43 - 160 Meningococcal Infections

160 Meningococcal Infections

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Gram-Negative Bacteria Manish Sadarangani, Andrew J. Pollard

Meningococcal

Infections ■ ■DEFINITION Infection with Neisseria meningitidis most commonly manifests as asymptomatic colonization in the nasopharynx of healthy adolescents and adults. Invasive disease occurs rarely, usually presenting as either bacterial meningitis or meningococcal septicemia. Patients may also present with occult bacteremia, pneumonia, septic arthritis, conjuncti vitis, and chronic meningococcemia. ■ ■ETIOLOGY AND MICROBIOLOGY N. meningitidis is a gram-negative aerobic diplococcus that colonizes humans only and causes disease after transmission to a susceptible individual. Several related neisserial organisms have been recognized, including the

pathogen N. gonorrhoeae and the commensals N. lactam ica, N. flavescens, N. mucosa, N. sicca, and N. subflava. N. meningitidis is a catalase- and oxidase-positive organism that utilizes glucose and maltose to produce acid. Meningococci associated with invasive disease are usually encap sulated with polysaccharide, and the antigenic nature of the capsule determines an organism's capsular group (serogroup) (Table 160-1).

TABLE 160-1 Structure of the Polysaccharide Capsule of Common Disease-Causing Meningococci MENINGOCOCCAL CAPSULAR GROUP CHEMICAL STRUCTURE OF OLIGOSACCHARIDE CURRENT DISEASE EPIDEMIOLOGY A 2-Acetamido-2-deoxyD-mannopyranosyl phosphate Epidemic disease mainly in sub-Saharan Africa; sporadic cases worldwide B α-2,8-Nacetylneuraminic acid Sporadic cases worldwide; propensity to cause hyperendemic disease C α-2,9-O-acetylneuraminic acid Small outbreaks and sporadic disease Y 4-O-α-D-glucopyranosylN-acetylneuraminic acid Sporadic disease and occasional small institutional outbreaks W 4-O-α-Dgalactopyranosyl-Nacetylneuraminic acid Sporadic disease; outbreaks of disease associated with mass gatherings; epidemics in subSaharan Africa X (α1→4) N-acetylD-glucosamine-1phosphate Sporadic disease and large outbreaks in the meningitis belt of Africa In total, 12 capsular groups have been identified (A–C, X–Z, E, W, H–J, and L), but just six of these—A, B, C, X, Y, and W (formerly W135)—account for the majority of cases of invasive disease. Group D is often listed as the thirteenth capsular group but has been identified as an unencapsulated variant of group C. Meningococci are commonly isolated from the nasopharynx in studies of carriage; the lack of capsule often is a result of phase variation of capsule expression, but as many as 16% of isolates lack the genes for capsule synthesis and assembly. These "capsule-null" meningococci and those that express capsules other than A, B, C, X, Y, and W are only rarely associated with invasive disease and are most commonly identified in the nasopharynx of asymptomatic carriers. Beneath the capsule, meningococci are surrounded by an outer phospholipid membrane containing lipopolysaccharide (LPS, endo toxin) and multiple outer-membrane proteins (Figs. 160-1 and 160-2). Antigenic variability in porins expressed in the outer membrane defines the serotype (PorB) and serosubtype (PorA) of the organ ism, and structural differences in LPS determine the immunotype. Serologic methods for typing meningococci are restricted by the limited availability of serologic reagents that can distinguish among the organisms' highly variable surface proteins. Where available, high-throughput antigen gene sequencing has superseded serology for FIGURE 160-1 Electron micrograph of Neisseria meningitidis. Black dots are gold-labeled polyclonal antibodies binding surface opacity proteins. Blebs of outer membrane can be seen being released from the bacterial surface (arrow). (Photo courtesy of D. Ferguson, Oxford University.)

Iron-binding proteins e.g., FetA RmpM Pilus Phospholipid bilayer NadA LPS PorA Opa PorB fHbp Transporter protein e.g., FbpA, SodC Pilus assembly apparatus Inner membrane transporter complex e.g., FbpB, FbpC FIGURE 160-2 Cross-section through surface structures of Neisseria meningitidis. LPS, lipopolysaccharide. (Reproduced with permission from M Sadarangani, AJ Pollard: Serogroup B meningococcal vaccines–an unfinished story. Lancet Infect Dis 10:112, 2010.) meningococcal typing. A large database of antigen gene sequences for the outer-membrane proteins PorA, PorB, FetA, Opa, NadA, neisse rial heparin binding antigen (NHBA), and factor H–binding protein (fHbp) is available online (pubmlst.org/organisms/neisseria-spp). The number of specialized iron-regulated proteins found in the meningo coccal outer membrane (e.g., FetA and transferrin-binding proteins) highlights the organisms' dependence on iron from human sources. A thin peptidoglycan cell wall separates the outer membrane from the cytoplasmic membrane. The

structure of meningococcal populations involved in local and global spread was first studied with multilocus enzyme electro phoresis (MLEE), which characterizes isolates according to differ ences in the electrophoretic mobility of cytoplasmic enzymes, followed by multilocus sequence typing (MLST), in which meningococci are characterized by sequence types assigned on the basis of sequences of internal fragments of seven housekeeping genes and, more recently, whole genome sequencing (>60,000 genomes are listed in PubMLST [https://pubmlst.org/organisms/neisseria-spp/]). While many distinct genotypes exist, a limited number of hyperinvasive lineages of N. men ingitidis have been recognized, persist over decades, and are responsi ble for the majority of cases of invasive meningococcal disease worldwide. Hyperinvasive lineages may be associated with more than one capsular group. The apparent genetic stability of these meningo coccal clones over decades and during wide geographic spread indi cates that they are well adapted to the nasopharyngeal environment of the host and to efficient transmission. The group B meningococcal genome is >2 megabases in length and contains 2158 coding regions. Many genes undergo phase variation that makes it possible to control their expression; this capacity is likely to be important in meningococcal adaptation to the host environment and evasion of the immune response. Meningococci can obtain DNA from their environment and can acquire new genes—including the capsular operon—such that capsule switching from one capsular group to another can occur. ■ ■EPIDEMIOLOGY Patterns of Disease Up to 500,000 cases of meningococcal disease are thought to occur worldwide each year, although the numbers have been declining recently as a result of both immunization programs and secular trends. About 10% of affected individuals die. There are several patterns of disease: epidemic, outbreak (small clusters of cases), hyper endemic, and sporadic or endemic. Epidemics have continued since the original descriptions of menin gococcal disease, especially affecting the sub-Saharan meningitis belt of

Africa, where tens to hundreds of thou sands of cases (caused mainly by capsular group A but also by capsular groups C, W, and X) may be reported over a season and rates may be as high as 1000 cases per 100,000 population. Capsular group A epidemics took place in Europe and North America after the First and Sec ond World Wars, and capsular group A outbreaks have been documented over the past 40 years in New Zealand, China, Nepal, Mongolia, India, Pakistan, Poland, and Russia. However, 65% of outbreaks reported in the meningitis belt between 2010 and 2017 were caused by capsular group C and 35% by capsular group W meningococci, following an immuniza tion campaign to control capsular group A outbreaks. New vaccines covering A, C, W, Y, and X are becoming available globally to extend control of outbreaks.

