Review Article

Medical Progress

MENINGOCOCCAL DISEASE

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REPORTS of illness resembling meningococcal disease date back to the 16th century. The description reported by Vieusseux in 1805 is generally thought to be the first definitive identification of the disease,[1] and the causative organism, *Neisseria meningitidis*, was first isolated in 1887.[2] Yet meningococcal disease remains a leading cause of bacterial meningitis and sepsis in the United States and a major cause of epidemics in sub-Saharan Africa. Short of abolishing tobacco use, which is thought to be responsible for almost one third of cases,[3] routine vaccination of high-risk populations is likely to be the most effective public health strategy for controlling meningococcal disease. Several companies are in the final stages of developing and testing meningococcal conjugate vaccines for licensure in the United States. These vaccines have been developed with the techniques used to develop *Haemophilus influenzae* type b conjugate vaccines. Progress is also being made in the use of subcapsular antigens to develop vaccines against serogroup B disease, but for this serogroup, substantial work and probably various approaches are needed to find the right one. There are formidable challenges involved in designing strategies to introduce conjugate vaccines, but these vaccines provide an important new opportunity to control and prevent meningococcal disease.[4]

EPIDEMIOLOGIC FEATURES OF MENINGOCOCCAL DISEASE

In the United States

Since 1960, rates of meningococcal disease in the United States have remained relatively stable, at approximately 0.9 to 1.5 cases per 100,000 population per year, or 2500 to 3000 cases per year.[5] Meningococcal disease occurs year-round, but the majority of cases occur during the winter and early spring.[6] The rates of disease are highest among infants in whom protective antibodies have not yet developed; the rates drop after infancy and then increase during adolescence and early adulthood.[6] Although the rates of meningococcal disease once again drop after early adulthood, more cases occur in persons 23 to 64 years old than in any other age group (unpublished data). The proportion of cases among adolescents and young adults has increased in recent years; during the period from 1992 to 1996, 28 percent of affected persons were between 12 and 29 years old.[6] This change has important implications for preventive strategies.

Since the new meningococcal conjugate vaccines, like the currently available quadrivalent polysaccharide vaccine, will provide serogroup-specific protection, the distribution of serogroups is a key factor in the design of vaccination programs. From 1988 to 1991, most cases of meningococcal disease in the United States were due to either serogroup C or serogroup B, and serogroup Y accounted for only 2 percent of cases.[7] In recent years, the number of cases involving serogroup Y has increased; from 1996 to 1998, one third of cases were due to serogroup Y, which is also more commonly associated with pneumonia than are serogroups B and C.[6,8] In the 1970s, serogroup Y was also recognized as a frequent cause of sporadic disease in some U.S. populations[9,10] and was associated with several outbreaks among military personnel.[11] Similarly, serogroup W-135, which is also associated with pneumonia and which currently accounts for only 4 percent of cases in the United States,[6] was reported in 15 to 20 percent of isolates received by the Centers for Disease Control and Prevention between 1978 and 1980.[12] In 2000, an international outbreak among pilgrims returning from the hajj (the pilgrimage to Mecca) and their close contacts, including four persons from the United States, was due to serogroup W-135.[13] Although outbreaks of serogroup A meningococcal disease were common in industrialized countries early in the 20th century, outbreaks as well as sporadic cases have been rare in these countries since World War II. These changes are not completely understood but may reflect immunologic changes in the general population, the introduction of new strains of *N. meningitidis* into populations, or cross-reactive protection provided by exposure to bacteria with a similar structure (e.g., *Bacillus pumilus*).[14]

Another recent change in the epidemiology of meningococcal disease in the United States has been in the frequency of outbreaks. In the 1980s, outbreaks of meningococcal disease were rare, but since 1991,

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the frequency of localized outbreaks has increased. These outbreaks have been caused by groups of closely related strains and probably represent the introduction of new clones into the population.[15-17] Most of these outbreaks have been due to serogroup C; in the past five years, however, there have also been outbreaks due to serogroup Y.[16] Although such outbreaks cause tremendous public concern and attract considerable attention in the media, they account for only 2 to 3 percent of the total number of cases in the United States.

Worldwide

Serogroups A, B, and C account for most cases of meningococcal disease throughout the world, with serogroups B and C responsible for the majority of cases in Europe and the Americas and serogroups A and C predominating throughout Asia and Africa.[18-20] Israel and Sweden are the only countries other than the United States that have reported an increase in serogroup Y disease.[19] Serogroup B meningococcal disease caused 68 percent of cases reported in Europe between 1993 and 1996[19] and has also caused outbreaks in developed countries, with attack rates of 5 to 50 cases per 100,000 persons.[21] In the late 1970s, a serogroup B strain belonging to a clonal group known as ET-5 emerged, causing outbreaks in northwestern Europe and Central and South America.[21] In the early 1990s, an outbreak of serogroup B disease due to the same clonal group occurred in Oregon and Washington, with a rate of 4.6 cases per 100,000 in 1994.[22,23] The outbreak did not spread to other states and now appears to be waning.[24] In the absence of an effective vaccine against serogroup B, a more widespread outbreak would result in substantial morbidity and mortality.

In the African "meningitis belt," a region of savannah that extends from Ethiopia in the east to Senegal in the west, serogroup A meningococcal disease has posed a recurrent threat to public health for at least 100 years.[25] Rates of meningococcal disease are several times higher in this region than in industrialized countries, and the reported mortality is usually approximately 10 percent, a rate similar to that in industrialized countries; however, because many patients die before reaching a hospital, the true mortality in the meningitis belt is probably substantially higher.[26] In addition, outbreaks occur every 8 to 12 years, frequently resulting in attack rates of 500 to 1000 cases per 100,000 population.[20] In 1996, the largest outbreak ever reported occurred in the meningitis belt; the total number of cases reported to the World Health Organization (probably a substantial underestimate) was 152,813, with 15,783 deaths.[27]

MICROBIOLOGIC FEATURES AND PATHOGENESIS

N. meningitidis are gram-negative, aerobic diplococci (Fig. 1) that are best isolated on chocolate agar. They are classified into serogroups according to the immunologic reactivity of their capsular polysaccharides, which are the basis for currently licensed meningococcal vaccines.[28] Although there are at least 13 serogroups, most cases of meningococcal disease are caused by serogroups A and C, for which polysaccharide vaccines are effective, and serogroup B, which has a polysaccharide capsule that is poorly immunogenic in humans. The capsular polysaccharide is either a homopolymer or a heteropolymer consisting of monosaccharide, disaccharide, or trisaccharide repeating units. The main meningococcal capsular polysaccharides associated with invasive disease, except for serogroup A, are composed of sialic acid derivatives; the serogroup A capsule consists of repeating units of *N*-acetyl-mannosamine-1-phosphate. Meningococci are further classified on the basis of their class 1 outer-membrane proteins (serosubtype), class 2 or 3 outer-membrane proteins (serotype), and lipooligosaccharides (immunotype) (Fig. 2 and Table 1). Molecular subtyping with the use of multilocus enzyme electrophoresis, pulsed-field gel electrophoresis, or DNA-sequence analysis can be helpful in identifying closely related strains with the potential to cause outbreaks and in understanding the genetic characteristics of *N. meningitidis*.[29] Meningococci also have the capacity to exchange the genetic material responsible for capsule production and thereby switch from serogroup B to C or vice versa.[30] Capsule switching may become an important mechanism of virulence with the widespread use of vaccines that provide serogroup-specific protection.

