment of gonorrhea and should not be used.



Quinolone-containing regimens were also recommended for treatment of gonococcal infections; the fluoroquinolones offered the advantage of antichlamydial activity when administered for 7 days. However, quinolone-resistant *N. gonorrhoeae* (QRNG) appeared soon after these agents were first used to treat gonorrhea. QRNG is particularly common in the Pacific Islands (including Hawaii) and Asia, where, in certain areas, all gonococcal strains are now resistant to quinolones. At present, QRNG is also common in parts of Europe and the Middle East. In the United States, QRNG has been identified in midwestern and eastern areas as well as in states on the Pacific coast, where resistant strains were first seen. Alterations in DNA gyrase and topoisomerase IV have been implicated as mechanisms of fluoroquinolone resistance.

Resistance to spectinomycin, which has been used in the past as an alternative agent, has been reported. Because this agent usually is not