Polysaccharide capsule Outer membrane Periplasmic space Cytoplasmic membrane Clusters of cases occur where there is an opportunity for increased trans mission—i.e., in closed or semi-closed communities such as schools, colleges, universities, military training centers, and refugee camps. Over the past 4 decades, such clusters have been especially strongly linked with a particular clone (sequence type 11) that is mainly associated with capsular group C or W but was first described in association with capsular group B. Clusters of capsular group W disease associated with the Hajj pilgrimage in 2000/2001 led to a requirement for vaccination against meningococcal disease for travel to Saudi Arabia. Wider and more prolonged community outbreaks (hyper endemic disease) due to single clones of capsular group B meningococci account for ≥10 cases per 100,000. Regions affected in the past 35 years include the U.S. Pacific Northwest, New Zealand (both islands), and the province of Normandy in France. CHAPTER 160 Meningococcal Infections Most countries experience predominantly sporadic cases (0.0–2.8 cases per 100,000

population, but recently rates up to 10 cases per 100,000 have been reported in Africa), with many different disease-causing clones involved and usually no clear epidemiologic link between one case and another. The disease rate and the distribution of meningococcal strains vary in different regions of the world and also in any one location over time. For example, in the United States, the rate of meningococcal dis ease fell from 1.2 cases per 100,000 population in 1997 to 0.06 cases per 100,000 in 2021 (Fig. 160-3). Meningococcal disease in the United States was previously dominated by capsular groups B and C; however, in 2011– 2021, group B alone was predominant in children age <5 years, whereas disease in children over 11 years of age, adolescents, and adults was dominated by capsular groups C, W, and Y (Fig. 160-4). There has been a sharp, but small, increase in capsular group Y starting in 2022, with the highest rates in Americans of black ethnicity, individuals over 30 years of age, and those living with HIV. In contrast, rates of disease in England and Wales rose to >5 cases per 100,000 during the 1990s because of an increase in cases caused by the ST11 capsular group C clone. A mass immunization program against capsular group C was undertaken begin ning in 1999 and resulted in a large impact against the disease, leaving capsular group B meningococci as the predominant cause of infection in the past quarter century (87% of United Kingdom cases in 2021–2022). Introduction of a group B meningococcal (MenB) vaccine for infants in the United Kingdom in 2015 also led to a significant reduction in group B cases. A hyperinvasive ST11 clone bearing a W capsule emerged in South America and spread to various countries in Europe and in Aus tralia with cases peaking in 2016 in the United Kingdom. During the same decade, increases in capsular group Y disease were noted in various countries including Europe, Canada, and South Africa, highlighting the continuing emergence and re-emergence of capsular groups and geno types over time. Nevertheless, over the past 15 years, most industrialized nations have observed a decrease in meningococcal disease linked to the introduction of immunization against capsular group C meningococci

1.4 1.2 Cases per 100,000 population

0.8 0.6 0.4 0.2

FIGURE 160-3 Meningococcal disease in the United States, 1997–2021. ABCs, active bacterial cores. (Adapted from ABC Surveillance data, Centers for Disease Control and Prevention; https://www.cdc.gov/abcs/reports-findings/surv-reports.html.) in young children or teenagers and the use of adolescent immunization programs for capsular groups A, C, Y, and W. However, other factors, including changes in natural population immunity (induced by exposure from nasopharyngeal colonization) and prevalent clones of meningo cocci (factors that, in combination, probably explain the historical cyclic nature of meningococcal disease rates) as well as a reduction in smoking and passive exposure to tobacco smoke (driven by bans on smoking in buildings and public spaces) across wealthy countries, are likely to have contributed to the fall in cases. There are also data from the United King dom indicating that reductions in contacts between individuals during the COVID-19 pandemic led to further substantial declines in meningo coccal disease and that contact patterns remain altered and could have a sustained effect on transmission. PART 5 Infectious Diseases Factors Associated with Disease Risk and Susceptibility The principal determinant of disease susceptibility is age, with the peak incidence in the first year of life (Fig. 160-5). The susceptibility of the Quebec (Canada) January–July 2017

Europe

Israel

United States*

Brazil† African meningitis belt countries‡

A B

C Chile

W Argentina

Y

Other

NG FIGURE 160-4 Global percentage distribution of meningococcal capsular groups causing invasive meningococcal disease, 2017–2019. NG, non-groupable plus capsular groups other than B, C, W, and Y. (Adapted from C Pardo de Santayana et al: Epidemiology of invasive meningococcal disease worldwide from 2010–2019: A literature review. Epidemiol Infect 151:e57, 2023.)

B C Y Other

Year very young presumably results from an absence of specific adaptive immunity in combination with very close contact with colonized indi viduals, including parents. Compared with other age groups, infants appear to be particularly susceptible to capsular group B disease: >30% of capsular group B cases in the United States occur during the first year of life. In the early 1990s prior to use of vaccines in North Amer ica, the median ages for patients with disease due to capsular groups B, C, Y, and W were 6, 17, 24, and 33 years, respectively. In populations where capsular group A, C, W, and Y vaccines are being used with good coverage, disease from these capsular groups has become very rare in children. After early childhood, a second peak of disease occurs among ado lescents and young adults (15–25 years of age) in Europe and North America. It is thought that this peak relates to social behaviors and environmental exposures in this age group, as discussed below. Most cases of infection with N. meningitidis in developed countries today are sporadic, and the rarity of the disease suggests that individual Russia

