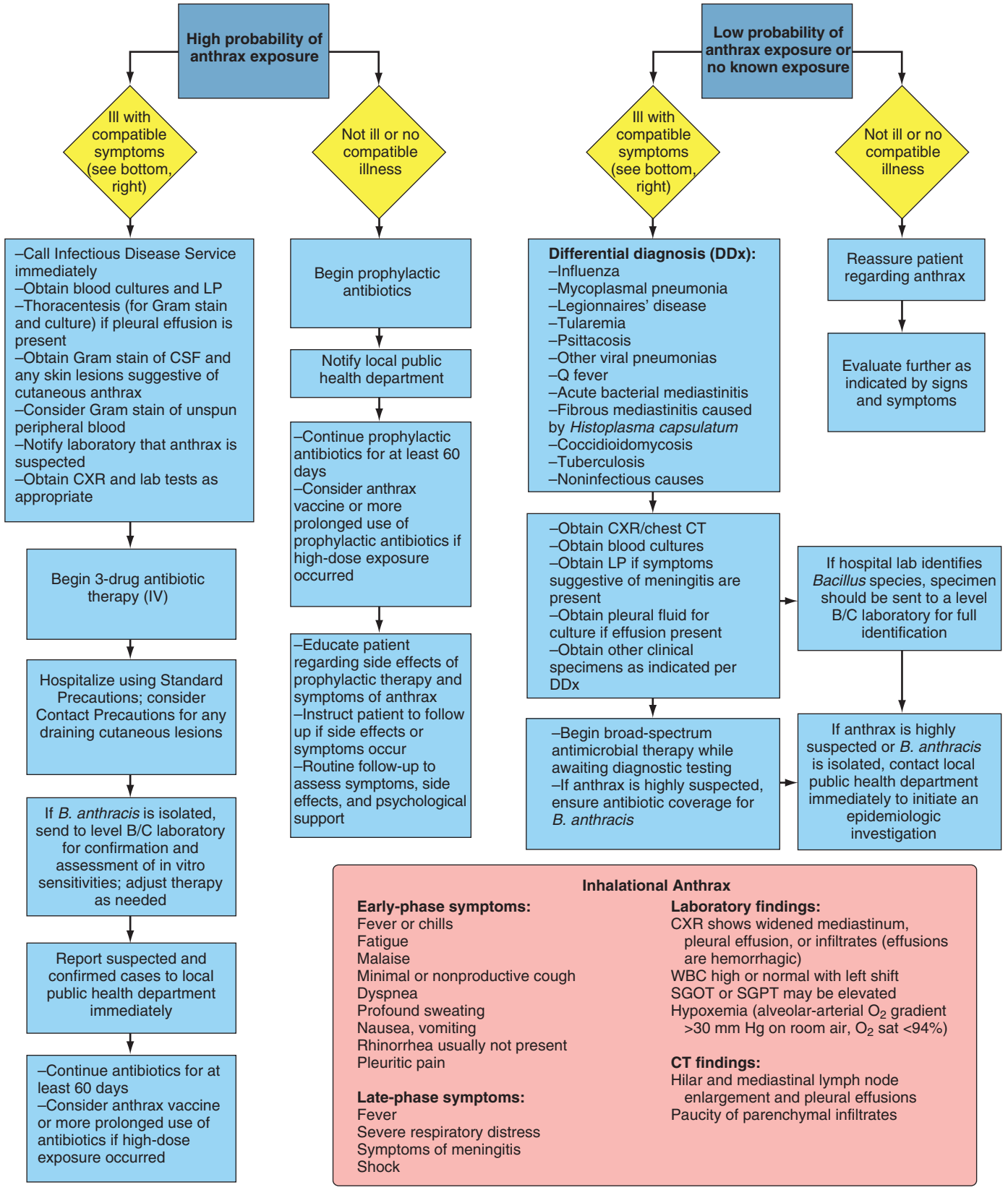

FIG. 207.10 Clinical pathway: anthrax inhalational exposure. *CSF,* Cerebrospinal fluid; *CT,* computed tomography; *CXR,* chest radiograph; *IV,* intravenous; *LP,* lumbar puncture; *SGOT,* serum glutamic oxaloacetic transaminase; *SGPT,* serum glutamic pyruvate transaminase; *WBC,* white blood cell count. *(Modified from the Center for Infectious Disease Research and Policy.)*

TABLE 207.6 Assessing the Probability of Anthrax Exposure

High Probability
During a Known Anthrax Event

Persons exposed to an airspace where a suspicious material may have been aerosolized (e.g., near a suspicious letter containing powder during opening)
Persons who shared an airspace likely to be the source of an inhalational anthrax case (e.g., being exposed to a shared ventilation system)
Persons who may have been exposed to an item contaminated with *Bacillus anthracis* (e.g., an envelope or other vehicle) along the transit path of the item (e.g., a postal sorting facility in which an envelope containing *B. anthracis* was processed)

In Situations in Which Anthrax Has Not Previously Been Identified[a]

Persons who opened a suspicious letter or package that was found to contain a white powder suspected to be a source of *B. anthracis*
Persons exposed to an airspace where suspicious material may have been aerosolized (e.g., near a suspicious letter containing powder during opening)
Sudden appearance of multiple patients with acute onset of characteristic illness (suggests common source exposure such as would be seen with a bioterrorist attack)

Low Probability

No history of exposure to an item (e.g., an envelope or other vehicle) or powder confirmed or suspected to harbor *B. anthracis* spores
No history of exposure to an airspace where a suspicious material could have been aerosolized (e.g., being present at the time a letter containing powder was opened)
No history of exposure to an airspace likely to have been the source for a confirmed case of inhalational anthrax

[a]In situations in which anthrax exposure is suspected but no prior cases of anthrax have been confirmed, a risk assessment should be conducted by local public health and law enforcement officials. If the probability of anthrax exposure is considered high on the basis of the risk assessment, prophylactic antimicrobial therapy should be initiated for asymptomatic exposed persons while the suspect material is being tested for *B. anthracis*. Any persons who have symptoms compatible with anthrax should be treated with appropriate antibiotics until anthrax can be confirmed or ruled out.
From the Center for Infectious Disease Research and Policy (www.cidrap.umn.edu).

TABLE 207.7 Centers for Disease Control and Prevention Recommendations for Postexposure Prophylaxis After Exposure to *Bacillus Anthracis* Spores

Recommended Initial Antibiotic

Ciprofloxacin 500 mg orally bid[b]
or
Doxycycline 100 mg orally bid[b]
or
Levofloxacin 750 mg orally once daily
or
Moxifloxacin 400 mg orally once daily
or
Clindamycin 600 mg orally q8h

Alternatives: Penicillin-Sensitive Strains

Amoxicillin 1 g orally q8h
or
Penicillin VK 500 mg orally q6h

[a]Duration 60 days (or with anthrax vaccine administered continue for 14 days after third dose of vaccine).
[b]Ciprofloxacin and doxycycline are considered equal preferred initial agents.[42]
From Hendricks KA, Wright ME, Shadomy SV, et al; Workgroup on Anthrax Clinical Guidelines. Centers for Disease Control and Prevention expert panel meetings on prevention and treatment of anthrax in adults. Emerg Infect Dis. *2014;20. doi:10.3201/eid2002.130687.*

TABLE 207.8 Comparison of Anthrax Vaccine Adsorbed for Preexposure and Postexposure Use

CLINICAL SETTING	NO. AND ROUTE OF DOSES	SCHEDULE
Preexposure	5, intramuscular	Weeks 0, 4 Months 6, 12, 18
Postexposure	3, subcutaneous	Weeks 0, 2, 4

to PA have been approved by the FDA. These assays can be used on serum to diagnose all types of anthrax or demonstrate seroconversion after immunization. Retrospectively, it was positive in 100% of both cutaneous and inhalation cases from 2001. However, it becomes positive only after approximately 1 week of symptoms. This was demonstrated in the 2006 inhalational anthrax case.[19,52] Numerous other assays are in the development stages including assays for anti-LF antibodies.[161] Further research on new rapid diagnostic tests yielding results in a few hours, based on detection of toxin proteins[48,162] and capsule in the serum,[163] are in development and anticipated to be licensed in the near future.

To ensure they are obtaining all the appropriate specimens[26] and preparing and shipping[41] them correctly, clinicians considering anthrax in the differential diagnosis should refer to Table 207.1 or the CDC website at https://www.cdc.gov/anthrax/specificgroups/lab-professionals/cdcspecimens.html.

Antibiotics

The role of antibiotics in preventing the development of anthrax after exposure to inhaled spores has been well documented in animal studies since the 1940s and in humans after the 2001 anthrax attacks. Antibiotic PEP and therapy are the most important countermeasures currently available for bioterrorism-associated anthrax. The antibiotic regimens recommended by the CDC were reviewed in previous sections. The focus of the discussion here is on PEP and newer agents approaching approval for anthrax.

Current recommendations for PEP have been repeatedly updated and are for initiation of 60 days of antibiotic prophylaxis with appropriate drugs and use of anthrax vaccine. These are summarized in Tables 207.7 and 207.8.[42,90,164] In the event of a release of anthrax spores, the determination of which antibiotic should be used will be guided by the sensitivity profile of the *B. anthracis* isolated. Although ciprofloxacin 500 mg and doxycycline 100 mg administered orally twice daily have been recommended by the CDC as first-line agents to be used as PEP, it is relatively easy to develop resistant strains of anthrax through serial passages in low concentrations of antibiotics, and a terrorist may develop and use a highly resistant strain.[86] Furthermore, in an unrecognized outbreak of inhalation disease many patients may have had treatment initiated for community-acquired pneumonia with third-generation cephalosporins, to which even most natural-occurring strains of *B. anthracis* are resistant.[87,165]

Initiation of antibiotics as soon as possible after (or before) exposure ensures the presence of antibiotics as spores germinate. Ungerminated spores, sequestered in the lung or macrophages, do not appear to be affected by antibiotics, which are active only on germinated spores or vegetative bacilli. The question of how long antibiotics should be maintained remains unanswered. A competing-risks model to determine the optimal duration of PEP suggests that this is dependent on the size of the inhaled inoculum, with small exposures requiring shorter courses and large exposures requiring courses of 4 months or more.[62]

The concern about prolonged PEP is that adherence to a 60-day course of antibiotics is quite poor. In the 2001 anthrax attacks, the overall adherence with 60 days of antibiotics was 44%. Adverse events were common, reported in 57% of patients during the first 60 days of PEP, and occurred nearly equally with either ciprofloxacin or doxycycline. These data are deceptive in that many of the approximately 10,000 individuals placed on PEP did not perceive themselves to have been at high risk and so were less likely to continue PEP if they were experiencing even a mild adverse event. Conversely, individuals who enrolled in the investigational new drug (IND) application, involving the use of anthrax vaccine and prolonged antibiotics, actually had the best adherence.[166] This was reported and personally observed by one of us (G.J.M.) to be a surrogate marker of individuals' perceived risk for exposure but also

reflected the recommendations of clinicians who strongly advised individuals who had been most highly exposed in US Senate offices to maintain strict adherence with PEP as well as enroll in the IND anthrax vaccine protocol.

There were similar findings reported in 2014 when the CDC experienced inadvertent potential aerosolization of anthrax spores in two laboratories. PEP was recommended for 42 individuals. Of individuals who initiated PEP, 74% did not complete either 60 days of antibiotics or postexposure anthrax immunization. Of individuals who discontinued PEP, 38% did so due to their perceived low risk of infections, whereas 31% discontinued due to minor PEP-related adverse events, and 10% cited both reasons.[167]

A number of new or recently developed antibiotics are being tested for their efficacy in the prophylaxis and treatment of anthrax. Oritavancin, a novel lipoglycopeptide in late development for skin and soft tissue infections, was very effective in the mouse model for preexposure and postexposure use. In addition, development of resistance to oritavancin in the laboratory has been much more difficult than with current drugs used for anthrax.[168] Cethromycin, a novel ketolide in development for pneumonia and sinusitis, has also demonstrated promise for *B. anthracis* infection. It can be administered orally once daily, and it showed efficacy equal to that of ciprofloxacin in the mouse model.[81]

Vaccines

Current CDC guidelines are for 60 days of PEP with either doxycycline or ciprofloxacin and initiation of postexposure anthrax immunization. AVA, the currently approved vaccine in the United States, is now approved for use in preventing anthrax preexposure as well as for PEP. The recommendation to add postexposure anthrax immunization to antibiotic PEP is due to the concern that retained spores may still be present at the end of 60 days and could germinate and lead to inhalational anthrax after discontinuance of antibiotics. Even after heavy spore exposures, animals taking antibiotics do not usually develop a significant humoral immune response. By initiating anthrax immunization, antibodies develop while the individual is protected by antibiotics. After the 60-day course of antibiotics is completed, there should be an adequate immune response to immunization to prevent any remaining spores that might germinate from causing anthrax.

For PEP, AVA given as three doses subcutaneously at 0, 2, and 4 weeks results in excellent antibody responses in nearly 100% of recipients.[169] Although the FDA approved eliminating the week 2 dose in the preexposure regimen, it is maintained in the postexposure IND regimen, and doses are given subcutaneously.[108] The preexposure and postexposure schedules are outlined in Table 207.8.

Animal studies have demonstrated the prospect of shorter courses of antibiotics for individuals who are immunized. Among rhesus macaques given approximately 1600 LD_{50} of inhaled spores and begun on PEP with oral ciprofloxacin for 14 days, 44% survived, whereas 100% of those administered three doses of anthrax vaccine in conjunction with the same course of 14 days of ciprofloxacin survived.[170]

AVA is a PA vaccine produced from filtration of the supernatant of *B. anthracis* and has been the source of much controversy even before the anthrax attacks of 2001. The frequency of side effects, requirement for numerous doses, and stability of the vaccine while stockpiled led the US government to fund development of a second-generation recombinant PA vaccine. As some products moved into human trials, stability of the vaccine became a problem, and the candidate vaccine stalled in development. This remains an active area of research, and a new recombinant PA vaccine is likely to be approved in the United States in the near future. Candidate products have been injectable or nasally or orally administered.[44,101,110,171–173] In addition, a new formulation of AVA combined with the synthetic immunostimulatory oligonucleotide adjuvant CpG 7909 has shown a more rapid and enhanced immune response in human clinical trials and is being developed for PEP.[174]

Antitoxin Immunotherapy

The role of anthrax hyperimmune sera in the treatment of anthrax in the preantibiotic era is well documented,[96] and the role of immunotherapy in potential future bioterrorist attacks has not been defined but is almost certain. Through Project BioShield, the US government has purchased supplies of AIG and the approved anti-PA MAb products raxibacumab, Valortim (MDX-1303), and obiltoxaximab for the Strategic National Stockpile.