Humans are the only natural reservoir of *N. meningitidis*, and the nasopharynx is the site from which meningococci are transmitted by aerosol or secretions to others. Meningococci overcome host defenses and attach to the microvillous surface of nonciliated colum-

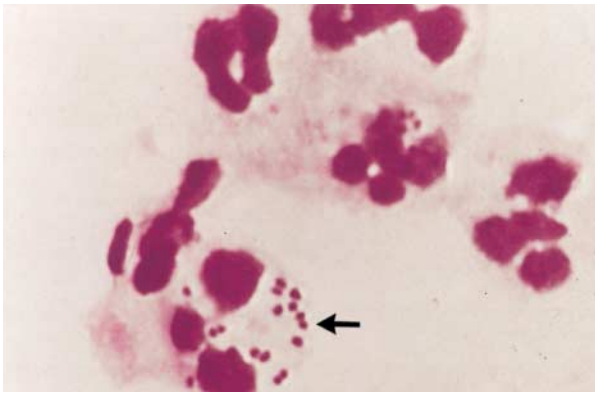

Figure 1. *Neisseria meningitidis* (Arrow) in Cerebrospinal Fluid (Gram's stain, ×1000).

The organisms are intracellular, gram-negative diplococci.

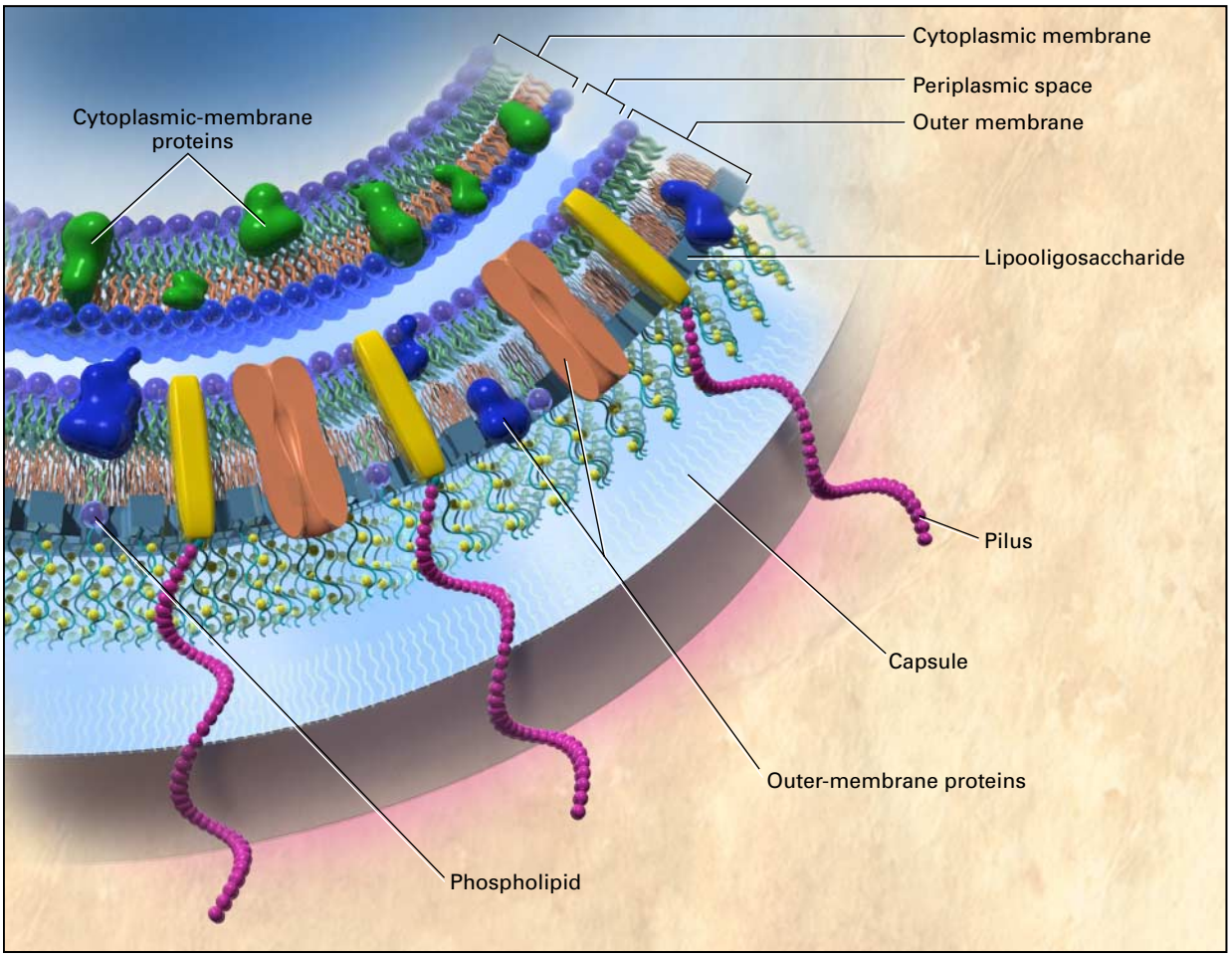

Figure 2. Cross-Sectional View of the Meningococcal Cell Membrane.

nar mucosal cells of the nasopharynx, where they multiply (i.e., colonize) (Fig. 3).[31] Pili (Fig. 2) are the major adhesins that may target the CD46 receptor, a membrane cofactor protein; subsequently, the opacity-associated proteins, Opa and Opc,[32] bind to CD66[33] and heparan sulfate proteoglycan receptors, respectively. Binding stimulates engulfment of the meningococci by epithelial cells, which may then traverse the mucosal epithelium through phagocytic vacuoles.[31] The survival of meningococci in the epithelial cells may be promoted by the IgA1 protease and by porB.[34] Five to 10 percent of adults are asymptomatic nasopharyngeal carriers of strains of *N. meningitidis*,[35,36] most of which are not pathogenic. In a small number of persons, *N. meningitidis* penetrates the mucosa and gains access to the bloodstream, causing systemic disease.[37] In most persons, however, carriage is an immunizing process, resulting in a systemic protective antibody response.[38]

RISK FACTORS

Meningococci are diverse organisms and are usually commensal bacteria in humans. Only a minority of the nasopharyngeal isolates cause invasive disease. Meningococci associated with invasive disease elaborate a capsule, which provides protection from desiccation during transmission and aids in the evasion of host immune mechanisms. In addition, adhesins, such as pili, and specific nutrient-acquisition factors, especially mechanisms for acquiring iron from human lactoferrin, transferrin, and hemoglobin enhance their pathogenic potential.[39] Finally, a major factor in the virulence of the organism is the release of outer-membrane vesicles that consist of lipooligosaccharide (endotoxin), outer-membrane proteins, phospholipids, and capsular polysaccharides. The endotoxin of *N. meningitidis* is structurally distinct from the lipooligosaccharide of enteric gram-negative bacteria.[40] Meningococci also undergo autolysis, releasing DNA and

TABLE 1. FUNCTION AND CLASSIFICATION OF THE OUTER-MEMBRANE COMPONENTS OF *NEISSERIA MENINGITIDIS*.

COMPONENT	FUNCTION	CLASSIFICATION
Capsule	Protects against host-mediated, complement-dependent bacteriolysis and phagocytosis	13 Serogroups (A, B, C, E-29, H, I, K, L, M, W-135, X, Y, Z)
Outer-membrane proteins		
Porins	Create pores through which small hydrophilic solutes pass, cation-selective or anion-selective	
PorA		Class 1 outer-membrane protein (serosubtyping)
PorB		Class 2 or 3 outer-membrane protein (serotyping)
Opacity-associated proteins		
Opa	Promotes adherence to host cells and leukocytes	Class 5 outer-membrane proteins
Opc	Promotes adherence to host cells	
Reduction-modifiable protein	Unknown	Class 4 outer-membrane protein
Lipooligosaccharide	Has potent endotoxic activity	13 Immunotypes*
Pili	Promote initial adherence to epithelial and endothelial cells and erythrocytes	Class I and II*

*The classification is based on differences in antigenicity.

cell-wall components, which induce the inflammatory cascade. The reasons for the clonality of invasive isolates are not fully understood, but they may possess particular virulence factors or they may have antigenic characteristics that are not recognized by the host and hence escape adaptive immune mechanisms.