A–0.23

Australia

New Zealand

South Africa

0.6 Incidence rate per 100,000 persons 0.5 0.4 0.3 0.2 0.1

<1 1–4 5–10 11–14 15–18 19–22 23–26 27–64 65+ Age in years FIGURE 160-5 Age distribution of capsular groups B and ACWY meningococcal disease United States, 2012–2021. (Adapted from https://www.cdc.gov/meningococcal/php/surveillance/.) susceptibility may be important. A number of factors probably contrib ute to individual susceptibility, including the host's genetic constitu tion, environment, and contact with a carrier or a case. The best-documented genetic association with meningococcal dis ease is complement deficiency, chiefly of the terminal complement components (C5–9), properdin, or factor D or those treated with complement inhibitors such as eculizumab; such a deficiency increases the risk of disease by up to 600-fold and may result in recurrent attacks. Complement components are believed to be important for the bacteri cidal activity of serum, which is considered the principal mechanism of immunity against invasive meningococcal disease. However, when inves tigated, complement deficiency is found in only a very small proportion of individuals with meningococcal disease (0.3%). Conversely, 7–20% of persons whose disease is caused by the less common capsular groups (W, X, Y, Z, E) have a complement deficiency. Complement deficiency appears to be associated with capsular group B disease only rarely. Indi viduals with recurrences of meningococcal disease, particularly those caused by non-B capsular groups, should be assessed for complement deficiency by measurement of total hemolytic complement activity. There is also limited evidence that hyposplenism (through reduction in phagocytic capacity), hypogammaglobulinemia (through absence of specific antibody), and HIV increase the risk of meningococcal disease. Genetic studies have revealed various associations with disease suscep tibility, including complement and mannose-binding lectin deficiency, single-nucleotide polymorphisms in Toll-like receptor (TLR) 4 and complement factor H, and variants of Fc gamma receptors. Factors that increase the chance of a susceptible individual's acquir ing N. meningitidis via the respiratory route also increase the risk of meningococcal disease. Acquisition occurs through close contact with carriers as a result of overcrowding (e.g., in poor socioeconomic settings, in refugee camps, during the Hajj pilgrimage to Mecca, dur ing freshman-year residence in college dormitories), recruitment into the military, and certain social behaviors (e.g., attendance at bars and nightclubs, kissing). Secondary cases may occur in close contacts of an index case (e.g., household members, persons kissing the infected individual); the risk to these contacts may be as high as 1000 times the background rate in the population. Factors that damage the naso pharyngeal epithelium also increase the risk of both colonization with N. meningitidis and invasive disease. The most important of these factors are tobacco smoking (odds ratio, 4.1) and passive exposure to tobacco smoke. In addition, recent viral respiratory tract infection, infection with Mycoplasma species, and winter or the dry season (in sub-Saharan Africa) have been associated with meningococcal disease; all of these factors presumably either increase the expression of adhe sion molecules in the nasopharynx, thus enhancing meningococcal adhesion, or facilitate meningococcal invasion of the bloodstream. ■ ■PATHOGENESIS N. meningitidis has evolved as an effective colonizer of the human nasopharynx, with asymptomatic infection rates of >25% described in some series of adolescents and young adults and among residents

of crowded communities. Point-prevalence stud ies reveal widely divergent rates of carriage for different types of meningococci. This variation suggests that some types may be adapted to a short duration of carriage with frequent transmission to maintain the population, while others may be less efficiently transmitted but may overcome this dis advantage by colonizing for a long period. Despite the high rates of carriage among adolescents and young adults, only ~10% of adults carry menin gococci, and colonization is very rare in early childhood. Many of the same factors that increase the risk of meningococcal disease also increase the risk of carriage. Colonization of the

nasopharynx involves a series of interactions of meningococcal adhesins (e.g., Opa proteins and pili) with their ligands on the epithelial mucosa. N. meningitidis produces an IgA1 protease that is likely to reduce interruption of colonization by mucosal IgA.

B ACWY Colonization should be considered the normal state of meningococ cal infection, with an increased risk of invasion being the unfortunate consequence (for both host and organism) of adaptations of hyperin vasive meningococcal lineages to favor their survival. The meningo coccal capsule is an important virulence factor: acapsular strains only very rarely cause invasive disease. The capsule provides resistance to phagocytosis and may be important in preventing desiccation during transmission between hosts. Antigenic diversity in surface structures and an ability to vary levels of their expression probably have evolved as important factors in maintaining meningococcal populations within and between individual hosts. CHAPTER 160 Invasion through the mucosa into the bloodstream occurs rarely, usually within a few days of acquisition of an invasive strain by a sus ceptible individual. Only occasional cases of prolonged colonization prior to invasion have been documented. Once the organism is in the bloodstream, its growth may be limited if the individual is partially immune, although bacteremia may allow seeding of another site, such as the meninges or the joints. Alternatively, unchecked proliferation may continue, resulting in high bacterial counts in the circulation. During growth, meningococci release blebs of outer membrane (Fig. 160-1) containing outer-membrane proteins and LPS. Endotoxin binds cell-bound CD14 in association with TLR4 to initiate an inflammatory cascade with the release of high levels of various mediators, including tumor necrosis factor (TNF) α, soluble TNF receptor, interleukin (IL) 1, IL-1 receptor antagonist, IL-1β, IL-6, IL-8, IL-10, plasminogenactivator inhibitor 1 (PAI-1), and leukemia inhibitory factor. Soluble CD14-bound endotoxin acts as a mediator of endothelial activation. The severity of meningococcal disease is related both to the levels of endotoxin in the blood and to the magnitude of the inflammatory response. The latter is determined to some extent by polymorphisms in the inflammatory response genes (and their inhibitors), and the release of the inflammatory cascade heralds the development of meningococ cal septicemia (meningococcemia). Endothelial injury is central to many clinical features of meningococcemia, including increased vas cular permeability, pathologic changes in vascular tone, loss of throm boresistance, intravascular coagulation, and myocardial dysfunction. Endothelial injury leads to increased vascular permeability (attributed to loss of glycosaminoglycans and endothelial proteins), with subse quent gross proteinuria. Leakage of fluid and electrolytes into the tis sues from capillaries (“capillary leak syndrome”) leads to hypovolemia, tissue edema, and pulmonary edema. Initial compensation results in vasoconstriction and tachycardia, although cardiac output eventually falls. While resuscitation fluids may restore circulating volume, tissue edema will continue to increase, and, in the lung, the consequence may be respiratory failure. Meningococcal Infections Intravascular thrombosis (caused by activation of procoagulant pathways in association with upregulation of tissue factor on the endothelium) occurs in some patients with meningococcal disease and results in purpura fulminans and infarction of areas of skin or even of whole limbs. At the same time, multiple anticoagulant pathways

are downregulated through loss of endothelial thrombomodulin and protein C receptors and decreases in levels of antithrombin III, protein C, protein S, and tissue factor pathway inhibitor. Thrombolysis is also profoundly impaired in meningococcal sepsis through the release of high levels of PAI-1.