The protective effect of anthrax antitoxin therapy in animals has been dramatic when given early after exposure and after detection of antigen in serum or onset of fever.[100] Expert opinion is mixed about the appropriate timing and which antitoxin immunotherapeutic to use in a postexposure but presymptomatic scenario. PEP antibiotics are considered most important but whether PEP antitoxin therapy should be added to antibiotics would probably be determined by the number of individuals exposed, the intensity of the exposure, and the availability of antitoxin products. Considering the low toxicity the antitoxin therapies have demonstrated and the high mortality with systemic anthrax infections, adding antitoxin to antibiotic therapy should be considered with expert consultation. Additionally, the prospect of a highly antibiotic-resistant strain of anthrax being used by a terrorist may make the role of antitoxin therapy critical to prevent infection or to treat established disease.[99,101]

Infection Control

B. anthracis has not been demonstrated to spread in household or health care settings from individuals who are infected with anthrax, with the exception of two cases associated with direct contact with cutaneous lesions.[175] Inhalational anthrax is not an airspace disease and is usually not associated with sputum production; when it is, sputa usually do not contain *B. anthracis*. Furthermore, vegetative anthrax bacteria, in contrast to the spores, are not hardy in the environment.

Anthrax-infected patients may be managed in a standard hospital room with standard universal precautions. Cutaneous lesions should be covered and dressings from lesions, chest tube drainage, blood, and so on, should be considered potentially infectious and incinerated or autoclaved. Hand washing with soap and water, 2% chlorhexidine, or chlorine-containing towels decreased spores of other *Bacillus* spp. in testing, but the use of waterless ethyl alcohol–containing hand sanitizers was not effective in removing or destroying spores.[176]

The main concern for health care workers, especially in emergency departments, is from exposed individuals who have not been decontaminated and may pass spores from clothing, skin, or hair to people caring for them. Similarly, hazardous materials and remediation teams may inadvertently carry spores outside the contaminated areas and expose other individuals. These teams often wear personal protective equipment in buildings with the heating, ventilation, and air conditioning systems shut down, so they are prone to heat-associated injuries and emergency department visits. Potentially exposed individuals should be decontaminated outside the emergency department if possible by individuals wearing personal protective equipment. Patients' clothes should be removed and bagged, they should shower, and skin and hair should be washed thoroughly with soap and water and thoroughly rinsed. Surfaces they contact (e.g., ambulances, benches) should be wiped down with a solution of 1:10 household bleach. PEP antibiotic prophylaxis should be considered for people who have cared for patients before their decontamination. Further consideration for postexposure anthrax immunization and antitoxin administration should be done with public health authorities.

Inadvertent contamination of laboratory workers may also occur because *B. anthracis* sporulates on agar while being cultured, and, if not handled carefully under BSL-2 or higher conditions, it may be associated with secondary infections. In the 2001 Capitol Hill anthrax events all the anthrax-positive nasal swabs produced extensive *B. anthracis* growth on culture plates within 12 hours of being streaked.[177]

Remediation (Decontamination)

One of the more controversial topics regarding bioterrorist-associated use of anthrax is the method and cost associated with making spore-contaminated areas safe. This is an additional advantage to the terrorist of using an agent that has the demonstrated persistence of the anthrax spore. As a result of the massive cleanup effort in the wake of the 2001 attacks, there has been increased understanding of decontamination of spores. The Environmental Protection Agency outlined eight steps in the remediation process of contaminated sites, and these are presented in Table 207.9.[133]

TABLE 207.9 Recommended Steps in Remediation of Sites Contaminated With Anthrax Spores

1. Perform a site assessment to include environmental sampling to assess contamination.
2. Isolate contaminated areas.
3. Remove any critical items, artifacts, antiques, etc.
4. Perform source reduction if ongoing contamination.
5. Remediate contaminated areas and contaminated articles removed from areas.
6. Perform postremediation environmental sampling.
7. Perform repeat remediation of persistently contaminated areas; consider using a different remediation method.
8. Safely dispose of all contaminated waste.

Modified from Canter D. Remediating sites with anthrax contamination: building on experience. Presented at the AWMA/EPA Indoor Air Quality Problems and Engineering Solutions Specialty Conference and Exhibition, Research Triangle Park, NC. 2003.

One of the least expensive and most commonly available compounds used to destroy anthrax spores is household bleach, and many of the high-tech remediation methods use bleach in some manner. Bleach, chlorine dioxide, ethylene oxide, hydrogen peroxide, peroxyacetic acid, methyl bromide, paraformaldehyde, and vaporized hydrogen peroxide all were used to some degree in the federal decontamination process in 2001 and 2002.[176] As might be expected, one agent is not suitable for all applications. Chlorine dioxide gas and liquid were used extensively in the US Capitol Hart Senate Office Building but were not found to be very effective for porous surfaces such as carpeting, chairs, and fabric surfaces, which were subsequently decontaminated with other agents.

In the event of widespread contamination of individuals and households where the public will be expected to be performing much of the decontamination efforts, it is likely that household bleach in 1 : 10 dilution will be recommended because it is readily available. Contaminated individuals should be advised to remove clothing and place it in a bag either before entering their home or immediately after entering (to minimize spores coming off clothes into the home). They should shower using soap and water and shampoo their hair. Clothes can be decontaminated by washing in hot water with bleach and machine drying. Dry cleaning will also destroy spores.

How extensively remediation must be performed remains controversial. Because it is well known from studies of wool mill workers and nonhuman primates that the innate immune system can eradicate an as yet undefined number of spores, preventing the development of inhalational anthrax, must every spore be removed from every surface? There may be an acceptable level of contamination that will allow for a timelier and cost-effective remediation effort after a city-wide exposure without serious compromise to the public health of the community. The National Academy of Sciences reviewed remediation of buildings after anthrax contamination and addressed many of these controversial areas but concluded that it cannot be determined what lowest level of spore contamination is acceptably safe for exposure.[178]

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The complete reference list is available online at Expert Consult.

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208 *Bacillus* Species and Related Genera Other Than *Bacillus anthracis*

Thomas Fekete

SHORT VIEW SUMMARY

Definition
- Gram-positive spore-forming bacilli

Epidemiology
- Worldwide distribution
- Commonly found in soil and water
- Major pathogens of insects
- Infrequent cause of infection in mammals (including humans)
- Normal flora in children and adults

Microbiology
- Aerobic or facultatively anaerobic
- Easily cultivated with standard culture technique
- Numerous genera (>56) and species (>545)
- Frequently toxin producing, and toxin contributes to many clinical manifestations of disease
- Susceptibility tests not standardized but can be helpful

Diagnosis
- Culture on routine media at standard temperatures (25°–37°C)
- Can be challenging to distinguish true pathogen from contaminant
- Characteristic Gram stain properties but can be confused with *Clostridium*
- For food poisoning, can be isolated from food products
- Should be suspected when sterilization of equipment is inadequate
- Infection may follow traumatic injury

Therapy
- Food poisoning is normally self-limited and requires only supportive treatment
- Deep infection requires antibiotics
- Vancomycin and fluoroquinolones usually active
- May require removal of foreign body such as vascular catheter

Prevention
- Optimal management and storage of food
- Careful attention to sterilization techniques
- Early removal of unneeded devices

MICROBIOLOGY

Bacteria of the genus *Bacillus* are well adapted to their normal environment of soil. This includes *Bacillus anthracis,* discussed elsewhere in this text (see Chapter 207). These gram-positive or gram-variable, aerobic or facultatively anaerobic, rod-shaped bacilli have rounded or squared-off ends, form endospores, tolerate extremes of temperature and moisture, and are ubiquitous. They are found in superficial lake and ocean sediment, even in deep water. Their hardiness under conditions of desiccation and heat has been used to determine the efficacy of heat sterilization *(Bacillus stearothermophilus)* and fumigation procedures *(Bacillus subtilis).* For many members of the genus *Bacillus,* an association with animals (either saprophytic or pathogenic) has also been noted. These animals range from small insects to large mammals, including humans.

Genomic tools have reshaped the taxonomy of *Bacillus* spp. Earlier changes included the movement of *Bacillus alvei* into the genus *Paenibacillus* and placement of both *Bacillus brevis* and *Bacillus laterosporus* into the genus *Brevibacillus.*[1] Newer changes indicate upwards of 56 genera and 545 total species of aerobic, gram-positive, spore-forming bacteria, although few of them can cause human disease.[2] Recent analyses of *Bacillus cereus* (sensu lato) have shown it to be essentially a pangenome with clonality throughout *B. cereus*, *B. thuringiensis*, *B. mycoides*, *B. weihenstephanensis*, *B. pseudomycoides,* and *B. anthracis.* Environmental strains resemble those found in cultures of human clinical material.[3] For practical purposes, we retain the current species because they are fairly easy to distinguish, and because it is useful to make distinctions around the public health threat of *B. anthracis* and to recognize the commercial role of *B. thuringiensis.*[3] Another organism in the *B. cereus* group, *Bacillus cytotoxicus,* has been associated with foodborne illness.[4] This species can produce a number of toxins and has unusual thermotolerance, being able to grow up to 50°C. Less-related species of *Bacillus* that may occasionally be encountered in the human clinical microbiology laboratory are *B. subtilis, Bacillus licheniformis, Bacillus megaterium, Bacillus pumilus*, and *Bacillus sphaericus. Bacillus* spp. grow quickly at 25° to 37°C on the usual culture media of the clinical laboratory. By definition, all have the capacity to form spores, but they vary widely in motility, colony morphology, and nutritional requirements. They are fairly large bacteria, with dimensions ranging from 3×0.4 to 9×2 µm. Although they are usually gram positive in early growth, old cultures can be gram variable or even gram negative.[5] In most clinical laboratories, the most urgent task is to distinguish *B. anthracis* from other *Bacillus* spp. *B. anthracis* is nonhemolytic on sheep or horse blood agar and nonmotile, whereas most other clinical isolates are motile and β-hemolytic. Strains of *B. anthracis* that are slightly hemolytic have been reported, and some of the less frequently isolated non-*anthracis* strains are nonmotile and nonhemolytic. For the latter strains, detailed biochemical analysis and toxin testing may be required. It is perhaps surprising, yet fortunate, that the commercial tests to distinguish *B. anthracis* from its near relatives generally are easily carried out on widely available commercial kits. Some species, such as *B. sphaericus* and *Bacillus badius,* are biochemically unreactive and difficult to identify using commercial biochemical kits. Fortunately, newer technologies, such as matrix-assisted laser desorption/ionization time-of-flight mass spectrometry, have been shown to be reliable for species determination.[5]

EPIDEMIOLOGY

The widespread distribution in nature of *Bacillus* spp. explains its frequent isolation in the laboratory. In many cases the isolation of *Bacillus* spp. from a clinical specimen raises the possibility of contamination because environmental spores can germinate quickly on various laboratory media. *Bacillus* spp. are infrequently cultured but commonly present in human intestinal contents when a genomic analysis is performed.[6] They represent the most common members of Actinobacteria, the phylum that also includes mycobacteria, corynebacteria, nocardia, and actinomyces. Using more conventional culture techniques, children and adults were tested for the presence of *B. cereus* in the stool, and rates of recovery from 0% to 43% were found in the absence of diarrhea. The density of *B. cereus* in stool is usually low (≈100 viable organisms/g) but can be considerably higher. Strains of *B. cereus* in the stool are the same as

those found in the food supply, and the ubiquity of *B. cereus* is reflected in a large number of different strains in fecal cultures of healthy people. However, during outbreaks, it can be shown that the strain of *B. cereus* causing food poisoning is consistent by biotype, serotype, toxin production, and phage type among patients.[7]

Hospital outbreaks of *Bacillus* spp. infection include one in which *B. cereus* was an ongoing cause of positive respiratory cultures and morbidity, including two cases of true bacteremia and one fatal pneumonia, in an intensive care unit.[8] This epidemic was the consequence of inadequate sterilization of respiratory circuits. No other bacterial infections occurred at higher than usual rates during the epidemic period because the degree of sterilization was sufficient to eradicate non–spore-forming bacteria but not *B. cereus.* Failure to sterilize surgical instruments has been associated with a number of postoperative infections, including those caused by *Bacillus* spp. In a Scottish outbreak, *Bacillus* spp. and coagulase-negative staphylococci were isolated from a variety of autoclaved instruments, and a number of patients had infections in operative sites caused by various bacteria, including coliforms, staphylococci, and *Bacillus* spp.[9] A more dramatic example of a large-scale outbreak occurred at a hospital in Singapore during a period of major construction.[10] A 10-fold increase in isolates of *Bacillus* spp. (including true infections) was noted in association with drilling and excavation. Linens were heavily contaminated by *Bacillus,* and more meticulous handling of hospital linens reduced the rate of infections, but a relaxation of linen cleaning standards allowed a resurgence of *Bacillus* infections.

Other species of *Bacillus* can persist for a long period and then cause intermittent medical problems, such as 12 cases in 10 years of *B. sphaericus* bacteremia in a children's cancer hospital in Italy.[11]

PSEUDOINFECTION AND CONTAMINATION

More common than true outbreaks are pseudoepidemics, in which a strain or strains of *Bacillus* spp. are recovered from patients with a common source of contamination.[12,13] In these settings biochemical and molecular studies can show that a single strain is found, even though it was not actually causing disease. Conversely, clusters of *Bacillus* spp. infection may look like point source outbreaks when they represent a higher than expected rate of infection by environmental organisms. One small cluster of serious *Bacillus* spp. infections, all of which were accompanied by bacteremia, occurring over 10 days in a children's cancer ward showed that the strains recovered were different from one another and from other isolates submitted for analysis.[14] Because *Bacillus* spp. is such a common contaminant and such a rare cause of disease, many laboratories do not identify *Bacillus* to the species level, except to exclude the possibility of *B. anthracis. Bacillus* spp. can survive in high concentrations of ethyl alcohol, up to 95%, including the sprays of 70% ethanol that are sometimes used for hand hygiene.[12] The failure of alcohol to kill *Bacillus* spp. led to a serious problem when a manufacturing defect in alcohol prep pads allowed for an outbreak of some serious infections.[15] Fresh prep pads tested positive for *Bacillus* spp., whereas other sterilizing liquids were, in fact, sterile.