Persons who lack or have a deficiency of antibody-dependent, complement-mediated immune lysis (bactericidal activity) are most susceptible to meningococcal disease.[41,42] The importance of humoral immunity was indirectly demonstrated in a study that showed an inverse correlation between the age-related incidence of disease and the age-related acquisition of serum bactericidal antibodies.[42] The direct correlation between susceptibility to meningococcal disease and the absence of detectable bactericidal antibodies was further demonstrated by the finding that military recruits who had detectable bactericidal antibodies frequently became carriers but did not contract the disease.[42] Recently, opsonophagocytic activity has been found to play a part in providing protection against meningococcal disease.[43]

Underlying immune defects that confer a predisposition to invasive meningococcal infection include functional or anatomical asplenia, a deficiency of properdin, and a deficiency of terminal complement components.[44,45] Persons with these conditions have a substantially elevated risk of meningococcal infection, but infections in such persons account for only a small proportion of cases. Those infected with the human immunodeficiency virus are probably also at increased risk for sporadic meningococcal disease, but the risk is not nearly as high as that of infection with other encapsulated organisms, such as *Streptococcus pneumoniae*.[46,47] Additional research is needed to clarify the role of genetic immune defects, such as polymorphisms in the genes for mannose-binding lectin and tumor necrosis factor α, that may have major roles in altering the susceptibility to meningococcal disease.[48,49]

The acquisition of infection depends on the chance that a person will encounter and acquire a virulent bacterium. In households where a case of meningococcal disease has occurred, the risk of invasive disease in family members is increased by a factor of 400 to 800.[9] In the United States, blacks and persons of low socioeconomic status have consistently been found to be at higher risk for meningococcal disease than whites and persons of higher socioeconomic status.[6,7] Black race and low socioeconomic status are likely to be markers for differences in factors such as household crowding, urban residence, and exposure to tobacco smoke. Active or passive exposure to tobacco smoke, as well as concurrent viral infection of the upper respiratory tract, increases the risk of meningococcal disease by enhancing the formation and spread of respiratory droplets or diminishing the functional and mechanical integrity of the respiratory mucosa as a barrier to invasion.[3,50,51]

New military recruits have consistently been found to have a higher risk of both sporadic meningococcal disease and outbreaks of disease than other military personnel or the general population.[52] The increased risk is probably related to crowded living conditions among persons from various geographic areas who

have diverse strains of *N. meningitidis*. Recent studies have also shown that college freshmen living in dormitories have an elevated risk of disease, perhaps for similar reasons, but overall, U.S. college students are not at higher risk for meningococcal disease than other people of similar age.[53,54]

CLINICAL MANIFESTATIONS

One of the challenges of diagnosing meningococcal disease is that its clinical manifestations (Table 2) are difficult to distinguish from those of more common but less serious illnesses. Meningeal infection, resulting from hematogenous spread, occurs in about 50 percent of patients[6] and is similar to other forms of acute purulent meningitis, with a sudden onset of headache, fever, and stiffness of the neck, sometimes accompanied by nausea, vomiting, photophobia, and an altered mental status. In infants, meningeal infection may have a slower onset, with nonspecific signs and without stiffness of the neck; a bulging fontanelle is occasionally noted. *N. meningitidis* can be isolated from the bloodstream in up to three quarters of patients, but meningococcal sepsis, which is also called meningococcemia, occurs in only 5 to 20 percent of patients.[6,55] Meningococcemia is characterized by an abrupt onset of fever and a petechial or purpuric rash, which may progress to purpura fulminans, and is often associated with the rapid onset of hypotension, acute adrenal hemorrhage (the Waterhouse–Friderichsen syndrome), and multiorgan failure.[55]

Pneumonia occurs in 5 to 15 percent of patients with invasive meningococcal disease.[8,56] Meningococcal pneumonia may not always be diagnosed, because isolation of the organism from sputum does not distinguish persons who are carriers of the bacteria from those with pneumonia caused by *N. meningitidis* and because physicians may not consider the organism as a possible cause of pneumonia.[11,57,58] Much less frequently, other syndromes are associated with meningococcal disease, including conjunctivitis,[59] otitis media, epiglottitis, arthritis,[60] urethritis, and pericarditis.[6,61] In rare cases, patients may present with chronic meningococcemia, a syndrome characterized by prolonged, intermittent fevers, rash, arthralgias, and headaches.[55]

Before the 1920s, meningococcal disease was fatal in up to 70 percent of cases.[62] The use of serum therapy and the discovery of sulfonamides and other antimicrobial agents led to a substantial decline in case fatality rates. Despite treatment with appropriate antimicrobial agents and optimal medical care, the overall case fatality rates have remained relatively stable over the past 20 years, at 9 to 12 percent, with a rate of up to 40 percent among patients with meningococcal sepsis.[5] Eleven to 19 percent of survivors of meningococcal disease have sequelae, such as hearing loss, neurologic disability, or loss of a limb.[63,64]

DIAGNOSIS

The classic laboratory diagnosis of meningococcal disease has relied on bacteriologic culture, but the sensitivity of culture may be low, especially when performed after the initiation of antibiotic treatment.[65] Gram's staining of cerebrospinal fluid is still considered an important method for rapid and accurate identification of *N. meningitidis*.[66] Nonculture methods, such as the use of commercially available kits to detect polysaccharide antigen in cerebrospinal fluid, have been used to enhance the laboratory diagnosis. These methods are rapid and specific and can provide a serogroup-specific diagnosis, but false negative results are common, especially in cases of serogroup B disease.[67] Antigen tests of urine or serum are unreliable for the diagnosis of meningococcal disease. Serologic testing, primarily with enzyme-linked immunosorbent assays, can be used as part of the evaluation if meningococcal disease is suspected but should not be used to establish the diagnosis.[68] Polymerase-chain-reaction (PCR) analysis offers the advantages of detecting serogroup-specific *N. meningitidis* DNA and of not requiring live organisms for a positive result. PCR tests for *N. meningitidis* are not commercially available in the United States, but this approach has been widely used in the United Kingdom since late 1996, and in 1998, 35 percent of cases of meningococcal disease in the United Kingdom were confirmed by PCR alone (Kaczmarski

Figure 3 (facing page). Colonization of *Neisseria meningitidis* in the Nasopharynx and Entry into the Bloodstream and Cerebrospinal Fluid.

N. meningitidis enters the nasopharynx and attaches to nonciliated epithelial cells, probably through the binding of the pili to the CD46 receptor (a membrane cofactor protein) and the subsequent binding of opacity-associated proteins, Opa and Opc, to the CD66e (carcinoembryonic antigen) and heparan sulfate proteoglycan receptors, respectively. The attached organisms are engulfed by the cells, enter phagocytic vacuoles, and may then pass through the cells. IgA1 protease (an outer-membrane protein) cleaves lysosome-associated membrane protein and may promote the survival of *N. meningitidis* in epithelial cells. PorB (another outer-membrane protein) crosses the cell membrane and arrests the maturation of the phagosome. In the bloodstream, the organisms release endotoxin in the form of blebs (vesicular outer-membrane structures) that contain 50 percent lipooligosaccharide and 50 percent outer-membrane proteins, phospholipids, and capsular polysaccharide. The endotoxin and probably other components stimulate cytokine production and the alternative complement pathway. *N. meningitidis* crosses the blood–brain barrier endothelium by entering the subarachnoid space, possibly through the choroid plexus of the lateral ventricles.