Shock in meningococcal septicemia appears to be attributable to a combination of factors, including hypovolemia, which results from the capillary leak syndrome secondary to endothelial injury, and myo cardial depression, which is driven by hypovolemia, hypoxia, meta bolic derangements (e.g., hypocalcemia), and cytokines (e.g., IL-6). Decreased perfusion of tissues as a result of intravascular thrombosis, vasoconstriction, tissue edema, and reduced cardiac output in menin gococcal septicemia can cause widespread organ dysfunction, includ ing renal impairment and—later in the disease—a decreased level of consciousness due to central nervous system involvement. Bacteria that reach the meninges cause a local inflammatory response—with release of a spectrum of cytokines similar to that seen in septicemia—that presents clinically as meningitis and is thought to determine the severity of neuronal injury. Local endothelial injury may result in cerebral edema and rapid onset of raised intracranial pressure in some cases. ■ ■CLINICAL MANIFESTATIONS As discussed above, the most common form of infection with N. men ingitidis is asymptomatic carriage of the organism in the nasopharynx. Despite the location of infection in the upper airway, meningococcal pharyngitis is rarely reported; however, upper respiratory tract symp toms are common prior to presentation with invasive disease. It is not clear whether these symptoms relate to preceding viral infection (which may promote meningococcal acquisition and/or invasion) or to meningococcal acquisition itself. After acquiring the organism, suscep tible individuals develop disease manifestations in 1–10 days (usually <4 days, although colonization for 11 weeks has been documented). PART 5 Infectious Diseases Along the spectrum of presentations of meningococcal disease, the most common clinical syndromes are meningitis and meningo coccal septicemia. In fulminant cases, death may occur within hours of the first symptoms. Occult bacteremia is also recognized and, if untreated, progresses in two-thirds of cases to focal infection, includ ing meningitis or septicemia. Meningococcal disease may also present as pneumonia, pyogenic arthritis or osteomyelitis, purulent pericar ditis, endophthalmitis, conjunctivitis, primary peritonitis, or (rarely) urethritis. Perhaps because it is difficult to diagnose, meningococcal pneumonia is not commonly reported but is associated with capsu lar groups Y, W, and Z and appears most often to affect individuals

> 10 years of age. Rash A nonblanching rash (petechial or purpuric) develops in 80% of cases of meningococcal disease; however, the rash is often absent early in the illness. Usually initially blanching in nature (mac ules, maculopapules, or urticaria) and indistinguishable from more common viral rashes, the rash of meningococcal infection becomes petechial or frankly purpuric over the hours after onset. In the most severe cases, large purpuric lesions develop (purpura fulminans; Fig. A1-41). Some patients (including those with overwhelming sepsis) may have no rash. While petechial rash and fever are important signs of meningococcal disease, <10% of children (and, in some clinical settings, <1% of patients) with this presentation are found to have meningococcal disease. Most patients presenting with a petechial or purpuric rash have a viral infection (Table 160-2). The skin lesions exhibit widespread endothelial necrosis and occlusion of small vessels in the dermis and subcutaneous tissues, with a neutrophilic infiltrate. Meningitis Meningococcal meningitis commonly presents as non specific manifestations, including fever, vomiting, and (especially in infants and young children) irritability, and is indistinguishable from other forms of bacterial

> meningitis unless there is an associated pete chial or purpuric rash, which occurs in two-thirds of cases. Headache is rarely reported in early childhood but is more common in later child hood and adulthood. When headache is present, the following features, in association with fever or a history of fever, are suggestive of bacterial

TABLE 160-2 Common Causes of Petechial or Purpuric Rashes Enteroviruses Influenza and other respiratory viruses Measles virus Epstein-Barr virus Cytomegalovirus Parvovirus Deficiency of protein C or S (including post-varicella protein S deficiency) Platelet disorders (e.g., idiopathic thrombocytopenic purpura, drug effects, bone marrow infiltration) Henoch-Schönlein purpura, connective tissue disorders, trauma (including nonaccidental injuries in children) Pneumococcal, streptococcal, staphylococcal, or gram-negative bacterial sepsis meningitis: neck stiffness, photophobia, decreased level of conscious ness, seizures or status epilepticus, and focal neurologic signs. Classic signs of meningitis, such as neck stiffness and photophobia, are often absent in infants and young children with bacterial meningitis, who more usually present with fever and irritability and may have a bulging fontanelle. While 30–50% of patients present with a meningitis syndrome alone, up to 40% of meningitis patients also present with some features of septicemia. Most deaths from meningococcal meningitis alone (i.e., without septicemia) are associated with raised intracranial pressure presenting as a reduced level of consciousness, relative bradycardia and hypertension, focal neurologic signs, abnormal posturing, and signs of brainstem involvement—e.g., unequal, dilated, or poorly reac tive pupils; abnormal eye movement; and impaired corneal responses (Chap. 30). Septicemia Meningococcal septicemia alone accounts for up to 20% of cases of meningococcal disease. The condition may progress from early nonspecific symptoms to death within hours. Mortality rates among children with this syndrome have been high (25–40%), but early aggressive management (as discussed below) may reduce the figure to <10%. Early symptoms are nonspecific and suggest an influ enza-like illness with fever, headache, and myalgia accompanied by vomiting and abdominal pain. As discussed above, the rash, if present, may appear to be viral early in the course until petechiae or purpuric lesions develop. Purpura fulminans occurs in severe cases (Fig. A1-41), with multiple large purpuric lesions and signs of peripheral ischemia. Surveys of patients have indicated that limb pain, pallor (including a mottled appearance and cyanosis), and cold hands and feet may be prominent. Shock is manifested by tachycardia, poor peripheral per fusion, tachypnea, and oliguria. Decreased cerebral perfusion leads to confusion, agitation, or decreased level of consciousness. With progressive shock, multiorgan failure ensues; hypotension is a late sign in children, who more commonly present with compensated shock (tachycardia, poor peripheral perfusion, and normal blood pressure). Poor outcome is associated with an absence of meningism, hypoten sion, young age, coma, relatively low temperature (<38°C), leukopenia, and thrombocytopenia. Spontaneous hemorrhage (pulmonary, gastric, or cerebral) may result from consumption of coagulation factors and thrombocytopenia. Chronic Meningococcemia Chronic meningococcemia, which is rarely recognized, presents as repeated episodes of petechial rash (Fig. A1-42) associated with fever, joint pain, features of arthritis, and splenomegaly that may progress to acute meningococcal septicemia if untreated. During the relapsing course, bacteremia characteristically clears without treatment and then recurs. The differential diagnosis includes bacterial endocarditis, acute rheumatic fever, Henoch-Schön lein purpura, infectious mononucleosis, disseminated gonococcal

infection, and immune-mediated vasculitis. This condition has been associated with complement deficiencies in some cases and with inad equate sulfonamide therapy in others.