Bacillus spp. contamination has resulted in false-positive rates of up to 0.1% to 0.9% of all blood cultures submitted.[16] Construction on a hospital driveway resulted in a 13-fold increase in the number of blood cultures that tested positive for *Bacillus* spp., although no true infections were identified.[13] The problem was related to direct contamination of stored blood culture bottles and inadequate cleaning of the bottles before introduction of the specimen. Even in the absence of a pseudoepidemic, it can be difficult to separate true *Bacillus* spp. infection from contamination. The best indicator of true bacteremia is the presence of multiple positive cultures or recurrent bacteremia. In one study that compared patients for whom both bottles were positive in a set with *Bacillus* spp. against patients with only a single bottle positive, 29% (5/17) of episodes with both bottles positive were associated with a subsequent positive blood culture, as opposed to 3% (2/59) in patients with only a single bottle positive.[17] This suggests that skin preparation may be less important than specimen handling in false-positive blood cultures for *Bacillus* spp. In a Japanese hospital 29 patients were noted to have *Bacillus* spp. Bacteremia; more than half of these were *B. cereus*.[18] However, these patients were not treated for *Bacillus* spp. and did well clinically. Review of infection control policies showed suboptimal approaches to handling the catheters—wrong disinfectant, pauses during infusion, and reuse of caps on stopcocks. When these shortcomings were corrected, the *Bacillus* spp. bacteremia pseudoepidemic ceased. False-positive cultures of cerebrospinal fluid (CSF) for *Bacillus* spp. have also been reported.[19] A Polish study of microbial contamination of postcollection and postprocessing peripheral blood and bone marrow products found a contamination rate of 0.87% in the postprocessing products, of which 67% were *Bacillus* spp.[20]

COMMERCIAL USES OF *BACILLUS* SPECIES

The toxins of the insect pathogen *B. thuringiensis* (Bt) have been purified and are among the most widely used "natural" control agents in agriculture. Bt organisms or their purified toxins can be applied to commercially important plants to reduce damage from insect pests, and these can be easily purchased in garden centers to spray or dust in areas of insect activity. Despite its close genetic relatedness to potential pathogens, Bt used for farming and horticulture is very safe for humans.[21] Genetic engineering has allowed the insertion of the toxin gene from Bt into other bacteria that can live closely with plants (e.g., among their roots or even between their cells) and protect them. Bt toxin genes have been inserted into commercially farmed plants, such as tobacco, tomato, and cotton, making them naturally resistant to insects. *Bacillus* spp. spores have been marketed in nonchemical drain cleaners that work when the spores germinate and enzymatically digest part of the clog.[22] There is a growing practice of including *Bacillus* spp. in commercial probiotic formulations.[23] In one case a *B. subtilis* probiotic resulted in infection of an immunocompromised patient.[24]

ADHERENCE PROPERTIES

Adherence of some *Bacillus* spp. to plastic intravascular catheters may help account for the frequency with which *Bacillus* spp. infection presents as bacteremia, accounting for 26 of 38 patients in one series.[25] Scanning electron microscopy of a Hickman catheter removed from a cancer patient with persistent *Bacillus* spp. bacteremia showed vegetative organisms embedded in a layer of glycocalyx.[26] The spores of *B. cereus* are also sticky and have tendrils that stick out from the dense spore and provide a mode of attachment to various surfaces.[27] *B. licheniformis* is often mucoid in colonial morphology, which may account in part for its ability to cause somewhat indolent but difficult-to-treat infections in patients with long-term indwelling vascular catheters.[28]

CLINICAL MANIFESTATIONS

Food Poisoning

Intoxication from the ingestion of *Bacillus* species–derived toxins is an uncommon but well described form of food poisoning. A report from England and Wales in the mid-1980s showed that there was 1 food poisoning from *Bacillus* spp. for every 129 of *Campylobacter,* 95 of other bacteria (e.g., *Salmonella, Shigella*), and 5.6 of *Clostridium perfringens.*[29] Like other toxin-mediated food poisonings, *Bacillus* spp. food poisoning occurs within 24 hours of eating, often within a few hours of the offending meal. *Bacillus* spp. toxins can produce one of two distinct syndromes: diarrheal and emetic. The diarrheal syndrome is characterized by profuse diarrhea and cramping but rarely vomiting or fever. The onset is about 8 to 16 hours after the ingestion of contaminated food, and the illness is brief (median duration, 24 hours). The emetic form (similar to *Staphylococcus aureus* food enterotoxin) has an even faster onset (1–5 hours) and is characterized by nausea, vomiting, and cramps, although diarrhea can occur in about one-third of cases. It also resolves within 24 hours. The toxins responsible for these two clinical syndromes are quite different. The diarrheal toxin is a mixture of two or more proteins with molecular weights of 36 to 45 kilodaltons (kDa). The precise mode of action is unknown, although in animal models the toxins disrupt cell membranes and may have sphingomyelinase activity. The diarrheal toxin is heat labile and can be reduced or eliminated by heating food to a high enough temperature to kill the vegetative phase of the organism. This is important because it is believed that the ingestion of toxin-producing *Bacillus* spp. can lead to diarrheal food poisoning by elaboration of toxin in the gastrointestinal (GI) tract. Foods most commonly

associated with *Bacillus* spp. diarrheal food poisoning include meats, vegetables, and sauces.[29] Because diarrheagenic toxin genes are found in most strains of *B. cereus,* vegetative cells are adherent to mucosal surfaces, and the organism is ubiquitous in the environment, it is not known why food poisoning is so infrequent.[27,30] Although most isolates of the diarrheal form of *Bacillus* spp. food poisoning are *B. cereus,* there have been outbreaks related to *B. licheniformis* and *B. pumilus.*[31]

The emetic toxin is a small peptide of about 10 kDa. It is heat stable and associated with starchy foods, such as rice. This problem is worsened when rice is kept at room temperature overnight (to prevent clumping during refrigeration) and reheated the next day (e.g., fried rice). Heating or reheating food may eliminate viable *Bacillus* spp. organisms and the diarrheal toxin but not the emetic toxin. Strains of *Bacillus* may produce one toxin or the other but rarely both. Genetic studies of strains that produce emetic toxin show that they belong to a single *B. cereus* genetic group (III) and subgroup (BC05), whereas strains producing diarrheal toxin may belong to any one of five of the seven *B. cereus* genetic groups.[32] More recent scholarship has shown that affiliation with group rather than with species is helpful in understanding the enterotoxigenic properties within the *B. cereus* group.[33] At least one outbreak of *B. licheniformis* food poisoning was clinically comparable with the emetic syndrome of *B. cereus,* but the polypeptide toxin of *B. licheniformis* differs from that found in *B. cereus.*[34] On rare occasions emetic toxin can lead to significant liver disease, including fulminant hepatic failure.[35] This is thought to be the result of inhibition of mitochondrial fatty acid oxidation.

Both types of food poisoning can be diagnosed by culturing food, feces, or vomitus. Although cultivation of the *Bacillus* spp. organisms is easily done, it is not routine in the evaluation of diarrhea when stool cultures are submitted. Testing for the toxins themselves is difficult because commercial assays are not widely available. Sometimes, the cause of food poisoning is inferred rather than documented. Large studies of restaurant-associated outbreaks have allowed a probabilistic determination of the cause of foodborne illness based on the relative contributions of poor hygiene, poor cooking, poor holding, or contaminated equipment.[36] Improper food holding is the most likely culprit for *B. cereus*–associated disease, as is the case for *C. perfringens* and *S. aureus* toxin–related vomiting and diarrhea. Although *Bacillus* spp. food poisoning often occurs in point source epidemics, the exact infective or toxic dose of *Bacillus* spp. in food is not known. Food screening that finds concentrations of *B. cereus* higher than 10^3/g of food is worrisome and should lead to a careful assessment of food handling and storage, even in the absence of known food poisoning.[37] In one outbreak in which *B. cereus* food poisoning was associated with mayonnaise in potato salad, only 10^3 bacteria were recovered per gram of mayonnaise.[38] Diners may have been exposed to a higher concentration of *B. cereus* because the potato salad was left at room temperature. In London diarrheal *B. cereus* food poisoning involved at least 139 out of almost 1000 people who ate a barbeque meal together.[39] Of the responders with food poisoning, one-fifth had fever (low grade) and one-third developed symptoms outside the usual 6- to 24-hour window (mostly 6 hours) after exposure. Some people were ill for up to 20 days after the start of symptoms, although the median duration was 2 days. Leftover pork had more than 10^3/g *B. cereus*. In an outbreak from a hospital cafeteria, 160 of 249 (64%) employees reported an illness compatible with the diarrheal form of *Bacillus* spp. food poisoning related to rice or chicken, both of which cultured positive for *B. cereus.*[40]

A distinct form of food poisoning has been associated with *B. subtilis.* This syndrome is characterized by a short incubation period (median, 2.5 hours); vomiting; diarrhea (in about 50% of cases); and various other manifestations, such as flushing, sweating, and headaches, in about 10% of patients.[29] Large amounts of *B. subtilis* are required to cause this syndrome; cultures of vomitus and food show 10^6 to 10^9 organisms/g.

Systemic Infections

The rare but definite association between *Bacillus* spp. and deep infection has been recognized for more than 4 decades (Table 208.1). Bacteremia has been the most common presentation, but distinguishing infection from contamination may be difficult.[8,18,41] In a review of positive blood cultures for *Bacillus* spp. in a North Carolina hospital in the 1980s, 5 of 78 isolates were thought to represent true infection.[42] All the definite infections were caused by *B. cereus,* whereas 70% of the possible and only 45% of the nonsignificant isolates were *B. cereus.* A series from an academic hospital in France of cases collected from 2008–12 found that *B. cereus* infection was associated with bacteremia in 24 of 57 cases. Skin infections were 28.1%, and bone and joint infections were 17.5%. Mortality was 11.8% and was significantly associated with β-lactam therapy.[43] The most common feature in true *Bacillus* spp. bacteremia is the presence of an intravascular catheter, particularly a surgically implanted catheter.[28] Catheter removal is often required for cure. The largest number of the bloodstream isolates of *Bacillus* are *B. cereus,* but other species, such as *B. licheniformis,* have also been reported.[28]

A case-control study from South Korea and correspondence related to it illustrate important points about *Bacillus* bacteremia in patients with cancer. In South Korea risk factors for bacteremia included the presence of a central venous catheter, consistent with many reports as noted earlier, and antecedent use of an extended-spectrum cephalosporin within the preceding month, consistent with poor susceptibility to this class of β-lactam antimicrobial drug. However, hematopoietic stem cell transplantation had a negative association.[44] A potential explanation was provided in a response reporting results from M.D. Anderson Cancer Center, where surveillance cultures are performed weekly, and quantitative cultures found that 97% of *Bacillus* spp. bacteremias had less than 10 colony-forming units/mL, which was interpreted as not representing a "true" bacteremia, but rather catheter colonization. The author suggests that therapy initiated to treat a catheter colonized with other low-grade pathogens, such as coagulase-negative staphylococci, as detected by routine surveillance, might lessen the number of *Bacillus* bacteremias, consistent with the Korean experience.[45]

Disseminated *Bacillus* spp. infections in neonates and young children have been described. These infections can cause multisystem involvement, and in neonates they seem to be acquired perinatally.[46] A case of probable maternal-fetal infection has been reported in an injection drug user.[47] An analysis of two preterm infants who died of *B. cereus* sepsis showed that the strains were different and indistinguishable from environmental strains making it likely that their risk factor was immature immunity.[48]

Bacillus spp. infections can be serious and even fatal, especially when the patient has major host defense compromise, such as neutropenia.[41,49] Injection drug users are at higher risk of serious although not usually

TABLE 208.1 *Bacillus* Species and Related Genera With Their Reported Clinical Syndromes, Other Than Anthrax

SPECIES	CLINICAL SYNDROMES
B. cereus	Bacteremia, pneumonia, ophthalmitis, keratitis, osteomyelitis, endocarditis, soft tissue infections, nosocomial infections, meningoencephalitis, fulminant hepatitis, diarrheal food poisoning, emetic food poisoning
B. circulans	Meningitis, cerebrospinal fluid shunt infection, endocarditis, wound infection, endophthalmitis
B. licheniformis	Bacteremia, catheter-related sepsis, food poisoning, central nervous system infections after surgery or trauma
B. megaterium	Meningitis, bacteremia
B. pumilus	Meningitis, bacteremia, soft tissue infection
B. sphaericus	Peritonitis, pleuritis, pericarditis, pseudotumor of the lung, meningitis, bacteremia
B. subtilis	Meningitis after lumbar puncture or head trauma, otitis, mastoiditis, wound infection, bacteremia, pneumonia, endocarditis, shunt infection, emetic food poisoning
Brevibacillus brevis	Keratitis, food poisoning
Brevibacillus laterosporus	Bacteremia
Paenibacillus alvei	Sepsis, meningitis, prosthetic joint infection, wound infection

fatal *Bacillus* spp. infection from injection of the organism from the drugs or injection paraphernalia.[50] *Bacillus* spp. can be disseminated via bacteremia to other body sites, such as the bones or eyes. *Bacillus* spp. are rarely the cause of native valve endocarditis, and when this occurs it is usually in injection drug users, although serious infections have occurred in other settings.[50,51,52] Although a central catheter was present in a case report of *B. cereus* endocarditis, a review showed that the major risk factors for valve infection were presence of a prosthetic valve and injection drug use.[53]

Central Nervous System Infections

Bacillus spp. usually enters the neuraxis through trauma or surgery, particularly implantation of a CSF shunt.[54] Removal of the hardware is usually required to achieve a cure. Lumbar puncture for diagnostic or therapeutic purposes can also lead to *Bacillus* spp. meningitis.[55] Brain abscess or encephalitis can be found alone or in combination with meningitis.[56] Five cases from a single institution presented with protean manifestations, including meningoencephalitis, brain abscess, ventriculitis, and catastrophic hemorrhage. All patients were in the neutropenic phase of therapy for acute leukemia, and mortality was 80%. Invasion of cerebral blood vessel walls by *B. cereus* with thrombosis and hemorrhage has been reported in a neutropenic leukemic patient with bacteremia and a rapidly fatal course.[57] Concomitant pathology in the gut of some cases with ulcerations colonized or infected by *B. cereus* and an extensive source investigation suggested that there could have been an association with a food source, perhaps bananas.[58,59] There were genetic differences between the strains in that report, arguing against a single source, and GI lesions have been uncommonly reported in *Bacillus* bacteremia. A retrospective review of *B. cereus* bacteremias in a single large center in Japan noted an association between brain abscess as a sequela and neutropenia in five cases over 9 years, in which GI complaints were present in four. Only one patient died, and empirical therapy was with a carbapenem and vancomycin.[60] A *B. cereus* brain abscess in a 5-year-old boy undergoing induction therapy for acute leukemia manifested only as fever and resolved after prolonged therapy with meropenem.[61]