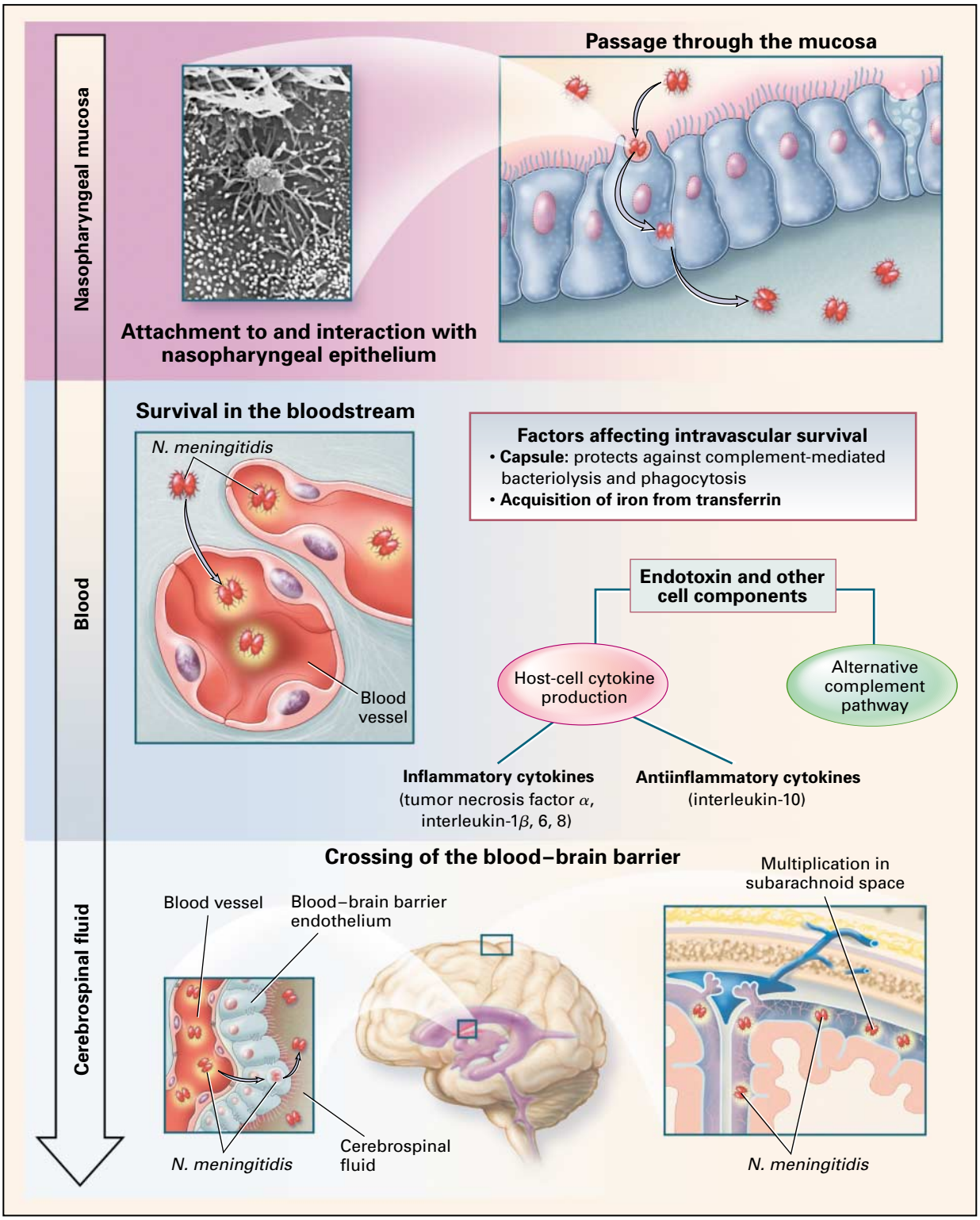

TABLE 2. INFECTIOUS SYNDROMES ASSOCIATED WITH MENINGOCOCCAL DISEASE.*

Meningococcal meningitis
Meningococcal bacteremia
Meningococcemia (purpura fulminans and the Waterhouse–Friderichsen syndrome)
Respiratory tract infection
Pneumonia
Epiglottitis
Otitis media
Focal infection
Conjunctivitis
Septic arthritis
Urethritis
Purulent pericarditis
Chronic meningococcemia

*More than one syndrome may be present in an individual patient.

E: personal communication). Although additional validation of this technique is needed, PCR will probably prove to be a useful tool for rapid diagnosis. In addition, newer molecular-based subtyping techniques may allow further characterization of *N. meningitidis* from PCR-derived products.

MANAGEMENT

The use of antibiotics has dramatically reduced mortality due to meningococcal disease, but studies have not definitively linked early antibiotic therapy with an improved outcome.[69-71] Because of the risks of severe illness and death, however, effective antibiotics should be promptly administered in patients suspected of having meningococcal disease. Many antimicrobial agents, including penicillin, are active against *N. meningitidis.* Although treatment with penicillin has reportedly failed in a few patients with strains of *N. meningitidis* that have intermediate resistance to the drug,[69,70] other patients with such organisms have been treated successfully with penicillin.[72,73] The absence of reports of treatment failure with penicillin in the United States may reflect clinical practices, since penicillin, although considered appropriate first-line therapy for meningococcal disease, is rarely the initial antimicrobial agent used to treat meningitis or sepsis.[74] The low prevalence of resistance to penicillin, as well as uncertainty about the clinical relevance of intermediate resistance, supports the continued use of penicillin to treat meningococcal infections.[74] Routine susceptibility testing of all meningococcal isolates is not necessary; however, such testing should be performed if a patient does not have an appropriate response to antimicrobial agents.

Since the clinical presentation of meningitis due to *N. meningitidis* is similar to that of other bacteria (e.g., *S. pneumoniae*), empirical therapy should be directed at the most likely pathogen on the basis of epidemiologic information. Because of the high prevalence of penicillin-resistant *S. pneumoniae,* empirical management of meningitis in children who are one month of age or older should include vancomycin plus cefotaxime or ceftriaxone.[75] For children who are less than one month old, the clinician should consider adding vancomycin to the usual antibiotic combination of a broad-spectrum cephalosporin and ampicillin.[74,75] If *N. meningitidis* is confirmed as the cause of illness, penicillin alone should be given.