A study from the Netherlands found that half of isolates from patients with chronic meningococcemia had an underacylated lipid A (part of the surface LPS molecule) due to an lpxL1 gene mutation, which markedly reduces the inflammatory response to endotoxin. Postmeningococcal Reactive Disease In a small proportion of patients, an immune complex disease develops ~4–10 days after the onset of meningococcal disease, with manifestations that include a maculopapular or vasculitic rash (2% of cases), arthritis (up to 8% of cases), iritis (1%), pericarditis, and/or polyserositis associated with fever. The immune complexes involve meningococcal polysaccharide antigen and result in immunoglobulin and complement deposition with an inflammatory infiltrate. These features resolve spontaneously without sequelae. It is important to recognize this condition since a new onset of fever and rash, and/or arthritis, can lead to concerns about relapse of meningococcal disease and unnecessarily prolonged antibiotic treatment. ■ ■DIAGNOSIS Like other invasive bacterial infections, meningococcal disease may pro duce elevations of the white blood cell (WBC) count and of values for inflammatory markers (e.g., C-reactive protein and procalcitonin levels or the erythrocyte sedimentation rate). Values may be normal or low in rapidly progressive disease, and a lack of rise in these laboratory test val ues does not exclude the diagnosis. However, in the presence of fever and a petechial rash, these elevations are suggestive of meningococcal disease. In patients with severe meningococcal septicemia, common laboratory findings include hypoglycemia, acidosis, hypokalemia, hypocalcemia, hypomagnesemia, hypophosphatemia, anemia, and coagulopathy. Although meningococcal disease is often diagnosed on clinical grounds, in suspected meningococcal meningitis or meningococcemia, blood should routinely be sent for culture to confirm the diagnosis and to facilitate public health investigations; blood cultures are positive in up to 75% of cases. Culture media containing sodium polyanethol sul fonate, which may inhibit meningococcal growth, should be avoided. Meningococcal viability is reduced if there is a delay in transport of the specimen to the microbiology laboratory for culture or in plating of cerebrospinal fluid (CSF) samples. In countries where treatment with antibiotics before hospitalization is recommended for meningococcal disease, the majority of clinically suspected cases are culture negative. Real-time polymerase chain reaction (PCR) analysis of whole-blood samples increases the diagnostic yield by >40%, and results obtained with this method may remain positive for several days after adminis tration of antibiotics. Unless contraindications exist (raised intracranial pressure, uncor rected shock, disordered coagulation, thrombocytopenia, respiratory insufficiency, local infection, ongoing convulsions), lumbar puncture should be undertaken to identify and confirm the etiology of suspected meningococcal meningitis, whose presentation cannot be distinguished from that of meningitis of other bacterial causes. Some authorities have recommended a computed tomography (CT) brain scan prior to lum bar puncture because of the risk of cerebral herniation in patients with raised intracranial pressure. However, a normal CT scan is not uncom mon in the presence of raised intracranial pressure in meningococcal meningitis, and the decision to perform a lumbar puncture should be made on clinical grounds. CSF features of meningococcal meningitis (elevated protein level and WBC count, decreased glucose level) are indistinguishable from those of other types of bacterial meningitis unless a gram-negative diplococcus is identified. (Gram’s staining is up to 80% sensitive for meningococcal meningitis.) CSF should be submit ted for culture (sensitivity, 90%) and (where available) PCR analysis. CSF antigen testing with latex agglutination is insensitive and should be replaced by molecular diagnosis when possible. Lumbar puncture

should generally be avoided in meningococcal septicemia, as positioning for the procedure may critically compromise the patient’s circulation in the context of hypovolemic shock. Delayed lumbar puncture may still be useful when the diagnosis is uncertain, particularly if molecular diagnostic technology is available.

In other types of focal infection, culture and PCR analysis of nor mally sterile body fluids (e.g., synovial fluid) may aid in the diagnosis. Although some authorities have recommended cultures of scrapings or aspirates from skin lesions, this procedure adds little to the diag nostic yield when compared with a combination of blood culture and PCR analysis. Urinary antigen testing also is insensitive, and serologic testing for meningococcal infection has not been adequately studied. Because N. meningitidis is a component of the normal human nasopha ryngeal flora, identification of the organism on throat swabs has lim ited diagnostic value, but strains identified in the nasopharynx in the context of a probable case are likely to be those responsible for disease.

TREATMENT Meningococcal Infections Death from meningococcal disease is associated most commonly with hypovolemic shock (meningococcemia) and occasionally with raised intracranial pressure (meningococcal meningitis). Therefore, management should focus on the treatment of these urgent clinical issues in addition to the administration of specific antibiotic ther apy. Delayed recognition of meningococcal disease or its associated physiologic derangements, together with inadequate emergency management, is associated with poor outcome. Since the disease is rare, protocols for emergency management have been developed (see https://www.meningitis.org/healthcare-professionals/resources). Airway patency may be compromised if the level of conscious ness is depressed as a result of shock (impaired cerebral perfusion) or raised intracranial pressure; this situation may require inter vention. In meningococcemia, pulmonary edema and pulmonary oligemia (presenting as hypoxia) require oxygen therapy or elec tive endotracheal intubation. In cases with shock, aggressive fluid resuscitation (with replacement of the circulating volume several times in severe cases) and inotropic support may be necessary to maintain cardiac output. If shock persists after volume resuscita tion at 40 mL/kg, the risk of pulmonary edema is high, and elective intubation is recommended to improve oxygenation and decrease the work of breathing. Metabolic derangements, including hypo glycemia, acidosis, hypokalemia, hypocalcemia, hypomagnesemia, hypophosphatemia, anemia, and coagulopathy, should be antici pated and corrected. However, aggressive fluid resuscitation with unbuffered electrolyte solutions was found to increase mortality in febrile African children. Studies of the effects of lower volumes of buffered solutions and similar studies in resource-rich settings are required. In the presence of raised intracranial pressure, manage ment includes correction of coexistent shock and neurointensive care to maintain cerebral perfusion. CHAPTER 160 Meningococcal Infections Empirical antibiotic therapy for suspected meningococcal disease consists of a third-generation cephalosporin such as ceftriaxone (75–100 mg/kg per d [maximum, 4 g/d] in one or two divided IV doses) or cefotaxime (200 mg/kg per day [maximum, 8 g/d] in four divided IV doses) to cover the various other (potentially penicillinresistant) bacteria that may produce an indistinguishable clinical syndrome. In many settings, vancomycin (usually 4–60 mg/kg