Respiratory Infections

Bacillus spp. are rarely the cause of pneumonia, but there have been sporadic cases of severe pneumonia associated with *B. cereus*.[62–64] Detailed evaluation of these strains has shown that they differ from typical *B. cereus* strains by virtue of capsule production and close genetic relatedness to *B. anthracis*. An example of such a case was a welder who presented with positive blood cultures and a rapidly progressive pneumonia with a striking preponderance of gram-positive bacilli in his respiratory secretions.[65] Ultimately, the patient died, and numerous cultures confirmed an organism that typed out as *B. cereus* but had some hallmarks of *B. anthracis*. Capsule, plasmid carriage, and animal virulence studies of *B. cereus* strains (*B. cereus* biovar *anthracis*) that caused an anthrax-like disease in great apes in Central Africa suggest that these lineages provide further evidence on the evolution and evolutionary advantages of *B. cereus* with increased pathogenic potential.[66]

Eye Infections

Bacillus spp., usually *B. cereus,* can cause a rapidly destructive endophthalmitis, resulting from ocular trauma, therapeutic injection or surgery, or hematogenous dissemination.[67–70] The latter route is usually in an injection drug user. A large case series of *Bacillus* spp. endophthalmitis from India, mostly but not entirely the result of trauma, has shown that aggressive therapy combining vitrectomy, topical and systemic antibiotics, and occasionally steroids could result in a surprisingly good outcome.[71] A similar series from the United States reported 22 patients with *Bacillus* spp. endophthalmitis who were treated with vitrectomy and antibiotics (intraocular vancomycin plus a cephalosporin or aminoglycoside), and 18% retained a visual acuity of 20/60 or better.[72]

Bacillus spp. keratitis is an uncommon sequela to eye trauma or other conditions that affect the cornea. Corneal scrapings reveal gram-positive or gram-variable rods that grow easily in culture.[73] The eye complaints usually begin soon after injury but may be delayed for weeks or even months. Topical ophthalmic treatment is often successful in curing the infection with reasonable visual acuity. There have also been reports of *B. cereus* keratitis as a result of contact lens wear.[74] In this study normal disinfection methods for the contact lens case were insufficient to eliminate *B. cereus.* One of the rare infectious complications of refractive surgery is keratitis from *Bacillus* sp. This was seen in a case of delayed lamellar keratitis caused by *B. megaterium* in a healthy adult despite aseptic surgical technique and perioperative antibiotics.[75]

Soft Tissue, Skin, and Muscle Infection

Bacillus spp. soft tissue and bone infection has been associated with injuries and wounds, notably including those received in motor vehicle accidents.[76] In one series of Swedish orthopedic patients with postoperative or posttraumatic wounds, about one patient per month had *Bacillus* spp. obtained from wounds, of which half were considered to represent moderate-to-severe infections.[77] *Bacillus* spp. were isolated from 25% of patients with wound complications after total hip arthroplasty, and these patients had a longer hospital stay than other patients. Ninety-four scalp infections occurred among 660 university military cadets in the summer of 2004.[78] Three cadets had scalp cultures with indistinguishable strains of *B. cereus,* whereas numerous environmental *B. cereus* strains (including from barber clippers) were distinct from one another and from the clinical isolates. The timing of the lesions suggested a point source outbreak abetted by microabrasions caused by the recent haircut. In a case series from Costa Rica, *B. cereus* was found in 14 of 18 patients with traumatic wounds acquired in the rain forest.[79] These isolates were toxin producers, and in most cases wound cultures showed *B. cereus* to be present in pure cultures and in large numbers. A drug abuser with *Bacillus* spp. crepitant cellulitis had the same isolate obtained from his heroin.[80]

PREVENTION

Guidelines for the safe preparation and handling of food are available at www.cdc.gov/foodsafety. Education of commercial food vendors is of obvious importance.[37] The best way to avoid both forms of food poisoning is to cook foods adequately and eat them immediately. Cooking will kill vegetative *Bacillus* spp. and destroy preformed diarrheal toxin, although not emetic toxin. If food cannot be consumed immediately, it should be refrigerated as soon as possible because *Bacillus* spp. metabolism and toxin production are inhibited by cold temperature. Cooked rice should not be held at room temperature for prolonged periods before preparation of fried rice. Education of contact lens wearers about proper decontamination is important in preventing keratitis.[74]

THERAPY

There is no specific treatment for the food poisoning syndromes other than supportive measures. For deep tissue infections, removal of prosthetic material, including infected intravascular catheters, is vital to achieve cure.[17] Most *Bacillus* spp. isolates are susceptible to vancomycin, clindamycin, fluoroquinolones, aminoglycosides, carbapenems, and, variably, penicillins and cephalosporins.[81] *B. cereus* is often resistant to all β-lactams, other than carbapenems, and serious infections are best treated with vancomycin, fluoroquinolones, or clindamycin, with or without an aminoglycoside.[27]

B. cereus, the most frequent species causing bacteremia, is uniformly susceptible to vancomycin, ciprofloxacin, levofloxacin, linezolid, and gentamicin.[82–84] *B. cereus* is usually, but not always, susceptible to carbapenems or clindamycin, in part depending on the testing method.[83] Resistance is usual in trimethoprim-sulfamethoxazole, tetracycline, macrolides, penicillins, amoxicillin-clavulanate, and cephalosporins.[84] There is little clinical outcome data on *B. cereus* bacteremia, but a Japanese group showed, in a case series, that treatment with "appropriate" antibiotics (based on in vitro susceptibility data) had a better 2-day defervescence rate than treatment with inappropriate therapy.[85] The study was underpowered to show other benefits. The β-lactamase of *B. cereus* and several other *Bacillus* spp. is a zinc-based enzyme that is evolutionarily different from β-lactamases in other gram-positive bacteria. For strains other than *B. cereus,* various β-lactams are active in vitro,[19] but clindamycin is less reliably active. Vancomycin appears to be active in vitro

against most *Bacillus* strains, but resistance via the *vanA* gene cluster has been reported.[86]

For native valve endocarditis a long course of therapy has been reported to be successful,[49] and clindamycin has been surprisingly effective in a few cases, despite its variable susceptibility and bacteriostatic activity. For prosthetic valve disease, valve replacement is usually performed.[50] In patients with positive cultures of blood or other body fluid, the challenge is to be certain the isolate is not a contaminant.[19] Surgical drainage and removal of necrotic debris or implanted devices, including central venous catheters, are vital. In endophthalmitis, pars plana vitrectomy and intravitreal antibiotics have been advocated, but prognosis is poor. *Bacillus* spp. keratitis is treated topically, for example, with a fluoroquinolone. A good visual outcome is most likely when the lesion is treated early and does not involve the central part of the cornea.[69]

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The complete reference list is available online at Expert Consult.

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209 *Erysipelothrix rhusiopathiae*

Annette C. Reboli

SHORT VIEW SUMMARY

Definition
- *Erysipelothrix rhusiopathiae* is a pleomorphic, nonsporulating gram-positive bacillus.
- It causes three major forms of disease in humans: erysipeloid (localized cutaneous infection), diffuse cutaneous infection, and systemic or invasive infection (bacteremia with or without endocarditis or vocal organ or deep tissue infection).

Epidemiology
- A zoonosis, it is widespread in nature and infects wild and domestic animals, including swine, poultry, sheep, and fish.
- Infection in humans is usually due to occupational exposure.
- Portal of entry is usually through abrasions or puncture wounds of the skin, but infection may also follow ingestion of undercooked pork or seafood.

Microbiology
- It is an aerobe or facultative anaerobe.
- Most strains produce hydrogen sulfide, a diagnostically important reaction.
- It is sometimes confused with other gram-positive bacilli.
- Vitek 2, the API Coryne system, the API ID 32 Strep system, and matrix-assisted laser desorption/time-of-flight (MALDI-TOF) mass spectroscopy are reliable for identification.

Diagnosis
- A provisional diagnosis can often be made based on a history of appropriate epidemiologic exposure and, in the case of erysipeloid, characteristic physical findings.
- Definitive diagnosis requires isolation of the organism from blood, other sterile body fluid, or a biopsy specimen.
- Standard methods for culturing blood or biopsy tissue suffice.
- The polymerase chain reaction assay has been used for rapid diagnosis in swine and has been applied successfully to human and environmental samples.

Therapy
- *E. rhusiopathiae* is highly susceptible to penicillins, cephalosporins, clindamycin, imipenem, linezolid, daptomycin, and ciprofloxacin.
- Most strains are resistant to vancomycin, sulfa drugs, and aminoglycosides.
- Erysipeloid may resolve in the absence of therapy; however, appropriate therapy shortens the illness and reduces the risk for relapse.
- Penicillin is the drug of choice for all forms of infection. When β-lactams are contraindicated, use of fluoroquinolones, daptomycin, linezolid, or clindamycin may be considered.

Prevention
- Hand hygiene, use of protective attire such as gloves, and disinfection of contaminated surfaces are essential.
- Commercial vaccines are available for veterinary use.

Erysipelothrix rhusiopathiae is a thin, pleomorphic, nonsporulating gram-positive rod. First isolated from mice by Robert Koch in 1878 and from swine by Louis Pasteur in 1882, it was established as the etiologic agent of swine erysipelas in 1886 by Löffler and as a human pathogen in 1909 when Rosenbach isolated it from a patient with localized cutaneous lesions.[1] Rosenbach coined the term *erysipeloid* to avoid confusion with *erysipelas,* a superficial cellulitis with prominent lymphatic involvement that is almost always caused by group A streptococci.[2]

MICROBIOLOGY

E. rhusiopathiae is a straight or slightly curved aerobic or facultatively anaerobic bacillary organism; it is 0.2 to 0.4 μm in diameter and 0.8 to 2.5 μm in length. It is gram positive but may appear gram negative because it decolorizes readily. Organisms may be arranged singly, in short chains, in pairs in a V configuration, or grouped randomly. Nonbranching filaments, which can be longer than 60 μm, are sometimes seen. Colonial and microscopic appearance varies with the medium, pH, and temperature of incubation.[1] After growing for 24 hours at 37°C, colonies are small and transparent, with a smooth, glistening surface. On blood agar, the organism may be α-hemolytic. *E. rhusiopathiae* is negative for catalase, oxidase, indole, Voges-Proskauer, and methyl red.[2] Acid without gas is produced from the fermentation of glucose, fructose, lactose, and galactose. Most strains produce hydrogen sulfide, a diagnostically important reaction. On triple sugar iron (TSI) agar slants, hydrogen sulfide causes a blackened butt. In gelatin stab cultures, *E. rhusiopathiae* produces a distinctive "pipe cleaner" pattern of growth. *E. rhusiopathiae* is sometimes confused with other gram-positive bacilli, in particular, *Listeria monocytogenes, Trueperella (Arcanobacterium) pyogenes,* and *Arcanobacterium haemolyticum,* but these three species are β-hemolytic on blood agar and do not produce hydrogen sulfide in the butt on TSI agar slants. Furthermore, *L. monocytogenes* is catalase positive and motile.[1] The Vitek 2 and Phoenix automated systems and the API Coryne and API ID 32 Strep systems are reliable for the identification of *E. rhusiopathiae.*[3] Matrix-assisted laser desorption/time-of-flight (MALDI-TOF) mass spectroscopy has been shown to accurately and rapidly identify *Erysipelothrix.*[4–6]

EPIDEMIOLOGY

E. rhusiopathiae is found worldwide. It has been reported as a commensal or a pathogen in a wide variety of vertebrate and invertebrate species, but the major reservoir is believed to be domestic swine.[2] Mites may serve as a vector of the organism, allowing it to persist in coops and pens.[7] It does not appear to cause disease in fish but can persist for long periods in the mucoid exterior slime of these animals. It may live long enough in soil to cause infection weeks or months after initial contamination. The greatest commercial impact of *E. rhusiopathiae* infection is the result of disease in swine, but infection of poultry and sheep is also important. Human infection is a zoonosis. The organism is communicable from animals to humans by direct cutaneous contact. Abrasions or puncture wounds of the skin probably serve as the portal of entry of *Erysipelothrix* organisms in most cases of infection in humans and animals. There have been reports of bacteremia, one with endocarditis, which occurred after ingestion of undercooked pork. There was an outbreak of *E. rhusiopathiae* in racing pigeons after ingestion of compost.[8]

The risk for human infection with *Erysipelothrix* is closely related to the opportunity for exposure to the organism; accordingly, most human cases are related to occupational exposure. Although infection with *Erysipelothrix* has been associated with many occupations, people at greatest risk include fishermen, fish handlers, butchers, farmers, slaughterhouse workers, veterinarians, and homemakers.[2] Infection is especially common among people who handle fish.[9] "Whale finger" is erysipeloid seen in people who sustain cuts to the fingers and hands while engaged in whaling. Human-to-human transmission of infection has not been reported. Cases of infection that do not have an occupational link have occurred mainly in immunocompromised hosts, including children, and suggest that colonization of the oropharynx or gastrointestinal tract may occur.[10,11] Chronic alcoholism is a common underlying condition. There have been a few reports of erysipeloid after cat and dog bites.[12] Most human infections are caused by serovars 1 and 2.[3] Ribotyping, randomly amplified polymorphic DNA, pulsed-field gel electrophoresis, and nucleotide sequence analysis of the *spaA* gene are useful for typing isolates.[3]

PATHOGENESIS

Progress has been made in the understanding of the pathogenesis of *E. rhusiopathiae.* Virulence factors include a capsule, enzymes (neuraminidase and hyaluronidase), and cell wall–associated proteins such as transporter and adhesion proteins.[13,14,15,16] The capsule is composed of polysaccharide antigen and confers resistance to phagocytosis. Neuraminidase is important in attachment and entry into host cells. The surface protective antigen proteins, SpaA, SpaB, and SpaC, are major protective antigens. SpaA and SpaC elicit a protective immune response in swine and murine animal models.[17] In the absence of specific antibodies, *E. rhusiopathiae* evades phagocytosis, but even if phagocytized it is capable of intracellular replication.[13]

CLINICAL MANIFESTATIONS

Three well-defined clinical categories of human disease have been described: (1) erysipeloid, a localized skin lesion; (2) a diffuse cutaneous eruption with systemic symptoms; and (3) systemic infection, predominately bacteremia, which is often associated with endocarditis.