During an epidemic in a developing country, the need to treat a large number of patients makes repeated injections with crystalline penicillin or even ceftriaxone impractical. A single intramuscular dose of an oily suspension of chloramphenicol has been shown to be as effective as a five-day course of crystalline penicillin in the treatment of meningococcal meningitis.[76] Isolates with high-level resistance to chloramphenicol have recently been reported in Vietnam and France,[77] but the clinical significance of such resistance has not been evaluated, and chloramphenicol remains a useful first-line drug for the treatment of cases during epidemics in developing countries.[20]

The high rates of morbidity and mortality associated with meningococcal disease, even among patients who receive early antibiotic treatment, have led to studies of adjuvant therapies. Some studies have shown that treatment with intravenous corticosteroids reduces the risk of hearing loss in patients with meningitis caused by *H. influenzae* type b[63,78,79]; however, corticosteroid therapy has not been shown to be effective for meningococcal disease, and such treatment remains controversial. New clinical trials of therapies aimed at modulating endotoxin, cytokines, and the inflammatory cascade show promising initial results, but these adjuvant treatments should still be considered experimental.[63]

CONTROL AND PREVENTION

Chemoprophylaxis

Persons in close contact with patients who have meningococcal disease are at elevated risk for contracting the disease. Antimicrobial chemoprophylaxis is the primary means of preventing the spread of meningococcal disease in the United States. The rarity of secondary cases is attributable to effective chemoprophylaxis in household members, contacts at day care centers, and anyone else directly exposed to an infected patient's oral secretions — for example, through kissing or mouth-to-mouth resuscitation.[6] Because the risk of secondary disease among close contacts is highest during the first few days after the onset of disease in the index patient, chemoprophylaxis should be administered as soon as possible. If it is given more than 14 days after the onset of disease, chemoprophylaxis is probably of limited or no benefit.[17] Oropharyngeal or nasopharyngeal cultures are not helpful in determining the need for chemoprophylaxis and may

unnecessarily delay the use of this effective preventive measure. Mass chemoprophylactic programs are not recommended to control large outbreaks of disease; multiple sources of exposure, the prolonged risk of exposure, logistic problems, and high cost make this approach impractical and unlikely to be successful. Systemic antibiotics that effectively eliminate nasopharyngeal carriage of *N. meningitidis* include rifampin, ciprofloxacin, and ceftriaxone (Table 3). Studies have documented secondary cases of infection in patients who received prophylaxis with rifampin but who had rifampin-resistant strains, although such cases remain relatively rare.[80-82]

Table 3. Schedule for Administering Chemoprophylaxis against Meningococcal Disease.

Drug and Age Group	Dosage*
Rifampin†	
Children <1 mo	5 mg/kg of body weight every 12 hr for 2 days
Children ≥1 mo	10 mg/kg every 12 hr for 2 days
Adults	600 mg every 12 hr for 2 days
Ciprofloxacin‡	
Children	—
Adults	500 mg given in a single dose
Ceftriaxone	
Children <15 yr	125 mg given in a single intramuscular dose
Children ≥15 yr and adults	250 mg given in a single intramuscular dose

*The drug is administered orally unless otherwise indicated.

†Rifampin is not recommended for pregnant women, because the drug is teratogenic in laboratory animals. Because the reliability of oral contraceptives may be affected by rifampin therapy, consideration should be given to using alternative contraceptive measures while rifampin is being administered.

‡Ciprofloxacin is not generally recommended for persons younger than 18 years of age or for pregnant or lactating women, because the drug causes cartilage damage in immature laboratory animals. However, ciprofloxacin can be used for chemoprophylaxis in children if no acceptable alternative therapy is available.

Meningococcal Polysaccharide Vaccine

The quadrivalent polysaccharide vaccine that provides protection against serogroups A, C, Y, and W-135 is the only meningococcal vaccine that is licensed and available in the United States. Extensive experience with this vaccine has demonstrated its safety; adverse effects are generally mild, consisting principally of pain and redness at the site of injection.[83-85] The antibody responses to each of the four polysaccharides in the quadrivalent vaccine are serogroup-specific and independent. The serogroup A and C vaccines have good immunogenicity, with clinical efficacy rates of 85 percent or higher among children five years of age or older and adults.[86,87] Serogroup Y and W-135 polysaccharides are safe and immunogenic in older children and adults; although clinical protection has not been documented, vaccination with these polysaccharides induces bactericidal antibody.[88,89] In infants and young children, measurable levels of antibodies against serogroup A and C polysaccharides, as well as clinical efficacy, decrease markedly during the first three years after a single dose of the vaccine has been administered. Antibody levels also decrease in healthy adults, but antibodies are still detectable up to 10 years after immunization.[90-92] Although a reduction in clinical efficacy has not been demonstrated in persons who have received multiple doses of vaccine, recent serologic studies suggest that multiple doses of serogroup A and C polysaccharides may cause immunologic tolerance of the polysaccharides.[93,94]

Routine childhood vaccination with the quadrivalent meningococcal polysaccharide vaccine is not recommended because of its relative ineffectiveness in young children, who have the highest risk of sporadic disease and a relatively short duration of protection.[17] However, the vaccine is recommended for the control of outbreaks due to serogroup C. For this purpose, an outbreak is defined as the occurrence of three or more confirmed or probable cases of serogroup C meningococcal disease during a period of three months or less, with a primary attack rate of at least 10 cases per 100,000 population.[17]

The Advisory Committee on Immunization Practices and the American Academy of Pediatrics have recently issued revised guidelines for the use of meningococcal vaccine in college students.[54,95] They recommend that health care providers and colleges educate freshmen, especially those who live in dormitories, and their parents about the increased risk of meningococcal disease and the potential benefits of immunization, so that they can make informed decisions about vaccination.

Improved Vaccines

Unlike serogroup A and C polysaccharides, the serogroup B polysaccharide has a capsule ([α2-8]-linked polysialic acid) that is identical in structure to polysialic acid in fetal neural tissue and is poorly immunogenic in humans.[56] Strategies for developing vaccines against serogroup B disease have therefore focused primarily on noncapsular antigens (e.g., outer-membrane proteins).[96] Several of these vaccines, developed from strains of serogroup B meningococci that have caused outbreaks of disease, are safe, immunogenic, and effective in older children and adults and have been used successfully to control outbreaks.[97-99] The considerable diversity of outer-membrane proteins that cause sporadic serogroup B disease, as well as geographic and possibly temporal variations, may limit the usefulness of this approach.[100,101] Researchers are also exploring candidate vaccines against other, more homogeneous outer-membrane proteins, pili, and exotoxins, as well as vaccines that can be delivered intranasally.[96,102]

To improve the immunogenicity of the serogroup B polysaccharide, researchers have covalently linked it to carrier proteins and adsorbed it to aluminum; this

vaccine has induced a serogroup-specific response in animals.[96] Use of serogroup B polysaccharide vaccines in humans has been limited because of the theoretical risk that these vaccines will overcome immune tolerance and induce autoimmunity, and further development must be undertaken carefully.

Another approach to serogroup A and C polysaccharides has been the use of peptides that mimic the capsular polysaccharide in complex with or conjugated to potent carrier-protein molecules in order to elicit a T-cell–dependent response.[103] In addition, the recent completion of the genomic sequencing of a serogroup B meningococcus may make it possible to identify novel surface proteins that could be effective vaccines.[104]

As with *H. influenzae* type b conjugate vaccines, serogroup A, C, Y, and W-135 meningococcal polysaccharides have been chemically conjugated to carrier proteins. These meningococcal conjugate vaccines induce a T-cell–dependent response, resulting in an improved immune response in infants, priming immunologic memory, and leading to a booster response to subsequent doses.[89] These vaccines are expected to provide long-lasting immunity even when given as a series in infancy, and they may provide herd immunity through protection from nasopharyngeal carriage. Clinical trials of these vaccines are ongoing.[105-107] In the United Kingdom, where the rate of serogroup C meningococcal disease ranges from 1.4 to 2.0 cases per 100,000 population per year and where meningococcal disease is the leading cause of death from infection among young children (Stuart J: personal communication), serogroup C conjugate vaccines were added to the routine schedule of childhood immunizations in late 1999.[108] Preliminary data have shown good short-term efficacy of vaccination in toddlers and teenagers. Further assessment of the effect of these vaccines will be of great importance in all countries.