per d in two to four divided IV doses) is also recommended for the empiric management of sepsis and/or suspected bacterial menin gitis. Although unusual in most isolates, reduced meningococcal sensitivity to penicillin (a minimal inhibitory concentration of 0.12–1.0 μg/mL) has been reported.

Use of penicillin is appropriate once information on antimicrobial resistance patterns is available. Both meningococcal meningitis and meningococcal septicemia are conventionally treated for 7 days, although courses of 3–5 days may be equally effective. Furthermore, a single dose of ceftriaxone or an oily suspension of chloramphenicol has been used success fully in resource-poor settings. No data are available to guide the duration of treatment for meningococcal infection at other foci (e.g., pneumonia, arthritis); antimicrobial therapy is usually continued until clinical and laboratory evidence of infection has resolved. Cultures usually become sterile within 24 h of initiation

of appropriate antibiotic chemotherapy. Eye infections (including keratoconjunctivitis and endophthalmitis) should be treated with a combination of topical and systemic IV therapy, with some small studies suggesting an increased risk of bacteremia when treated with topical therapy alone.

The use of glucocorticoids for adjunctive treatment of meningo coccal meningitis remains controversial since no relevant studies have had sufficient power to determine true efficacy in this condi tion. One large study in adults did indicate a trend toward benefit, and in clinical practice, a decision to use glucocorticoids would best precede a definite microbiologic diagnosis. Therapeutic doses of glucocorticoids are not recommended in meningococcal septice mia, but many intensivists recommend replacement glucocorticoid doses for patients who have refractory shock in association with impaired adrenal gland responsiveness, management that is sup ported by limited evidence. Various other adjunctive therapies for meningococcal disease have been considered, but few have been subjected to clinical tri als and none can currently be recommended. An antibody to LPS (HA1A) failed to confer a demonstrable benefit. Recombinant bactericidal/permeability-increasing protein (which is not currently available) was tested in a study that had inadequate power to show an effect on mortality rates; however, there were trends toward lower mortality rates among patients who received a complete infu sion, and this group also had fewer amputations, fewer blood-prod uct transfusions, and a significantly improved functional outcome. Given that protein C concentrations are reduced in meningococcal disease, the use of activated protein C has been considered. A survival benefit was demonstrated in adult sepsis trials; however, trials in pediatric sepsis (of particular relevance for meningococcal disease) found no benefit and indicated a potential risk of bleeding complications with use of activated protein C. PART 5 Infectious Diseases The postmeningococcal immune-complex inflammatory syn drome has been treated with nonsteroidal anti-inflammatory agents until spontaneous resolution occurs. ■ ■COMPLICATIONS About 10% of patients with meningococcal disease die despite the availability of antimicrobial therapy and other intensive medical inter ventions. The most common complication of meningococcal disease (10% of cases) is scarring after necrosis of purpuric skin lesions, for which skin grafting may be necessary. The lower limbs are most often affected; next in frequency are the upper limbs, the trunk, and the face. On average, 13% of the skin surface area is involved. Amputations are necessary in 1–2% of survivors of meningococcal disease because of a loss of tissue viability after peripheral ischemia or compartment syn dromes. Unless there is local infection, amputation should usually be delayed to allow the demarcation between viable and nonviable tissue to become apparent. Approximately 5% of patients with meningococcal disease suffer hearing loss, and 7% have neurologic complications. In one study, pain was reported by 21% of survivors, and in an analysis of capsular group B meningococcal disease (the MOSAIC study), as many as one-quarter of survivors had psychological disorders. In some investigations, the rate of

complications is higher for capsular group C disease (mostly associated with the ST11 clone) than for capsular group B disease. In patients with severe hypovolemic shock, renal perfusion may be impaired and prerenal failure is common, but permanent renal replacement therapy is rarely needed. Several studies suggest adverse psychosocial outcomes after menin gococcal disease, with reduced quality of life, lowered self-esteem, and poorer neurologic development, including increased rates of attention deficit/hyperactivity disorder and special educational needs. Other studies have not found evidence of such outcomes. ■ ■PROGNOSIS Several prognostic scoring systems have been developed to identify patients with meningococcal disease who are least likely to survive. Factors associated with a poorer prognosis are shock; young age