The localized cutaneous form—the "erysipeloid" of Rosenbach—is a subacute cellulitis and is the most common type of *Erysipelothrix* infection seen in humans. Because the organism is acquired through contact with infected animals or fish, or with products made from them, gaining entrance via cuts or abrasions on the skin, most lesions are on the fingers. After an incubation period of 2 to 7 days, pain, which is often severe and described as burning, itching, or throbbing, and swelling of the involved digit or part of the hand develop. The lesion is well defined, slightly raised, and violaceous (Fig. 209.1).[2,18] As it spreads peripherally, the central area fades. Vesiculation may occur. Regional lymphadenopathy and lymphangitis occur in approximately one-third of cases.[18] There may be inflammation of an adjacent joint. Systemic symptoms are uncommon. Approximately 10% of the patients have low-grade fever and arthralgias.[18] Clinically, erysipeloid resembles staphylococcal or streptococcal cellulitis, but a history of occupational exposure, lesions on the hands, subacute course, absence of suppuration, lack of pitting edema, violaceous color, and the disproportionate pain should suggest the possibility of erysipeloid.[19] Because organisms are located only in deeper parts of the skin in erysipeloid, aspirates or biopsy specimens should incorporate the entire thickness of the dermis, and tissue from the periphery of the lesion, to maximize the chance of recovery of the organism. Erysipeloid usually resolves without treatment within 3 or 4 weeks.

FIG. 209.1 Lesion of erysipeloid.

The diffuse cutaneous form, which is rare, occurs when the violaceous cutaneous lesion progresses proximally from the site of inoculation or appears at remote areas.[1,2] Most cases arise from percutaneous exposure. Cases have also occurred after ingestion of contaminated seafood or undercooked pork and are presumed to occur after occult bacteremia. Lesions may appear urticarial, with the rhomboid pattern characteristic of swine erysipelas.[2] Fever and arthralgias are common. Blood cultures are negative. The course is more protracted than in the localized form, and recurrence is common.

Systemic infection with *E. rhusiopathiae* is unusual. More than 100 cases of bacteremia have been reported, most complicated by endocarditis.[20,21,22–28,29,30,31] This number may be falsely elevated because of reporting bias in case reports.[32,33] Although this organism has caused prosthetic valve endocarditis, most reported cases of endocarditis have involved native valves. There was a history of an antecedent or concurrent skin lesion of erysipeloid in 36% of patients.[21] When clinical features of *E. rhusiopathiae* endocarditis were compared with those of endocarditis caused by other bacteria, there was a higher male-to-female ratio (which probably reflects occupational exposure), a greater propensity for involvement of the aortic valve, and a much higher mortality rate among patients with *E. rhusiopathiae* endocarditis (38% vs. 20% in endocarditis caused by other organisms).[27,29] In approximately 60% of patients, *E. rhusiopathiae* endocarditis developed in previously normal heart valves. In patients with bacteremia, endocarditis, or both, routine blood culture techniques are adequate for recovery of the organism.[1,3] Complications of *Erysipelothrix* endocarditis include congestive heart failure, myocardial abscess, aortic valve perforation, meningitis, brain infarctions, glomerulonephritis, septic arthritis, and osteomyelitis.[20,21,22–25,27,28] More than one-third of the patients required valve replacement.[21]

Bacteremia without endocarditis has been reported with increasing frequency.[32,33,34,35] It has occurred primarily in immunocompromised hosts.[36–38] Brain abscess, endophthalmitis, pneumonia, necrotizing fasciitis, meningitis, epidural and paravertebral abscesses, peritonitis (including peritoneal dialysis–related peritonitis), intraabdominal abscesses, psoas abscess, tenosynovitis, osteomyelitis, and septic arthritis (including infection of native joints, prosthetic joints, and a reconstructed ligament) have also been reported.[a]

DIAGNOSIS

Definitive diagnosis of infection with *Erysipelothrix* requires isolation of the organism from a biopsy specimen, blood, or other sterile body fluid. Standard methods for culturing blood or biopsy tissue should suffice if incubation is continued up to 7 days. *Erysipelothrix* grows best at 35°C in 5% carbon dioxide. Culture-based methods can be problematic and may lead to an incorrect diagnosis.[52] Despite the use of selective media to improve isolation from contaminated specimens, it is difficult to isolate *E. rhusiopathiae* from heavily contaminated specimens because of its small colony size, its slow growth rate, and the inability to inhibit all contaminants. Recommended culture media for isolation include blood or chocolate blood agar, tryptic soy, Schaedler, or thioglycolate broth.[3] There are no reliable serologic tests for the diagnosis of infection in humans. The polymerase chain reaction assay has been used for rapid diagnosis in swine and has been applied successfully to human and environmental samples.[53]

THERAPY AND PREVENTION

Susceptibility data for *E. rhusiopathiae* are limited. Most strains are highly susceptible to penicillins, cephalosporins, clindamycin, imipenem, linezolid, ciprofloxacin, and daptomycin.[48,54,55] Penicillin and imipenem are the most active agents in vitro. Susceptibility to chloramphenicol, erythromycin, and tetracycline is variable. Resistance to macrolides has been reported to be plasmid mediated.[56] Most strains are resistant to vancomycin, sulfonamides, trimethoprim-sulfamethoxazole, novobiocin,

[a]References 2, 3, 35, 39–49, 50, 51.

teicoplanin, and aminoglycosides.[57] Resistance to vancomycin is important because this agent is often used empirically to treat bacteremia caused by gram-positive organisms. A Clinical and Laboratory Standards Institute guideline for broth microdilution susceptibility testing has been published.[58] Because minimal inhibitory concentrations (MICs) of penicillin range from 0.0025 to 0.06 μg/mL and minimal bactericidal concentrations (MBCs) have been reported in the range of 0.0025 to 0.75 μg/mL, penicillin G (12–20 million units/day) is the drug of choice for serious infections caused by *E. rhusiopathiae*. Ampicillin and ceftriaxone have also been used successfully. Ciprofloxacin has MIC and MBC values similar to those obtained with β-lactam antibiotics.[54,55] Daptomycin has demonstrated in vitro activity against clinical isolates of *E. rhusiopathiae*.[59] Use of fluoroquinolones, daptomycin, clindamycin, or linezolid may be considered in *Erysipelothrix* infections when β-lactams are contraindicated. In cases of endocarditis, the duration of intravenous antibiotic therapy should be 4 to 6 weeks, although shorter courses (2 weeks of intravenous therapy followed by 2–4 weeks of oral therapy) have been successful.[2] Although erysipeloid usually resolves spontaneously, healing is hastened by antibiotic therapy. Oral therapy with amoxicillin or a quinolone can be used.

Prevention of infection in people in high-risk occupations depends on adequate hand hygiene, the use of protective attire such as gloves, and disinfection of contaminated surfaces.[2,14] Unprotected direct contact with animal body tissues and secretions should be avoided. Although commercial vaccines are available for veterinary use, research to develop more immunogenic and safer vaccines continues.[17] Use of vaccination along with other measures, such as improved waste disposal, have helped control swine erysipelas.

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210 Whipple Disease

Thomas Marth and Thomas Schneider

SHORT VIEW SUMMARY

Definition
- Whipple disease (WD) is a rare systemic infectious disorder caused by the actinomycete *Tropheryma whipplei.*

Epidemiology
- Classic WD is rare and is found in middle-aged individuals, approximately three times more often in men than in women.
- *T. whipplei* is found frequently in the stools of children with acute diarrhea.
- *T. whipplei* can cause culture-negative endocarditis.

Microbiology and Pathogenesis
- *T. whipplei* is a gram-positive bacterium with high guanine and cytosine content.
- *T. whipplei* is resistant to glutaraldehyde.
- The hallmark of WD is the invasion of the intestinal mucosa with macrophages incompetent to degrade *T. whipplei.*
- An immunologic defect in the pathogenesis of WD is evident and includes macrophages, T cells, and an impaired humoral immune response.

Clinical Features and Diagnosis
- WD occurs as an acute transient disease (presenting, e.g., with fever and diarrhea in children).
- WD occurs in a localized form (e.g., endocarditis or central nervous system disease).
- WD occurs in various clinical manifestations in association with immunosuppression.
- WD occurs as a classic systemic disease with weight loss, arthralgia, diarrhea, and a possible broad spectrum of clinical signs and symptoms.
- Diagnosis is established usually by duodenal biopsy showing typical periodic acid–Schiff–positive cells in the lamina propria.
- Diagnosis should be confirmed by polymerase chain reaction assay or immunohistochemistry, which can be performed alternatively from various organ samples or body fluids.

Therapy
- Intravenous induction therapy with ceftriaxone for 2 to 4 weeks
- Followed by long-term therapy with oral trimethoprim-sulfamethoxazole for 1 year
- Close follow-up of treatment success over several years
- Complications: relapses, neurologic defects, heart valve destruction, immune reconstitution inflammatory syndrome

Prevention
- Ubiquitous bacterial agent, prevention not yet possible

Whipple disease (WD) is a rare systemic infectious disorder caused by the actinomycete *Tropheryma whipplei*. This chronic disease, first described by Whipple as "intestinal lipodystrophy," preferentially affects middle-aged white men, who may present with weight loss, arthralgia, diarrhea, and abdominal pain. Various other clinical patterns, such as involvement of the heart, lung, or central nervous system (CNS), are frequent. In addition, individuals with isolated heart valve involvement or asymptomatic carriers may be observed. The diagnosis often is established by small bowel biopsy, which is characterized by periodic acid–Schiff (PAS)–positive inclusions representing the causative bacteria. *T. whipplei* can be detected by a specific polymerase chain reaction (PCR) assay, immunohistochemistry, or electron microscopy, and it has been cultured. Several studies show that subtle defects of cell-mediated immunity exist in active and inactive WD, which may predispose individuals with a certain human leukocyte antigen (HLA) type to a clinical manifestation of *T. whipplei* infection. As confirmed in a more recent controlled trial, most patients respond well to prolonged antibiotic treatment, although some may develop an immune reconstitution inflammatory syndrome (IRIS) that may be successfully treated by corticosteroids. However, for a few patients with relapsing disease or with CNS manifestations, the prognosis may be poor.

ETIOLOGY

In 1907 Whipple found rod-shaped structures with silver stain in his original case but noted the following: "Whether this is the active agent in this peculiar pathological complex cannot be determined from the study of this single case but its distribution in the glands is very suggestive."[1] A characteristic, rod-shaped (0.25 × 1.5–2.5 µm) organism was observed by electron microscopy within cells in various stages of degradation and in the extracellular space (Fig. 210.1A). Morphologically, the organism uniformly possesses a trilaminar plasma membrane and a surrounding homogeneous cell wall of 20-nm thickness with two inner layers and an outer trilaminar membrane-like structure. The bacillus can be found typically in macrophages of the lamina propria of the small intestine and its lymphatic drainage but also has been observed in endothelial and epithelial cells, muscle cells, and various cells of the immune system, including polymorphonuclear leukocytes, plasma cells, mast cells, and intraepithelial lymphocytes.[2] The organisms disappear from the lamina propria on antibiotic-induced clinical improvement, which argues for their etiologic significance.[3]

Specific segments of bacterial 16S ribosomal RNA from duodenal lesions of patients were amplified genomically using PCR assay.[4] The sequence analysis enabled the classification of the causative organism phylogenetically as a new genus and species, and the name *Tropheryma whippelii* (*trophe*, "nourishment," and *eryma*, "barrier") was proposed.[4]

After several unsuccessful attempts at culture, the Whipple bacillus isolated from heart valve tissue tentatively had been propagated for a short time in peripheral blood mononuclear cells deactivated by interleukin (IL)-4 and IL-10.[5] In 1999 the growth of the organism was stably established in human fibroblast (HEL) cells in minimal essential medium with 10% calf serum.[6] Because the bacterial strains have been deposited in bacterial collections, the name of the Whipple bacillus officially was corrected to *T. whipplei.*[7] The bacterium is slow growing, with an estimated doubling time of 17 days; under certain in vitro conditions (e.g., axenic medium), it may be shorter.[6] The site of multiplication of *T. whipplei* in vivo remains controversial. It has been suggested that bacteria multiply in the digestive lumen, become phagocytized, and then are degraded in macrophages.[2] *T. whipplei* replicates within peripheral blood mononuclear cells (which release the bacteria), and within macrophages of WD patients; it also replicates within HeLa cells, where the bacillus actively multiplies in acidic vacuoles at pH 5.[8] This high acidity, which may impair antibiotic activity, is a probable cause

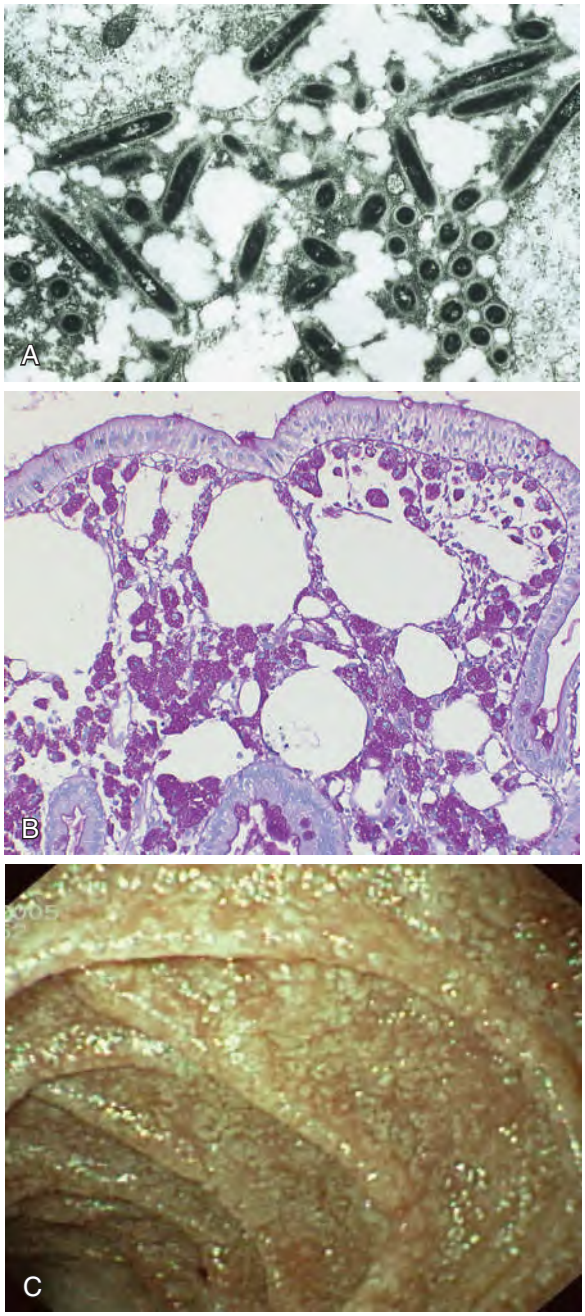

FIG. 210.1 Whipple disease. (A) Electron microscopic view of the Whipple bacillus, *Tropheryma whipplei.* The characteristic, rod-shaped (0.25 × to 2.5 μm) organism can be observed in the extracellular space in florid disease or within cells in various stages of degradation. The bacillus is found typically in macrophages of the lamina propria of the small intestine. *T. whipplei* is characterized by a trilaminar plasma membrane, a surrounding homogeneous cell wall of 20-nm thickness, and an outer trilaminar membrane-like structure (×20,000). (B) Periodic acid–Schiff stain of duodenal biopsy specimen in a patient with Whipple disease. Large numbers of purple-stained macrophages in the lamina propria and lymphectasia can be seen. (C) Endoscopic picture of distal duodenum with whitish yellow plaques representing engorged lymphatic vessels sometimes found in classic Whipple disease. *(B courtesy C. Loddenkemper, Berlin; C from Schneider T, Moos V, Loddenkemper C, et al. Whipple's disease: new aspects of pathogenesis and treatment.* Lancet Infect Dis. *2008;8:79–90.)*

for the lack of efficacy of some antibiotics. *T. whipplei* is resistant to glutaraldehyde.[8]