Conjugate meningococcal vaccines may dramatically improve the control of meningococcal disease, but decisions about their use will be complicated. Because the rates of meningococcal disease are low, phase 3 clinical trials of the efficacy of conjugate vaccines in developed countries are not feasible. The Food and Drug Administration is likely to consider licensure of these vaccines on the basis of data on their immunogenicity and safety, as was done in the United Kingdom. Recent changes in the distribution of meningococcal serogroups in the United States suggest that it will be important to include serogroup Y in a conjugate vaccine. Meningococcal disease has a broad age distribution, and a vaccination program, to be efficient, must address the risk of disease among older children and adolescents, as well as the risk in infancy. In addition, the already complicated schedule of childhood immunizations in the United States makes combination vaccines attractive. Finally, decisions about the use of vaccines in the United States have international implications, since many manufacturers of vaccines would prefer to have a single formulation for use throughout the world. Conjugate meningococcal vaccines would need to include a serogroup A component to maximize their effect on the control of disease in Africa and therefore the global burden of the disease.

CONCLUSIONS

Despite our improved understanding of the epidemiologic features and pathogenesis of meningococcal disease, risk factors, and advances in diagnosis and treatment, the disease remains a leading cause of meningitis and sepsis. Routine vaccination of high-risk populations is a reasonable public health strategy for controlling meningococcal disease, but the shortcomings of the quadrivalent polysaccharide vaccine limit its usefulness. New serogroup B vaccines, now being developed, are unlikely to be available in the next five years. How well meningococcal conjugate vaccines will work, especially with respect to the duration of protection and herd immunity, remains unclear, and there are unresolved strategic issues concerning formulations and target age groups. The greatest challenges may be integrating these vaccines into an already complicated immunization schedule in the United States and making them available, despite costs that may be relatively high, in sub-Saharan Africa. Although the problems are by no means solved, conjugate meningococcal vaccines have the potential to provide greatly improved control of meningococcal disease throughout the world.

REFERENCES

1. Vieusseux M. Mémoire sur la maladie qui a regné a Genêve au printemps de 1805. J Med Chir Pharmacol 1805;11:163.

2. Weichselbaum A. Ueber die Aetiologie der akuten Meningitis cerebrospinalis. Fortschr Med 1887;5:573-83.

3. Fischer M, Hedberg K, Cardosi P, et al. Tobacco smoke as a risk factor for meningococcal disease. Pediatr Infect Dis J 1997;16:979-83.

4. Perkins BA. New opportunities for prevention of meningococcal disease. JAMA 2000;283:2842-3.

5. Rosenstein NE, Perkins BA. Update on *Haemophilus influenzae* serotype b and meningococcal vaccines. Pediatr Clin North Am 2000;47:337-52.

6. Rosenstein NE, Perkins BA, Stephens DS, et al. The changing epidemiology of meningococcal disease in the United States, 1992-1996. J Infect Dis 1999;180:1894-901.

7. Jackson LA, Wenger JD. Laboratory-based surveillance for meningococcal disease in selected areas, United States, 1989–1991. MMWR CDC Surveill Summ 1993;42(SS-2):21-30.

8. Racoosin JA, Whitney CG, Conover C, Diaz PS. Serogroup Y meningococcal disease in Chicago, 1991-1997. JAMA 1998;280:2094-8.

9. Analysis of endemic meningococcal disease by serogroup and evaluation of chemoprophylaxis. J Infect Dis 1976;134:201-4.

10. Galaid EI, Cherubin CE, Marr JS, Schaefler S, Barone J, Lee W. Meningococcal disease in New York City, 1973 to 1978: recognition of groups Y and W-135 as frequent pathogens. JAMA 1980;244:2167-71.

11. Smilack JD. Group-Y meningococcal disease: twelve cases at an Army training center. Ann Intern Med 1974;81:740-5.

12. Band JD, Chamberland ME, Platt T, Weaver RE, Thornsberry C, Fraser DW. Trends in meningococcal disease in the United States, 1975-1980. J Infect Dis 1983;148:754-8.

13. Popovic T, Sacchi CT, Reeves MW, et al. *Neisseria meningitidis* serogroup W135 isolates associated with the ET-37 complex. Emerg Infect Dis 2000;6:428-9.

14. Filice GA, Hayes PS, Counts GW, Griffiss JM, Fraser DW. Risk of group A meningococcal disease: bacterial interference and cross-reactive bacteria among mucosal flora. J Clin Microbial 1985;22:152-6.