(infancy), old age, and adolescence; coma; purpura fulminans; dis seminated intravascular coagulation; thrombocytopenia; leukopenia; absence of meningitis; metabolic acidosis; low plasma concentrations of antithrombin and proteins S and C; high blood levels of PAI-1; and a low erythrocyte sedimentation rate or C-reactive protein level. The Glasgow Meningococcal Septicaemia Prognostic Score (GMSPS) performs well and may be clinically useful for severity assessment in meningococcal disease. However, scoring systems do not direct the cli nician to specific interventions, and the priority in management should be recognition of compromised airways, breathing, or circulation and direct, urgent intervention. Most patients improve rapidly with appro priate antibiotics and supportive therapy. Fulminant meningococcemia is more likely to result in death or ischemic skin loss than is meningitis; optimal emergency management may reduce mortality rates among the most severely affected patients. ■ ■PREVENTION Since mortality rates in meningococcal disease remain high despite improvements in intensive care management, immunization is the only rational approach to prevention at a population level. Secondary cases are common among household and “kissing” contacts of cases, and secondary prophylaxis with antibiotics is widely recommended for these contacts (see below). Polysaccharide Vaccines Purified meningococcal capsular poly saccharide was first used for immunization in the 1960s. Meningo coccal polysaccharide vaccines were formulated as either bivalent (capsular groups A and C) or quadrivalent (capsular groups A, C, Y, and W), with 50 µg of each polysaccharide per dose. Local reactions (erythema, induration, and tenderness) occurred in up to 40% of vac cinees, but serious adverse events (including febrile convulsions in young children) are very rarely reported. In adults, the vaccines are immunogenic, but immunity is relatively short-lived (with antibody levels above baseline for only 2–10 years), and booster doses do not induce a further rise in antibody concentration. Indeed, a state of immunologic hyporesponsiveness has been widely reported to follow booster doses of plain polysaccharide vaccines. The repeating sugar units of these vaccines cross-link B-cell receptors to drive specific memory B cells to become plasma cells and produce protective anti body. Because meningococcal polysaccharides are T cell–independent antigens, no memory B cells are produced after immunization, and the memory B-cell pool is depleted such that fewer polysaccharidespecific cells are available to respond to a subsequent dose of vaccine (Fig. 160-6). The clinical relevance of hyporesponsiveness is unknown. Plain polysaccharide vaccines generally are not immunogenic in early childhood, possibly because marginal-zone B cells are involved in polysaccharide responses and maturation of the splenic marginal zone is not complete until 18 months to 2 years of age. The efficacy of the meningococcal capsular group C component is >90% in young adults, but there is no protection in infants; no efficacy data are available for the capsular group Y and W polysaccharides in this age group. Group A meningococcal polysaccharides are exceptional in that they are effective in preventing disease at all ages. Two doses admin istered 2–3 months apart to children 3–18 months of age or a single

dose administered to older children or adults has a protective efficacy rate of >95%. The vaccine was previously used widely in the control of outbreaks of meningococcal disease in the African meningitis belt, pro viding protection for 3–5 years. The plain polysaccharide vaccines have been largely superseded by protein–polysaccharide conjugate vaccines. There is no meningococcal capsular group B plain polysaccharide vaccine because α-2,8-N-acetylneuraminic acid is expressed on the surface of neural cells in the fetus such that the B polysaccharide is perceived as “self” and therefore is not immunogenic in humans. Conjugate Vaccines The poor immunogenicity of plain polysac charide vaccines in infancy has been overcome by chemical conjuga tion of the polysaccharides to a carrier protein (CRM197, tetanus toxoid, or diphtheria toxoid). Conjugates that contain monovalent capsular group C polysaccharide and quadrivalent vaccines with A, C, Y, and W polysaccharides were developed, and vaccines with other antigen

Polysaccharide IgG2 and IgM BCR Depletion of memory B-cell pool B cell Plasma cell No production of memory B cells A Polysaccharide Carrier protein Polysaccharidespecific plasma cell IgG1 and IgG3 BCR Polysaccharidespecific B cell Internalization and processing of carrier protein MHC Class II CD40 CD80 or CD86 CD28 CD40L TCR Carrier peptide– specific T cell B FIGURE 160-6 A. Polysaccharides from the encapsulated bacteria that cause disease in early childhood stimulate B cells by cross-linking the B-cell receptor (BCR) and driving the production of immunoglobulins. There is no production of memory B cells, and the B-cell pool may be depleted by this process such that subsequent immune responses are decreased. B. The carrier protein from protein–polysaccharide conjugate vaccines is processed by the polysaccharide-specific B cell, and peptides are presented to carrier peptide–specific T cells, with the consequent production of both plasma cells and memory B cells. MHC, major histocompatibility complex; TCR, T-cell receptor. (Reproduced with permission from AJ Pollard: Maintaining protection against invasive bacteria with protein–polysaccharide conjugate vaccines. Nat Rev Immunol 9:213, 2009.) combinations were produced for some markets (e.g., tetanus conjugates with capsular group C and/or Y polysaccharide and Haemophilus influ enzae type b polysaccharide). After immunization, peptides from the carrier protein are conventionally thought to be presented by polysac charide-specific B cells to peptide-specific T cells in association with major histocompatibility complex (MHC) class II molecules. (Some data suggest that carrier protein peptide may actually be presented in association with an oligosaccharide and MHCII.) The result is a

T cell–dependent immune response that allows production of antibody and generation of an expanded B-cell memory pool. Unlike responses to booster doses of plain polysaccharides, responses to booster doses of conjugate vaccines have the characteristics of memory responses. Indeed, conjugate vaccines overcome the hyporesponsiveness induced by plain polysaccharides by replenishing the memory pool. The reacto genicity of conjugate vaccines is similar to that of plain polysaccharide vaccines. The first widespread use of capsular group C meningococcal conju gate vaccine (MenC) came in 1999 in the United Kingdom after a rise in capsular group C disease. A mass vaccination campaign involving all individuals <19 years of age was undertaken, and the number of

laboratory-confirmed capsular group C cases fell from 955 in 1998–1999 to just 29 in 2011–2012. The effectiveness of the immunization pro gram was attributed both to direct protection of immunized persons and to reduced transmission of the organism in the population as a result of decreased rates of colonization among the immunized (i.e.,

Differentiation Antibody production Antibody production CHAPTER 160 T-cell help Memory response Polysaccharidespecific memory B cell Meningococcal Infections herd immunity). Data on immunogenicity and effectiveness have shown that the duration of protection is short when the vaccine is administered in early childhood; thus, booster doses are needed to maintain population immunity. In contrast, immunity after a dose of vaccine given in adolescence appears to be more prolonged. In 2005, the first quadrivalent conjugate meningococcal vaccine containing A, C, Y, and W polysaccharides conjugated to diphtheria toxoid was initially recommended for all children >11 years of age in the United States and for persons 2–55 years of age in Canada. Such vaccines are now recommended by the Advisory Committee on Immu nization Practices (ACIP) for routine administration to individuals 11–12 years of age, with a booster dose at 16 years of age; only a single dose is given to persons >16 years of age. These vaccines are also rec ommended for high-risk persons from 2 months to 55 years of age (see https://www.cdc.gov/mmwr/volumes/69/rr/rr6909a1.htm). Uptake was slow initially, but U.S. data show an efficacy rate of 82% in the first year after vaccination and 69% at 8 years (diphtheria conju gate vaccine). Early reports of an increase in the risk of Guillain-Barré syndrome after immunization with the diphtheria conjugate vaccine have not been substantiated with further observation. Quadrivalent conjugate vaccines with tetanus or CRM197 as carrier protein are now available in many countries and are used for high-risk groups and in routine programs for toddlers and adolescents. Use of the A, C, W, and Y conjugate vaccine for adolescents since 2015 in the United Kingdom has led to a large reduction in meningococcal disease caused by these

capsular groups. This conjugate vaccine provided direct protection for vaccinated individuals (combined vaccine effectiveness of 94% against C, W, and Y disease) and marked reductions in carriage—a 36% reduc tion in carriage of capsular groups C, W, and Y combined at 2 months postvaccination—along with evidence of herd immunity. Indeed, modeling of the decline of cases and carriage in the United Kingdom indicates elimination of these capsular groups over the coming decade.