The genome of *T. whipplei* has been sequenced and deposited in Genbank.[9,10] *T. whipplei* has a single circular chromosome and small genome size (925 kilobases), and it seems to possess characteristics that suggest immune evasion and host interaction play an important role in its replication. In particular, *T. whipplei* seems to have a high degree of sequence variation and lacks several important biochemical pathways, including unique deficiencies in amino-acid biosynthesis (e.g., no thioredoxin) and carbohydrate metabolism, suggesting a host-dependent lifestyle.[9,10]

The organism has been placed phylogenetically within the subdivision of gram-positive bacteria with high guanine and cytosine content, the actinomycetes, and is closely related to several actinobacteria, nocardioforms, and cellulomonads. Genomic variants are associated with neither the geographic residence of the patients nor the organotropism of the agent.[11]

Similar to some of its phylogenetic relatives, *T. whipplei* occurs in the environment; it has been found by PCR assay in sewage water, in sewage plant workers, in saliva, and in human feces.[8,12,13] It is speculated that *T. whipplei* may contaminate humans through drinking water. Humans are the only known host in which *T. whipplei* can replicate, and all environmental sources are in relation to humans and their wastes; therefore it may be speculated that the agent has a sporelike formation that facilitates survival in the environment and may explain its high tenacity, even against glutaraldehyde.

EPIDEMIOLOGY AND PATHOGENESIS

The spectrum of infections resulting from *T. whipplei* has been increasingly recognized by the availability of molecular detection methods and new culture techniques. The bacterium was found in the stool of young children with gastroenteritis; in a study including 241 samples from children aged 2 to 4 years, *T. whipplei* was found in 15% of cases; one-third were coinfected with other diarrhea pathogens.[14] In Europe the prevalence of the bacterium in fecal samples from healthy adults ranges from 1% to 11%. In addition, the bacterium has been detected in sewage and is more prevalent in the fecal samples of healthy sewage workers (12%–26%) compared with the general population.[12,13] *T. whipplei* has also been associated with fever, cough, and sleep disturbances in rural West Africa.[15] These conditions, including isolated Whipple endocarditis, should be separated from the classic form of WD, which was described initially and is characterized by certain immune dysfunctions.

Tropheryma whipplei was also found more frequently in the bronchioalveolar lavage from human immunodeficiency virus (HIV)-positive individuals, compared with HIV-negative ones.[16]

Classic Whipple disease (CWD) is rare, and no valid estimation on the incidence is available. The prevalence recently has been estimated at approximately 10 per 1 million people.[16a] The disorder has been described most frequently in whites. Only rare occurrences have been reported in Hispanics, African Americans, Native Americans, and Asians.[2] It has been presumed that the disease may occur in local clusters, that many patients reside in rural areas, and that farming often is found among the documented occupations.[2,8] Specific environmental factors or habits have not yet been associated with WD.

WD occurs primarily in middle-aged individuals, with a mean age at diagnosis of about 50 years. In the published literature the disease is approximately eight times more common in men than in women[2,8]; newer series find a relatively higher incidence in women (male-to-female ratio 3:1).[17] There are only several case reports of familial clusters (brother pairs, father/daughter), and most of the analyzed cases do not exhibit familial components. A polygenic susceptibility was suggested, and in a larger European cohort, an HLA association (to DRB1*13 and DQB1*06, but not B27) has been observed. The cumulative odds ratios for disease were 2.23 for the DRB1*13 allele ($P < .0001$) and 2.25 for the DQB1*06 allele ($P < .0001$).[18] Recently, a gene defect of a transcription factor involved in immunity has been detected in some patients with familial WD.[18a] The interferon regulating factor 4 (IRF4) haploinsufficiency may be a rare but important factor to predispose for *T. whipplei* infection in certain individuals and in an age-dependent manner.

An immunologic defect in the pathogenesis of WD is probably based on the specific features of the *T. whipplei* genome, suggesting an immune evasion and host-adapted lifestyle, and the very low disease incidence despite the ubiquitously present bacteria. The protean clinical picture, years ago, led to immunologic studies. The immunologic defect in WD

is subtle and specific for the WD organism because patients with the disease usually are not predisposed to infections with other organisms. As an exception, a few case reports have pointed out that WD also may occur in immunodeficient states, in immunosuppression, or concomitant with other infections (e.g., in patients with acquired immunodeficiency syndrome [AIDS] or in patients with *Nocardia* or *Giardia* infections).[8] Newer data point to the possibility that intestinal manifestations (i.e., diarrhea) in WD are triggered by medical immunosuppression, which is given for the treatment of unclear arthropathy.[19]

The immunohistologic features of the lamina propria in WD are unique because the intestinal tissue shows a relative paucity of lymphocytic infiltration, including plasma cells, despite the massive and unusual influx of macrophages, which persist even after completion of treatment.[20] *T. whipplei* is found and replicates mostly intracellularly but also may be metabolically active extracellularly. Although the lack of lymphocytic infiltrate and disturbed immunity in WD could be attributed partially to an intestinal lymphangiectasia, many studies have found a more profound phenotypic and functional alteration of immunologic features in patients with WD.

It has been shown that lamina propria and circulating populations *on the T-cell level* in active WD are characterized by a reduced $CD4^+/CD8^+$ T-cell ratio, a shift toward mature T-cell subpopulations (e.g., CD45RO expression increased, CD45RA expression decreased), and increased cell activation markers.[21] In addition, disturbed function of peripheral T cells, that is, by reduced T-cell proliferative responses to various stimuli and impaired delayed-type hypersensitivity reaction to skin antigens (mostly recall antigens), has been found even in patients with long-standing remission.[21] Newer studies show that *T. whipplei*–specific $CD4^+$ cells are reduced in the periphery and on the mucosal level,[22] and patients exhibit diminished production of Th1 cytokines in response to *T. whipplei* and other antigens.[22,23] In contrast, there is an increase in functional Th2 responses in peripheral T cells,[22,23] lending support to the observation that *T. whipplei* replicates in cytokine (IL-4 and IL-10)-deactivated macrophages,[5] and that the cytokine milieu might inhibit dendritic cell maturation. In the lamina propria of untreated CWD patients, the number of $CD4^+$ T-regulatory (Treg) cells is increased, whereas the percentages in the peripheral blood were similar in CWD patients and healthy control subjects.[24] However, peripheral Treg cells of CWD patients were more activated than those of control subjects. Elevated secretion of IL-10 and transforming growth factor-β in the duodenal mucosa of CWD patients indicated locally enhanced Treg activity. Thus the increased numbers of Treg cells in the duodenal mucosa in untreated CWD might contribute to the deactivation of macrophages and to the chronic infection and systemic spread of *T. whipplei* in CWD. On the other hand, it may prevent a mucosal barrier defect by reducing local inflammation.[24] As a further indication for the pathogenetic relevance of the impaired cellular immune responses, it was reported that in one patient with WD refractory to antibiotic regimens and with reduced interferon-γ (IFN-γ) levels in vitro, treatment with antimicrobials and supplemental recombinant IFN-γ led to the rapid clearance of the infection.[25]

Studies *on the B-cell level* have found reduced numbers of immunoglobulin A (IgA)-positive cells but increased numbers of surface IgM-positive B cells in the lamina propria.[26] Recent studies on a greater number of Whipple patients revealed that all immunoglobulin-producing cells are reduced in Whipple patients compared with control subjects. Secretory IgA production is especially impaired in WD patients. However, this deficiency does not completely abolish *T. whipplei*–specific secretory IgA production.[27] Humoral immune responses to infectious agents in the periphery and total serum IgG levels usually are normal, whereas IgM and IgG2 subclass levels may be decreased, and IgA is increased in acute stages of the disease.[2,8,27,28]

Studies *on the macrophage level* in WD have been sparse for some years. Macrophages from patients with WD manifested decreased intracellular degradation of several organisms, and intestinal macrophages showed some decrease of phagocytosis. In addition, patients with WD have reduced numbers of circulating cells expressing CD11b, a molecule that serves as a facilitator of microbial phagocytosis/antigen processing and mediates IFN-γ–induced intracellular killing of ingested bacteria.[21,28] Impaired functions of antigen-presenting cells in WD may be related to reduced monocyte and macrophage IL-12 production.[20,28] IL-12 is a cytokine that has important functions in regulating cell-mediated immune responses. More recent investigations have shown that intestinal macrophages show an alternatively activated phenotype and express (the Th2-type cytokine) IL-10.[29] *T. whipplei* is able to replicate in monocytes and macrophages from normal individuals if deactivated with IL-16, and neutralizing antibodies to this cytokine inhibit the growth of the bacterium.[29] In addition, because IL-16 is a stimulator of macrophage apoptosis, high levels of IL-16 might promote the dissemination of *T. whipplei* and correlate with the activity of the disease. Recent studies on a greater number of WD patients confirmed the alternative activated phenotype of the macrophages in the lamina propria, which correlated with a lack of excessive local inflammation and may explain in part the hallmark of WD—invasion of the intestinal mucosa with macrophages incompetent to degrade *T. whipplei*.[20]

Together, the local immune response on the mucosal level is apparently insufficient to kill ingested bacteria in patients with WD. Despite the more recent findings describing the subtle and persistent immune disturbance causing a disturbed phagocytosis and intracellular degradation of *T. whipplei*, it remains unclear whether the immune defect is primarily macrophage or T-cell related.

PATHOLOGY

On gross inspection the duodenum and jejunum, which are the sites most frequently affected, often appear thickened and edematous.[2] The infiltration of the bowel wall is associated with a widening and flattening of the villi, with dilatated lacteals containing yellow lipid deposits that are the result of a blockade of villous lymphatics. Based on these and similar observations in the draining mesenteric lymph nodes, G. H. Whipple assumed, in 1907, a disorder of fat metabolism and suggested the name *intestinal lipodystrophy*.[1] Pathophysiologically, the disturbance of the villous architecture is presumably the cause of the steatorrhea and the subsequent malabsorption syndrome that accompany the disease. In addition, the intestinal lymphangiectasia and protein-losing enteropathy seem to be mainly secondary to the lymphatic blockage.[2]

Light microscopic examination of duodenal biopsy specimens in WD usually reveals the typical infiltration of the lamina propria with large macrophages (also called *sickle-form particle-containing cells*) containing granular-foamy, purple-stained, PAS-positive inclusions that are diastase resistant, silver positive, and often gram positive; they represent more or less intact remnants of ingested bacteria (see Fig. 210.1B).[2,3,8] The PAS positivity is believed to be a reaction with bacterial capsular mucopolysaccharides located in the cell wall, as noted first in 1949. In florid disease undigested extracellular bacteria also are seen.[2] Although it seems reasonable to assume that the route of infection occurs through the intestinal lumen, which results in a secondary accumulation of *T. whipplei* in the cells of the lamina propria, another possibility is the penetration of the bacillus through the intestinal lymphatics because the most viable organisms were seen at the base and not the apex of the epithelial cells.[2,8]

Because WD is a systemic disease, PAS-positive macrophages, positive reactions to *T. whipplei* with PCR or immunohistochemistry, and electron microscopically detectable bacilli have been shown in many cell types, as noted earlier, and in almost all organs and in body fluids, including the heart, lung, CNS, cerebrospinal fluid (CSF), eye, vitreous humor, liver, spleen, ascites, lymph nodes, endocrine glands, joints, synovium, and bone marrow.[2] The involvement of heart valves in histopathologic investigations, mostly the aortic and mitral valves, warrants special mention because it may lead frequently to clinical symptoms or isolated valve manifestations and is present in more than one-third of autopsy cases. Other frequent pathologic features include pericarditis or myocarditis, pleuritis, hepatosplenomegaly, ascites or polyserositis, uveitis and ependymitis, cortical atrophy, and demyelination of the CNS.[2]

CLINICAL FEATURES AND DIAGNOSIS

The molecular characterization of *T. whipplei* and new data based on its presence in acute disease, in localized body compartments, and in healthy people has led to a much better understanding of the nature of the infection. This allows definition of the following clinical categories (Table 210.1):

TABLE 210.1 Clinical Features and Spectrum of *Tropheryma Whipplei* Infection

	TRANSIENT AND ACUTE	ASYMPTOMATIC	LOCALIZED	CLASSIC	ASSOCIATED WITH IMMUNOSUPPRESSION
Acronym	TWD	AWD	LWD	CWD	IS→WD
Description	Occurs mostly in children with diarrhea and fever (in Africa)	Asymptomatic carriers. More frequent, e.g., in sewage workers	Localized infection, e.g., endocarditis or CNS disease without systemic symptoms	Classic form with weight loss, arthralgia, diarrhea, and a broad spectrum of other (systemic) symptoms	Occurrence of diarrhea or localized disease after immunosuppression. Coinfection in HIV patients, IRIS
Remarks	Newly recognized. Probably frequently occurring (up to 75%). Frequency in western countries yet unknown. Points to fecal-oral route of infection	Frequency varies from 1%–26%. Development to CWD unproven, presumably rare	LWD is most frequent form of culture-negative endocarditis. Severe CNS damage possible. LWD is very difficult to diagnose	CWD is rare. Published cases exemplify the immense spectrum of clinical symptoms	Protean clinical features hinder early diagnosis. IS→WD may be explained by parasitic features of *T. whipplei* and immune defects

AWD, Asymptomatic Whipple disease; *CNS,* central nervous system; *CWD,* classic Whipple disease; *HIV,* human immunodeficiency virus; *IRIS,* immune reconstitution inflammatory syndrome; *IS,* immunosuppression; *LWD,* localized Whipple disease; *TWD,* transient Whipple disease; *WD,* Whipple disease.