15. Jackson LA, Schuchat A, Reeves MW, Wenger JD. Serogroup C meningococcal outbreaks in the United States: an emerging threat. JAMA 1995;273:383-9.
16. Woods CR, Rosenstein N, Perkins BA. *Neisseria meningitidis* outbreaks in the United States, 1994-97. In: Abstracts of the 38th Annual Meeting of the Infectious Diseases Society of America, Denver, November 12–15, 1998:99. abstract.
17. Control and prevention of serogroup C meningococcal disease: evaluation and management of suspected outbreaks: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 1997;46(RR-5):13-21.
18. Schwartz B, Moore PS, Broome CV. Global epidemiology of meningococcal disease. Clin Microbiol Rev 1989;2:Suppl:S118-S124.
19. Connolly M, Noah N. Is group C meningococcal disease increasing in Europe? A report of surveillance of meningococcal infection in Europe 1993-6. Epidemiol Infect 1999;122:41-9.
20. World Health Organization Working Group. Control of epidemic meningococcal diseases: WHO practical guidelines. Lyon, France: Edition Foundation Marcel Merieux, 1995.
21. Fischer M, Perkins BA. *Neisseria meningitidis* serogroup B: emergence of the ET-5 complex. Semin Pediatr Infect Dis 1997;8:50-6.
22. Diermayer M, Hedberg K, Hoesly FC, et al. Epidemic serogroup B meningococcal disease in Oregon: the evolving epidemiology of the ET-5 strain. JAMA 1999;281:1493-7.
23. Serogroup B meningococcal disease — Oregon, 1994. MMWR Morb Mortal Wkly Rep 1995;44:121-4.
24. Sullivan A, Hedberg K, Reeves M, et al. Natural history of epidemic serogroup B meningococcal disease, Oregon 1998 and 1999. In: Abstracts of the International Conference on Emerging Infectious Diseases, Atlanta, July 16–19, 2000:143. abstract.
25. Greenwood BM, Bradley AK, Wall RA. Meningococcal disease and season in sub-Saharan Africa. Lancet 1985;2:829-30.
26. Greenwood BM, Bradley AK, Smith AW, Wall RA. Mortality from meningococcal disease during an epidemic in the Gambia, West Africa. Trans R Soc Trop Med Hyg 1987;81:536-8.
27. Response to epidemic meningitis in Africa, 1997. Wkly Epidemiol Rec 1997;42:313-8.
28. Gotschlich EC, Goldschneider I, Artenstein MS. Human immunity to the meningococcus. IV. Immunogenicity of group A and group C meningococcal polysaccharides in human volunteers. J Exp Med 1969;129:1367-84.
29. Maiden MCJ, Bygraves JA, Feil E, et al. Multilocus sequence typing: a portable approach to the identification of clones within populations of pathogenic microorganisms. Proc Natl Acad Sci U S A 1998;95:3140-5.
30. Swartley JS, Marfin AA, Edupuganti S, et al. Capsule switching of *Neisseria meningitidis.* Proc Natl Acad Sci U S A 1997;94:271-6.
31. Stephens DS, Hoffman LH, McGee ZA. Interaction of *Neisseria meningitidis* with human nasopharyngeal mucosa: attachment and entry into columnar epithelial cells. J Infect Dis 1983;148:369-76.
32. de Vries FP, Cole R, Dankert J, Frosch M, van Putten JP. *Neisseria meningitidis* producing the Opc adhesin binds epithelial cell proteoglycan receptors. Mol Microbiol 1998;27:1203-12.
33. Virji M, Evans D, Hadfield A, Grunert F, Teixeira AM, Watt SM. Critical determinants of host receptor targeting by *Neisseria meningitidis* and *Neisseria gonorrhoeae:* identification of Opa adhesiotopes on the N-domain of CD66 molecules. Mol Microbiol 1999;34:538-51.
34. Mosleh IM, Huber LA, Steinlein P, Pasquali C, Gunther D, Meyer TF. *Neisseria gonorrhoeae* porin modulates phagosome maturation. J Biol Chem 1998;273:35332-8.
35. Greenfield S, Sheehe PR, Feldman HA. Meningococcal carriage in a population of "normal" families. J Infect Dis 1971;123:67-73.
36. Caugant DA, Hoiby EA, Magnus P, et al. Asymptomatic carriage of *Neisseria meningitidis* in a randomly sampled population. J Clin Microbiol 1994;32:323-30.
37. Aycock WL, Mueller JH. Meningococcus carrier rates and meningitis incidence. Bacteriol Rev 1950;14:115-60.
38. Stephens DS. Uncloaking the meningococcus: dynamics of carriage and disease. Lancet 1999;353:941-2.
39. Pettersson A, Poolman JT, van der Ley P, Tommassen J. Response of *Neisseria meningitidis* to iron limitation. Antonie Van Leeuwenhoek 1997; 71:129-36.
40. Kahler CM, Stephens DS. Genetic basis for biosynthesis, structure, and function of meningococcal lipooligosaccharide (endotoxin). Crit Rev Microbiol 1998;24:281-334.
41. Goldschneider I, Gotschlich EC, Artenstein MS. Human immunity to the meningococcus. I. The role of humoral antibodies. J Exp Med 1969; 129:1307-26.
42. *Idem*. Human immunity to the meningococcus. II. Development of natural immunity. J Exp Med 1969;129:1327-48.
43. Fijen CA, Kuijper EJ, Drogari-Apiranthitou M, Van Leeuwen Y, Daha MR, Dankert J. Protection against meningococcal serogroup ACYW disease in complement-deficient individuals vaccinated with the tetravalent meningococcal capsular polysaccharide vaccine. Clin Exp Immunol 1998; 114:362-9.
44. Figueroa JE, Densen P. Infectious diseases associated with complement deficiencies. Clin Microbiol Rev 1991;4:359-95.
45. Francke EL, Neu HC. Postsplenectomy infection. Surg Clin North Am 1981;61:135-55.
46. Stephens DS, Hajjeh RA, Baughman WS, Harvey RC, Wenger JD, Farley MM. Sporadic meningococcal disease in adults: results of a 5-year population-based study. Ann Intern Med 1995;123:937-40.
47. Nuorti JP, Butler JC, Gelling L, Kod JL, Reingold AL, Vugia DJ. Epidemiologic relation between HIV and invasive pneumococcal disease in San Francisco County, California. Ann Intern Med 2000;132:182-90.
48. Hibberd ML, Sumiya M, Summerfield JA, Booy R, Levin M. Association of variants of the gene for mannose-binding lectin with susceptibility to meningococcal disease. Lancet 1999;353:1049-53.
49. Nadel S, Newport MJ, Booy R, Levin M. Variation in the tumor necrosis factor-alpha gene promoter region may be associated with death from meningococcal disease. J Infect Dis 1996;174:878-80.
50. Young LS, LaForce FM, Head JJ, Feeley JC, Bennett JV. A simultaneous outbreak of meningococcal and influenza infections. N Engl J Med 1972;287:5-9.
51. Moore PS, Hierholzer J, DeWitt W, et al. Respiratory viruses and mycoplasma as cofactors for epidemic group A meningococcal meningitis. JAMA 1990;264:1271-5.
52. Brundage JF, Zollinger WD. Evolution of meningococcal disease epidemiology in the U.S. Army. In: Vedros NA, ed. Evolution of meningococcal disease. Vol. 1. Boca Raton, Fla.: CRC Press, 1987:5-23.
53. Bruce M, Rosenstein NE, Capparella J, et al. Meningococcal disease in college students. In: Abstracts of the 39th Annual Meeting of the Infectious Diseases Society of America, Philadelphia, November 18–21, 1999: 63. abstract.
54. Meningococcal vaccine and college students: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2000;49(RR-7):11-20.
55. Gold R. Clinical aspects of meningococcal disease. In: Vedros NA, ed. Evolution of meningococcal disease. Vol. 2. Boca Raton, Fla.: CRC Press, 1987:69-97.
56. Griffiss JM, Yamasaki R, Estabrook M, Kim JJ. Meningococcal molecular mimicry and the search for an ideal vaccine. Trans R Soc Trop Med Hyg 1991;85:Suppl 1:S32-S36.
57. Koppes GM, Ellenbogen C, Gebhart RJ. Group Y meningococcal disease in United States Air Force recruits. Am J Med 1977;62:661-6.
58. Artenstein MS, Rust JH, Hunter DH, Lamson TH, Buescher EL. Acute respiratory disease and meningococcal infection in Army recruits. JAMA 1967;201:1004-7.
59. Barquet N, Gasser I, Domingo P, Moraga FA, Macaya A, Elcuaz R. Primary meningococcal conjunctivitis: report of 21 patients and review. Rev Infect Dis 1990;12:838-47.
60. Schaad UB. Arthritis in disease due to *Neisseria meningitidis.* Rev Infect Dis 1980;2:880-8.
61. Miller M, Millikin P, Griffin PS, Sexton RA, Yousuf M. Neisseria meningitidis urethritis: a case report. JAMA 1979;242:1656-7.
62. Flexner S. The results of serum treatment in thirteen hundred cases of epidemic meningitis. J Exp Med 1913;17:553-76.
63. Kirsch EA, Barton RP, Kitchen L, Giroir BP. Pathophysiology, treatment and outcome of meningococcemia: a review and recent experience. Pediatr Infect Dis J 1996;15:967-79.
64. Edwards MS, Baker CJ. Complications and sequelae of meningococcal infections in children. J Pediatr 1981;99:540-5.
65. Wylie PA, Stevens D, Drake W, Stuart J, Cartwright K. Epidemiology and clinical management of meningococcal disease in West Gloucestershire: retrospective, population based study. BMJ 1997;315:774-9.
66. Dunbar SA, Eason RA, Musher DM, Clarridge JE. Microscopic examination and broth culture of cerebrospinal fluid in diagnosis of meningitis. J Clin Microbiol 1998;36:1617-20.
67. Zollinger WD, Boslego J. Immunologic methods for diagnosis of infections by gram-negative cocci. In: Rose NR, Conway de Macario E, Folds JD, Lane HC, Nakamura RM, eds. Manual of clinical laboratory immunology. 5th ed. Washington, D.C.: ASM Press, 1997:473-83.
68. Carlone GM, Wenger JD, Perkins BA, Maslanka SE, Popovic T. *Haemophilus influenzae* type b, *Neisseria meningitidis, Streptococcus pneumoniae,* and *Corynebacterium diphtheriae* vaccines. In: Rose NR, Conway de Macario E, Folds JD, Lane HC, Nakamura RM, eds. Manual of clinical laboratory immunology. 5th ed. Washington, D.C.: ASM Press, 1997:458-69.
69. Turner PC, Southern KW, Spender NJB, Pullen H. Treatment failure in meningococcal meningitis. Lancet 1990;335:732-3.
70. Casado-Flores J, Osona B, Domingo P, Barquet N. Meningococcal