A monovalent capsular group A vaccine, manufactured in India, was licensed in 2010 and rolled out to countries in the sub-Saharan African meningitis belt in a mass immunization campaign. There is strong evidence that this vaccine has been highly effective in controlling epi demic meningococcal disease in the region, with >90% reduction in disease in vaccinated populations. New combination vaccines covering A, C, W, X, and Y have been developed and are set to replace monova lent MenA vaccines in Africa as part of the WHO’s global roadmap “Defeating Meningitis by 2030” (https://www.who.int/publications/i/ item/9789240026407). Vaccines Based on Subcapsular Antigens The lack of immu nogenicity of the group B capsule has led to the development of vac cines based on subcapsular antigens. Various surface components have been studied in early-phase clinical trials. Outer-membrane vesicles (OMVs) containing outer-membrane proteins, phospholipid, and LPS can be extracted from cultures of N. meningitidis by detergent treat ment (Fig. 160-7). OMVs prepared in this way were used in efficacy trials with a Norwegian outbreak strain and reduced the incidence of group B disease among 14- to 16-year-old schoolchildren by 53%. Sim ilarly, OMV vaccines constructed from local outbreak strains in Cuba and New Zealand have had reported efficacy rates of >70%. These OMV vaccines appear to produce strain-specific immune responses, with only limited cross-protection, and are therefore best suited to clonal outbreaks (e.g., those in Cuba and New Zealand as well as others in Norway and the province of Normandy in France). PART 5 Infectious Diseases Several purified surface proteins have been

evaluated in phase 1 clinical trials but have not yet been developed further because of anti genic variability or poor immunogenicity (e.g., transferrin-binding proteins, neisserial surface protein A). Other vaccine candidates have been identified since sequencing of the meningococcal genome. The combination vaccine 4CMenB, which includes the New Zealand OMV vaccine and three recombinant proteins (neisserial adhesin A, factor FIGURE 160-7 Illustration of meningococcal outer-membrane vesicle containing outer-membrane structures.

H–binding protein, and neisserial heparin-binding antigen), is immu nogenic from infancy and has been licensed for use in the United States, Canada, Europe, and Australia. This vaccine has been used with appar ent success in the control of several university outbreaks in the United States and in a community outbreak in an area of Quebec, Canada. The 4CMenB vaccine has an acceptable safety profile, with fever prominent among infants and injection-site pain frequently reported among older children and adults. In September 2015, 4CMenB was recommended for routine use in the United Kingdom for all infants born from May 2015 onward; a recent analysis reported a 75% reduction in age groups that were fully eligible for vaccination, with a high coverage rate of 95%. The licensed schedule is three priming doses before 6 months of age and a booster dose at 12 months of age (but is used in the United Kingdom as two priming doses under 6 months of age and a booster at 1 year). A nonsignificant vaccine effectiveness of 53% was seen after two doses, and 59% effectiveness was found after the booster dose at 1 year of age. As of 2022, protein-based MenB vaccines were authorized in 58 countries. Of these countries, 15 have a universal program in at least one age group, 21 have a recommendation for high-risk groups based on medical conditions, and 13 have a recommendation based on increased risk of exposure (e.g., laboratory staff). Because the disease is so rare, the cost-effectiveness of capsular group B vaccine in infant immunization programs, as assessed with conventional thresholds, is borderline in the United Kingdom. Since infants are not commonly colonized with capsular group B meningo cocci, any impact on the total population burden of carried organisms will be small. It is therefore unlikely that an infant immunization pro gram will provide additional value through induction of herd immu nity. Rates of capsular group B carriage are higher among teenagers and young adults than at other ages (apart from infancy). A large clusterrandomized trial in Australia found no effect of 4CMenB on carriage of disease-causing meningococci, highlighting that the benefit of this vaccine is likely to be via direct protection only. An immunogenic vaccine based on two variants of the lipoprotein factor H–binding protein (MenB-fHBP) has been developed for use in adolescents and is licensed in the United States and Europe. The vac cine is immunogenic against representative indicator strains, inducing fourfold rises in bactericidal antibody titer in 50–92% of individuals. MenB-fHBP has an acceptable safety profile, with pain at the injection site, fatigue, and headache commonly reported. This vaccine can be used with a range of vaccines routinely administered in adolescence, including Tdap (tetanus–diphtheria–acellular pertussis), human papil lomavirus, and MenACWY vaccines. MenB-fHBP has been used to control outbreaks of meningococcal disease in educational institutions in the United States, but no formal studies of its effectiveness have yet been undertaken due to the absence of any public health programs with this vaccine. Studies in the United Kingdom are currently evaluating the impact of both 4CMenB and MenB-fHBP against meningococcal carriage among teenagers. Both of the new capsular group B meningococcal vaccines are licensed for use in the United States for persons 10–25 years of age but are not recommended for routine use. ACIP advises that the vaccines can be used in a two-dose schedule following shared decision-making between the doctor, patient, and/or family. In addition, ACIP recom mends their administration to individuals at high risk of capsular group B disease in a two-dose schedule (4CMenB) or a three-dose schedule (MenB-fHBP). ■ ■MANAGEMENT OF CONTACTS

Close (household and kissing) contacts of individuals with meningo coccal disease are at increased risk of developing secondary disease (up to 1000 times the rate for the general population); a secondary case follows as many as 3% of sporadic cases. About one-fifth of secondary cases are actually co-primary cases—i.e., cases that occur soon after the primary case and in which transmission is presumed to have originated from the same third party. The rate of secondary cases is highest during the week after presentation of the index case. The risk falls rapidly but remains above baseline for up to 1 year after the index case; 30% of sec ondary cases occur in the first week, 20% in the second week, and most

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Revision #1
Created 2026-01-06 16:33:07 UTC by Omar Ayman
Updated 2026-01-06 16:33:07 UTC by Omar Ayman