1. *Transient and acute infection with T. whipplei/transient and acute Whipple disease (TWD).* This has been shown so far most impressively in French and African children. In the course of short-term and self-limiting diarrheal disease, up to 75% of patients may excrete *T. whipplei* in their stools, have *T. whipplei* bacteremia, or cough.[14,15,30] TWD argues, along with a high intrafamilial *T. whipplei* occurrence,[31] that the bacterium is a transmissible agent, for instance, via the fecal-oral route.
2. *Asymptomatic carriers of T. whipplei/asymptomatic Whipple disease (AWD).* In these cases most of the individuals pass the agent into their stool. *T. whipplei* is present in saliva, or individuals may carry serum antibodies. Presumably, most have acquired *T. whipplei* via a subclinical or short-term acute infection.[14,15,30] Very few will develop systemic WD later in their lives. An increased proportion (≈12%–26%) of asymptomatic carriers were found in workers who have close contact with sewage.[12,13] The bacterial load in the stool of these patients is lower than in untreated patients with CWD.
3. *Localized T. whipplei infection/localized Whipple disease (LWD)* without systemic or CWD. This manifestation occurs most frequently as culture-negative bacterial endocarditis, for instance, on degenerative valve lesions, leading to a slowly progressive valve damage.[32] In addition, LWD can be found in the eye, CNS, lymph nodes, and bone.
4. *Classic and systemic Whipple disease (CWD),* with the leading symptoms of weight loss, diarrhea, and arthropathies. In 75% of cases these symptoms are found together by the time of diagnosis.[8,33] The clinical presentation of patients may vary to a great extent, however, because of the differential organ involvement and the stage of the disease. In cases of CWD a reduced $CD4^+$ T-cell response against *T. whipplei* is present.[22]
5. *Whipple disease in association with immunosuppression (IS→WD).* In some instances immunosuppressive therapy, such as tumor necrosis factor blocker therapy, is initiated in patients with unclear arthritis. Some of these patients may be diagnosed with WD at a later time point and may present with a heterogeneous clinical picture.[34–36]

Immunosuppressive treatment may favor the occurrence of diarrheal disease, leading to the diagnosis of systemic WD.[19] Alternatively, medical immunosuppression therapy may lead to isolated endocarditis, spondylitis, or CNS manifestations.[32,35,37,38] In many of these cases the clinical picture before WD diagnosis is considered to reflect the symptoms of the underlying autoimmune disorders.[39] This form of WD, underscoring the role of *T. whipplei* as opportunistic invader,[9,10,19,22,23] is of major importance because the diagnosis probably often could be established earlier. In some cases WD is diagnosed in association with malignancies (e.g., lymphomas) that could be due to prior immunomodulation or chemotherapy.[8,38] In addition, after the use of immunosuppressive therapy, WD has a more complicated course after the initiation of therapy (see discussion of IRIS later) (see Table 210.1).

The clinical features of CWD are described in more detail, in many instances (63% in our large series)[33] with CWD beginning insidiously with arthropathy. This symptom may precede the diagnosis by a considerable length of time (mean, 8 years in one series, up to 30 years),[33] and consists usually of chronic migratory, nondestructive, and seronegative joint disease involving predominantly the peripheral joints; in addition, it often is accompanied by myalgias.[2,8] Because new diagnostic tools enable detection of *T. whipplei* in the synovial fluid, these patients may now be diagnosed earlier[40,40a] (Table 210.2).

Weight loss is found nearly invariably in all patients with CWD at the time of diagnosis. We found that weight loss was present in two-thirds of patients more than 4 years before diagnosis and was clinically relevant (often loss of ≥20% of initial weight).[17,33]

Gastrointestinal (GI) symptoms, which usually begin later and ultimately often lead to diagnosis, consist of episodic and watery diarrhea or steatorrhea, in many cases accompanied by colicky abdominal pain and occult blood in the stool.[41,42] These symptoms and concomitant anorexia may lead to the full picture of a malabsorption syndrome with severe weight loss, weakness, and general cachexia, and it may be associated with ascites.

Systemic symptoms occur frequently (i.e., in about half of patients with WD). These symptoms consist of intermittent, mostly low-grade fever and night sweats. Other frequent features of WD are peripheral and abdominal lymphadenopathy; mesenteric lymphadenopathy is found often in radiologic investigations but also may manifest as an abdominal mass. Skin hyperpigmentation, particularly affecting light-exposed skin, has been observed. Chronic, nonproductive cough, chest pain, and reversible pulmonary hypertension have been described.[43] In 3% of bronchioalveolar lavages of intensive care unit patients and in 13% of HIV patients, *T. whipplei* has been found by PCR assay.[16,44] Pleuritis, polyserositis, ascites, hypotension, and edema are among other frequently found signs and symptoms. Hepatomegaly or splenomegaly may be present in some patients with this disorder. Less frequently, involvement of the genitourinary system and the endocrine system have been reported (see Table 210.2).[2,8]

Cardiac involvement in CWD may occur. In recent years endocarditis with *T. whipplei* (LWD) is reported more frequently without CWD (no other evidence of clinical WD and duodenal biopsy may be negative).[32] These cases seem to be of increasing clinical relevance. Clinical symptoms depend on the stage of the disease and may include cardiac murmur and valve (often aortic or mitral) insufficiency, leading finally to valve replacement. Patients are typically diagnosed by histology and PCR assay on the explanted valve.[32,40] Patients often do not fulfill Duke criteria for infective endocarditis and progress more slowly than patients with typical streptococcal or staphylococcal endocarditis. In one large retrospective series, greater than 6% of all infective endocarditis cases were due to *T. whipplei* infection. Thus it was the most frequent cause of culture-negative endocarditis.[32]

A major and frequently overlooked area of involvement in CWD is the CNS. This involvement manifests most often as memory disorder, personality change, and dementia. Other frequent clinical signs include ophthalmoplegia, nystagmus, or myoclonia. These often may be found in combination with a disturbed sleep pattern, ataxia, seizure, or

TABLE 210.2 Signs and Symptoms in Classic Whipple Disease

	INCIDENCE RANGE (%)[a]
Major Clinical Features	
Weight loss	75–100
Arthropathy	70–100
Diarrhea	70–85
Abdominal pain	30–90
Frequent Signs and Symptoms	
Fever	35–60
Lymphadenopathy	35–60
Cardiac murmurs	30–40
Hyperpigmentation	25–60
Occult bleeding	20–30
Hypotension	15–60
Chronic cough	10–20
Splenomegaly	10–20
Hepatomegaly	5–15
Ascites	5–10
Other Clinical Features	
Pleuritis, pleural effusion, endocarditis, muscle wasting, glossitis, peripheral neuropathy, eye involvement (e.g., visual loss, uveitis, retinitis)	
Involvement of central nervous system (e.g., dementia, ophthalmoplegia, myoclonus, ataxia, nystagmus)	
Organ-Specific Involvement	
Gastrointestinal tract	95–100
Cardiac involvement	55
Pulmonary involvement	50
Central nervous system	20–30
Ocular involvement	10

[a]Incidence ranges reported in the literature: references 2, 8, 33, 38, and 45.

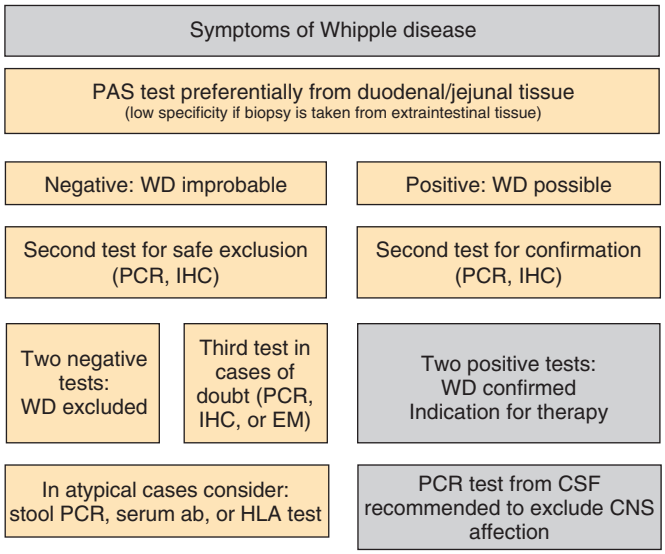

FIG. 210.2 Diagnostic algorithm for detection of Whipple disease *(WD)* based on classic histology, polymerase chain reaction, and immunohistology. Tissues for diagnostic sampling should be prepared in accordance with the symptoms of the patient. If only one diagnostic tool results in a positive finding, it should be confirmed by a second method. If alternative tests are not practicable with the samples available, additional tissue samples should be analyzed to avoid false-positive results. *ab,* Antibody; *CNS,* central nervous system; *CSF,* cerebrospinal fluid; *EM,* electron microscopy; *HLA,* human leukocyte antigen; *IHC,* immunohistochemistry; *PAS,* periodic acid–Schiff; *PCR,* polymerase chain reaction.

symptoms of cerebral compression (because of hydrocephalus). Various cranial nerve symptoms, such as hearing loss and blurred vision, have been reported. In some patients a specific, if not pathognomonic, oculomasticatory myorhythmia or myoclonus with ophthalmoplegia has been described.[38,45] There seem to exist some characteristic radiologic signs of CNS WD by using specific sequences ("flair" and "T1" sequences) of magnetic resonance imaging.[46] CNS symptoms have a frequency of about 15%. CNS and ocular symptoms, such as blurred vision or ophthalmoplegia, may occur with minimal or absent GI involvement (i.e., localized WD).[45]

The diagnosis of CWD usually is made by upper endoscopy. Endoscopically, WD findings often are described as a pale yellow shaggy mucosa alternating with an erythematous, erosive, or mildly friable mucosa in the postbulbar region of the duodenum or the jejunum; alternatively, whitish yellow plaques may be seen (see Fig. 210.1C). Magnification endoscopy may reveal edematous mucosa with blunted microvilli and yellow spots representing engorged lymphatic vessels. WD has been diagnosed recently with newer endoscopic techniques (e.g., i-scan, confocal laser, capsule endoscopy).[47,48] More than three sufficiently sized and deep specimens should be taken from different parts, such as from the proximal and the distal duodenum or the jejunum, because involvement can be patchy or submucosal.[8] The diagnosis usually can be established if the characteristic PAS-positive material is present in the lesions (see Fig. 210.1B). Endoscopy is also an important part of patient follow-up. The duodenal mucosa recovers during the first weeks to months of antibiotic therapy, whereas the PAS-positive material in the macrophages may persist in single cases for several years; an increase of PAS-positive material may be the first indicator of a relapse.[33] Based on clinical manifestations, other samples may be tested, such as CSF, cardiac valve tissue, lymph nodes, or synovial tissue (Fig. 210.2).[40]

There are several histopathologic pitfalls in the diagnosis of WD. Involvement of the GI tract or lymphatic tissue may be accompanied by noncaseating, epithelioid cell (sarcoid-like) granulomas. Sarcoid-like granulomas have been found in patients with CWD in other organ systems and the skin. Infections with *Rhodococcus equi* and *Mycobacterium tuberculosis* complex in patients with AIDS and infections with fungi, *Histoplasma* spp., and others, may be histologically similar to WD, some of which may be ruled out by a Ziehl-Neelsen stain. Lipid deposits and lymphangiectasia have to be differentiated. Biopsy specimens taken from the colon or the rectum can be misleading because of other conditions that are accompanied by PAS-positive cells (e.g., melanosis coli or histiocytosis).[2,40]

Although the clinical picture, together with a pathognomonic PAS-positive histology from the duodenum, usually may be sufficient to establish the diagnosis, a specific diagnostic test, such as PCR and/or immunohistochemistry, is recommended in every newly identified patient; it is mandatory in cases of doubt or if the diagnosis is based on extraduodenal tissue (see Fig. 210.2). This recommendation reflects the fact that PAS staining is of limited value in extraintestinal tissue and for monitoring the effect of therapy.

Electron microscopy now is used only infrequently for diagnosis.

A large amount of experience has been gained with PCR-based detection of *T. whipplei* DNA. PCR and quantitative PCR of *T. whipplei* in stool or saliva in individuals with TWD, AWD, LWD, or CWD differ to a great extent (e.g., in stool approximately 1%–75%).[12–15,30,48a] Quantitative PCR of saliva and stool are not helpful in establishing diagnosis of WD requiring therapy but could be used for noninvasive screening or follow-up purposes in the future. Newer studies show that PCR-based *T. whipplei* diagnosis by urine samples in untreated patients is interesting.[48b] The diagnosis of CWD is highly probable if the bacterial load is high in these specimens. In these cases the diagnosis should be confirmed by upper endoscopy and PAS staining of small intestinal biopsy specimens.

TABLE 210.3 Comparison of Clinical Data and Immunological Studies Versus Predictions From Newly Described Gene Defect (IRF4 Haploinsufficiency) in Patients with WD

	PREVIOUS DATA	PREDICTIONS FROM IRF4 GENE DEFECT
Age	Mean age at diagnosis approximately 50 years	Disease onset in older patients due to age-dependent incomplete penetrance
Sex	Male predominance (male:female ratio from 3:1–8:1)	Autosomal dominant; male preference possible
Organ involvement	Endoscopy and histopathologic studies: *Tropheryma whipplei* is almost invariably found in duodenum and jejunum	IRF4 gene and protein is expressed in a high level in the small bowel
Bacterial distribution	Although *T. whipplei* is ubiquitously present and high numbers of asymptomatic persons (carriers) have been found, only a small number of patients develop WD	Infection with *T. whipplei,* which is found in water and soil, develops to WD only in predisposed individuals. Heterozygous IRF4 mutation probably favors the development of chronic *T. whipplei* carriage.
Immunologic features	Defects in Th1 pathways, reduction of IFN-γ and IL-12, increase in Th2/Th17 cytokine and pathways, particularly on the mucosal level	IRF4 is a transcription factor involved in immunity. Affected patients have reduced Th1 and IFN signaling. Disease mechanism is subtle and specifically affects protective immunity to *T. whipplei.*
Disease course and relapses	Several relapses may occur in the same patient and even with different *T. whipplei* strains. Familial WD cases has been described.	Inheritance of a gene defect: autosomal-dominant genetic disease predisposing for infection
Open questions	—	IRF4 protein levels are higher in the cytoplasmic compartment (not in the nucleus) in patients with the mutation. It is therefore possible that a modifier allele at another locus contributes to the development of WD.