meningitis during penicillin therapy for meningococcemia. Clin Infect Dis 1997;25:1479.
71. Perez-Trallero E, Aldamiz-Echeverria L, Perez-Yarza EG. Meningococci with increased resistance to penicillin. Lancet 1990;335:1096.
72. Woods CR, Smith AL, Wasilauskas BL, Campos J, Givner LB. Invasive disease caused by *Neisseria meningitidis* relatively resistant to penicillin in North Carolina. J Infect Dis 1994;170:453-6.
73. Sutcliffe EM, Jones DM, el-Sheikh S, Percival A. Penicillin-insensitive meningococci in the UK. Lancet 1988;1:657-8.
74. Quagliarello VJ, Scheld WM. Treatment of bacterial meningitis. N Engl J Med 1997;336:708-16.
75. American Academy of Pediatrics Committee on Infectious Diseases. Therapy for children with invasive pneumococcal infections. Pediatrics 1997;99:289-99.
76. Pecoul B, Varaine F, Keita M, et al. Long-acting chloramphenicol versus intravenous ampicillin for treatment of bacterial meningitis. Lancet 1991;338:862-6.
77. Galimand M, Gerbaud G, Guibourdenche M, Riou J-Y, Courvalin P. High-level chloramphenicol resistance in *Neisseria meningitidis.* N Engl J Med 1998;339:868-74. [Erratum, N Engl J Med 1999;340:824.]
78. Quagliarello V, Scheld WM. Bacterial meningitis: pathogenesis, pathophysiology, and progress. N Engl J Med 1992;327:864-72.
79. Girgis NI, Farid Z, Mikhail IA, Farrag I, Sultan Y, Kilpatrick ME. Dexamethasone treatment for bacterial meningitis in children and adults. Pediatr Infect Dis J 1989;8:848-51.
80. Almog R, Block C, Gdalevich M, Lev B, Wiener M, Ashkenazi S. First recorded outbreaks of meningococcal disease in the Israel Defence Force: three clusters due to serogroup C and the emergence of resistance to rifampicin. Infection 1994;22:69-71.
81. Yagupsky P, Ashkenazi S, Block C. Rifampicin-resistant meningococci causing invasive disease and failure of chemoprophylaxis. Lancet 1993;341: 1152-3.
82. Cooper ER, Ellison RT, Smith GS, Blaser MJ, Reller LB, Paisley JW. Rifampin-resistant meningococcal disease in a contact patient given prophylactic rifampin. J Pediatr 1986;108:93-6.
83. Lepow ML, Beeler J, Randolph M, Samuelson JS, Hankins WA. Reactogenicity and immunogenicity of a quadrivalent combined meningococcal polysaccharide vaccine in children. J Infect Dis 1986;154:1033-6.
84. Scheifele DW, Bjornson G, Boraston S. Local adverse effects of meningococcal vaccine. CMAJ 1994;150:14-5.
85. Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2000;49(RR-7):1-10.
86. Rosenstein N, Levine O, Taylor JP, et al. Efficacy of meningococcal vaccine and barriers to vaccination. JAMA 1998;279:435-9.
87. Taunay AE, Feldman RA, Bactos CO, et al. Assessment of the protection conferred by anti-group C meningococcal polysaccharide vaccine to 6 to 36 month-old children. Rev Inst Adolfo Lutz 1978;38:77-82. (In Portuguese.)
88. Davies BI, Spanjaard L, Dankert J. Meningococcal chest infections in a general hospital. Eur J Clin Microbiol Infect Dis 1991;10:399-404.
89. Lepow ML, Perkins BA, Hughes PA, Poolman JT. Meningococcal vaccines. In: Plotkin SA, Orenstein WA, eds. Vaccines. 3rd ed. Philadelphia: W.B. Saunders, 1999:711-27.
90. Gold R, Lepow ML, Goldschneider I, Draper TF, Gotshlich EC. Kinetics of antibody production to group A and group C meningococcal polysaccharide vaccines administered during the first six years of life: prospects for routine immunization of infants and children. J Infect Dis 1979; 140:690-7.
91. Reingold AL, Broome CV, Hightower AW, et al. Age-specific differences in duration of clinical protection after vaccination with meningococcal polysaccharide A vaccine. Lancet 1985;2:114-8.
92. Zangwill KM, Stout RW, Carlone GM, et al. Duration of antibody response after meningococcal polysaccharide vaccination in US Air Force personnel. J Infect Dis 1994;169:847-52.
93. Granoff DM, Gupta RK, Belshe RB, Anderson EL. Induction of immunologic refractoriness in adults by meningococcal C polysaccharide vaccination. J Infect Dis 1998;178:870-4.
94. MacLennan J, Obaro S, Deeks J, et al. Immunologic memory five years after meningococcal A/C conjugate vaccination in infancy. J Infect Dis 2001;183:97-104.
95. Committee on Infectious Diseases. Meningococcal disease prevention and control strategies for practice-based physicians (addendum: recommendations for college students). Pediatrics 2000;106:1500-4.
96. Frasch CE. Vaccines for prevention of meningococcal disease. Clin Microbiol Rev 1989;2:Suppl:S134-S138.
97. Bjune G, Hoiby EA, Gronnesby JK, et al. Effect of outer membrane vesicle vaccine against group B meningococcal disease in Norway. Lancet 1991;338:1093-6.
98. Sierra GVG, Campa HC, Varcacel NM, et al. Vaccine against group B *Neisseria meningitidis:* protection trial and mass vaccination results in Cuba. NIPH Ann 1991;14:195-210.
99. Zollinger WD, Boslego J, Moran E. Meningococcal serogroup B vaccine protein trial and follow-up studies in Chile. NIPH Ann 1991;14:211-3.
100. Tondella MLC, Popovic T, Rosenstein NE, et al. Distribution of *Neisseria meningitidis* serogroup B serosubtypes and serotypes circulating in the United States. J Clin Microbiol 2000;38:3323-8.
101. Sacchi CT, Whitney AM, Popovic T, et al. Diversity and prevalence of PorA types in *Neisseria meningitidis* serogroup B in the United States, 1992-1998. J Infect Dis 2000;182:1169-76.
102. Haneberg B, Dalseg R, Wedege E, et al. Intranasal administration of a meningococcal outer membrane vesicle vaccine induces persistent local mucosal antibodies and serum antibodies with strong bactericidal activity in humans. Infect Immun 1998;66:1334-41.
103. Grothaus MC, Srivastava N, Smithson SL, et al. Selection of an immunogenic peptide mimic of the capsular polysaccharide of Neisseria meningitidis serogroup A using a peptide display library. Vaccine 2000;18:1253-63.
104. Pizza M, Scarlato V, Masignani V, et al. Identification of vaccine candidates against serogroup B meningococcus by whole-genome sequencing. Science 2000;287:1816-20.
105. Campagne G, Garba A, Fabre P, et al. Safety and immunogenicity of three doses of a *Neisseria meningitidis* A + C diphtheria conjugate vaccine in infants in Niger. Pediatr Infect Dis J 2000;19:144-50.
106. Twumasi PA, Kumah S, Leach A, et al. A trial of a group A plus group C meningococcal polysaccharide-protein conjugate vaccine in African infants. J Infect Dis 1995;171:632-8.
107. Leach A, Twumasi PA, Kumah S, et al. Induction of immunologic memory in Gambian children by vaccination in infancy with a group A plus group C meningococcal polysaccharide-protein conjugate vaccine. J Infect Dis 1997;175:200-4.
108. Ramsay ME, Andrews N, Kaczmarski EB, Miller E. Efficacy of meningococcal serogroup C conjugate vaccine in teenagers and toddlers in England. Lancet 2001;357:195-6.