IFN, Interferon; *IL-12,* interleukin-12; *WD,* Whipple disease.

Before definitive diagnosis, and particularly when atypical cases are reported, the use of at least two PCR tests, based on primers obtained from two different genes to avoid a false-positive result caused by contamination, or the use of immunohistochemistry is recommended. Sample specimens usable for PCR-based diagnosis of WD are duodenal biopsy, synovial fluid, lymph node, cardiac valve, vitreous humor, and CSF.[8,13,40] Culture of *T. whipplei* is performed only in highly specialized laboratories and requires several weeks.[6,7]

The clinician always has to interpret the histopathologic and laboratory findings, in diagnostic and monitoring situations, in the context of the clinical features of the patient (i.e., a positive PCR test without clinical correlation should not result in the initiation of treatment). In unclear situations it is advisable that specialists usually should be consulted. Fig. 210.2 is an algorithm for the suggested diagnostic approach.

Laboratory testing can reveal evidence of malabsorption and protein-losing enteropathy: reduced serum levels of β-carotene, various vitamins (B_{12}, D, K, and folic acid), albumin, cholesterol, and electrolytes; lymphocytopenia; elevated stool fat excretion; and reduced D-xylose absorption.[2,19,33] Some patients with WD have eosinophilia and abnormalities of serum immunoglobulins, such as low IgM, IgG2, or high IgA.[2,27,28,38] Finally, other, less specific laboratory abnormalities in WD include elevated erythrocyte sedimentation rate and elevated acute-phase proteins, such as C-reactive protein, thrombocytosis, and hypochromic anemia.[2,19,38]

Finally, it is interesting to note that many data and observations from previous clinical and immunological studies concur well with predictions from the newly described *IRF4* gene defect.[18a] This is depicted in Table 210.3.

THERAPY AND PROGNOSIS

WD was considered to be a fatal disorder before empirical establishment of antibiotic therapy in the 1950s. Antibiotic therapy leads to a rapid improvement of the clinical status in most patients with WD and to a lasting remission. Diarrhea and fever may disappear within 1 week of therapy, whereas arthropathy and other symptoms often are improved after 2 to 4 weeks. The laboratory findings normalize often over several weeks. Clinical improvement usually is accompanied by a gradual reconstitution of the villous architecture of the small intestine and by a disappearance of the bacteria over several weeks.[2,3,33] Finally, immunologic parameters, such as increased IgA or shifts in T-cell subpopulations, return to normal within several months. In contrast, the subtle defect in cell-mediated immunity persists for years, if not indefinitely.[21,22]

Current treatment recommendations are based not only on retrospective analysis of small patient cohorts but, since 2010, also on a prospective randomized controlled trial.[17] Recommendations include an induction treatment for 2 weeks with intravenous antibiotics that achieve high CSF levels, such as ceftriaxone or meropenem (Table 210.4). This is followed by 1-year (continuous) treatment with oral cotrimoxazole (trimethoprim-sulfamethoxazole) twice daily. The results of the therapy trial show a very high rate of clinical remission, which might be due to better adherence of medication intake during controlled studies.[17] Because new study data argue for a short treatment duration of, for instance, 3 months,[49] an issue that is currently still controversial, and others argue for a lifelong treatment, further treatment trials are awaited. So far, short-term treatment should be reserved for clinical studies.

TABLE 210.4 Recommended Treatment in Whipple Disease

Initial Parenteral Therapy (Intravenous)

General therapy: 2 weeks, ceftriaxone, 2 g daily
Central nervous system disease: 4 weeks, ceftriaxone, 2 g daily
Endocarditis: 4 weeks, ceftriaxone, 2 g daily; or penicillin G, 10 million units daily
Alternatives in cases of allergy or relapse: meropenem or penicillin

Long-Term Therapy (Oral)

At least 1 year of trimethoprim-sulfamethoxazole, 160/800 mg twice daily
Alternatives in cases of allergy or relapse: doxycycline, 100 mg twice daily plus hydroxychloroquine, 200 mg three times daily

Although most patients recover completely and long-lastingly after antibiotic therapy, on occasion, inflammation reappears (mostly as high and recurrent fevers) after initial improvement; this is often interpreted as refractory or recurrent disease. However, PCR assay for *T. whipplei* in tissue of these patients is frequently negative, indicating absence of vital bacteria, and this reinflammation does not respond to antimicrobials but does respond to corticosteroids. This pathologic condition was first described in HIV patients with low CD4 T cells after initiation of highly active antiretroviral therapy and was named immune reconstitution inflammatory syndrome (IRIS). In a recent study IRIS was found in approximately 10% of patients with WD, with an outcome that varied from mild to fatal. The great majority of WD patients who developed IRIS had previous immunosuppressive therapy, which has been given under the suspected diagnosis of rheumatic disease. IRIS should be considered in patients with WD in whom inflammatory symptoms recur after effective treatment. Early diagnosis and treatment with corticosteroids may be beneficial.[50]

In patients with CNS symptoms, neurologic defects are difficult to reverse. Although nonspecific focal lesions of the brain and

ophthalmoplegia and other movement disorders respond better to antibiotic treatment, other more structural changes, such as granulomas, infarcts, abscesses, or atrophic changes, may lead to persistent symptoms or even to fatal courses.[38,40,45] Additional treatment with corticosteroids has been beneficial in cases of severe structural CNS manifestations (and in patients with IRIS; see earlier), a therapy that may reduce local inflammation, edema, and endothelial damage.[40]

In cases of allergic reaction to ceftriaxone, an alternative induction therapy may consist of meropenem or penicillin. A possible alternative to long-term oral cotrimoxazole may be doxycycline (2 × 100 mg/day; in some cases minocycline has been used) in combination with hydroxychloroquine (600 mg/day), which enhances the in vitro activity of doxycycline by increasing the pH in the phagolysosomes of the macrophages.[51,52] This treatment is based on molecular data of resistance against sulfamethoxazole,[53] a finding that does not yet reflect broad clinical experience.

Relapsing disease may occur in some patients despite an adequate and prolonged antibiotic treatment, still after many years of remission, more than once, and remarkably even with different strains of *T. whipplei*.[8,54] Relapses of CNS disease, particularly, may have a detrimental course. Additional supportive therapy with Th1 cytokines (IFN-γ) has been described as beneficial.[25] As mentioned, the immunologic defect seems to be specific for *T. whipplei* because a correlation with other infectious diseases was not found.

All patients should be followed with duodenal biopsies and, in cases of cerebral involvement, with CSF analysis at 6 months and 1 year after diagnosis. If PAS-positive material is absent after 1 year and no bacteria are detected by PCR assay, antibiotic therapy can be stopped. We recommend, even in successfully treated patients in whom therapy has been discontinued, performing follow-up biopsies at increasingly longer intervals for at least 5 years after the establishment of diagnosis. If bacterial material persists after 1 year of treatment, therapy should be continued. Therapy probably can be stopped safely if the histology has been stationary for more than 2 years. Monitoring of therapy in the future may be improved with the use of PCR assay (e.g., from the stool), immunohistology, or serology.

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The complete reference list is available online at Expert Consult.

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211 *Neisseria meningitidis*

David S. Stephens

SHORT VIEW SUMMARY

Definition

- *Neisseria meningitidis,* the cause of epidemic cerebrospinal fever and septicemia, is an obligate human bacterial pathogen most often presenting as acute bacterial meningitis and/or mild bacteremia to devastating septicemia.

Microbiology

- *N. meningitidis* is a gram-negative diplococcus (0.6 × 0.8 μm) and member of the bacterial family Neisseriaceae, which includes the human pathogen *Neisseria gonorrhoeae.*

Biology and Pathogenesis

- Meningococcal biology and pathogenesis are defined by (1) *N. meningitidis* human-to-human transmission, acquisition, and colonization; (2) virulence factors that facilitate these events and invasive meningococcal disease; and (3) human "host" susceptibility to invasive meningococcal disease. Each of these components influences disease incidence, disease severity, and prevention strategies.

Epidemiology

- Meningococcal disease occurs worldwide, but overall incidence is declining. Capsular polysaccharides A, B, C, W, X, and Y expressed by specific meningococcal genetic clonal complexes (CCs) designated ST-5 and ST-7 (capsular serogroup A); ST-41/44, ST-32, ST-18, ST-269, ST-8, and ST-35 (usually serogroup B); ST-11 (usually serogroups C or W); ST-23 and ST-167 (serogroup Y); and ST-181 (serogroup X) meningococci cause almost all invasive meningococcal disease (see Fig. 211.4), but new virulent genotypes continue to emerge.

Clinical Manifestations and Pathophysiology

- The common presentations of invasive meningococcal disease are meningococcemia and acute meningitis. Less common presentations are primary pneumonia (up to 10%, especially with serogroups Y and W), septic arthritis (2%), purulent pericarditis, chronic meningococcemia, conjunctivitis, epiglottitis, sinusitis, otitis, urethritis, and proctitis.
- *Meningococcemia:* In 20% to 30% of cases, septicemia with shock is the dominant clinical finding, with sudden onset of fever, gastrointestinal symptoms, generalized malaise, weakness, cold extremities and skin pallor, leukocytosis or leukopenia, erythematous blanching, petechial or purpuric rash, headache and/or drowsiness, and hypotension.
- *Meningitis:* Meningitis is the most common presentation of invasive meningococcal disease and occurs in 40% to 65% of cases, reflecting the meningeal tropism of *N. meningitidis.* Findings include sudden-onset headache, fever, vomiting, myalgias, photophobia, irritability, decreased ability to concentrate, agitation, drowsiness and meningeal signs (neck stiffness, Kernig or Brudzinski sign), and cloudy cerebrospinal fluid. An erythematous, petechial, or purpuric rash may or may not be present.
- *Rash:* Skin lesions are present in 28% to 77% of patients with invasive meningococcal disease on admission.
- Complement system deficiencies increase the risk for meningococcal disease—for example, C5-C9 terminal pathway deficiencies, properdin deficiency, use of the complement inhibitor eculizumab, and C3 deficiency.
- Chronic meningococcemia manifests as intermittent fever (often low grade), migratory arthralgias or arthritis, and a nonspecific, often maculopapular rash.

Complications

- Immune complex–mediated complications, such as pericarditis or arthritis, may follow meningococcal disease.
- Overall mortality is 10% to 20% of cases. Long-term sequelae including learning disabilities or hearing or digit loss occur in 11% to 19% of cases.
- Family and community impact is very significant.

Diagnosis

- The definitive diagnosis of invasive meningococcal disease is based on bacteriologic isolation or antigen or DNA identification (by polymerase chain reaction assay) of *N. meningitidis* in a usually sterile body fluid, such as blood, cerebrospinal fluid, synovial fluid, pleural fluid, pericardial fluid, or other tissue.

Treatment

- Invasive meningococcal disease is a medical emergency, and early parenteral antibiotic treatment with ceftriaxone, cefotaxime, or meropenem should be the primary goal (see Table 211.1).
- Adjuvant therapy and supportive care should be provided.

Prevention

- Chemoprophylaxis eliminates meningococci from close contacts of confirmed or presumptive cases, protects susceptible individuals, and disrupts the further spread of meningococci. Recommended antibiotics for chemoprophylaxis are rifampin, ceftriaxone, ciprofloxacin, or azithromycin (see Table 211.2).
- Meningococcal capsular polysaccharide-protein conjugate vaccines are licensed for prevention of meningococcal disease due to serogroups A, C, Y, and W (see Table 211.3) and are recommended for children, adolescents, and others at risk for meningococcal disease.
- Two meningococcal outer membrane protein–based vaccines targeting serogroup B (MenB) are now available and currently licensed in the United States for use in children ≥10 years and adolescents and adults at risk for MenB meningococcal disease (see Table 211.3). They have efficacy against most currently circulating serogroup B strains, unlike previous MenB meningococcal vaccines.

DEFINITION AND HISTORY

Neisseria meningitidis (the meningococcus) is the cause of epidemic cerebrospinal fever, clusters and sporadic cases of acute bacterial meningitis,[1,2,3,4,5] mild bacteremia to devastating septicemia, pneumonia, and, less commonly, septic arthritis, pericarditis, chronic bacteremia, conjunctivitis, epiglottitis, otitis, sinusitis, urethritis, and proctitis. Historically, half a million cases of invasive meningococcal disease occur worldwide each year, but incidence is declining owing to the widespread use of conjugate vaccines that provide herd protection,[6] new vaccines for serogroup B,[7] targeted and widespread antibiotic use that eliminates carriage, and other factors including reductions in population risk factors for disease such as smoking and crowding. Mortality remains at approximately 10% to 15% in developed countries and is higher, approximately 20%, in the developing world.[4,8] Morbidity occurs in an additional 11% to 19% of systemically infected individuals and includes digit and limb loss, scarring, hearing loss, cognitive dysfunction, visual impairment, educational difficulties and developmental delays, motor nerve deficits, seizures, and behavioral problems.

Meningococcal disease was first clearly described in the late winter and spring in Geneva, Switzerland, in 1805, as "an epidemic outbreak of rapid onset, hemorrhagic eruption, febrile course, and high mortality with gross inflammation of the central nervous system; 33 deaths in three months were recorded."[9] In 1806, a similar epidemic outbreak was reported in New Bedford, Massachusetts.[10] Subsequently, large outbreaks were reported across Europe and in the United States from 1805 through World War II. Curiously, no description of this singular epidemic disease and its distinct presentation was reported before 1805, nor were there reports of epidemics in the meningitis belt of sub-Saharan Africa before the late 1800s.[11] This and meningococcal molecular phylogeny studies[12] have given rise to speculation that *N. meningitidis* epidemics were, at the time, a new emerging disease.

Marchiafava and Celli[13] (1884) first described intracellular oval micrococci in cerebrospinal fluid (CSF), and Anton Weichselbaum[14] (1887) identified and cultured the organism, which he named *Diplococcus intracellularis meningitidis* because of the organism's presence inside neutrophils from CSF, thus establishing the etiologic relationship between *N. meningitidis* and epidemic meningitis. Kiefer[15] in 1896 and Albrecht and Ghon[16] in 1901 found that healthy persons were nasopharyngeal carriers of the meningococcus. Outbreaks of meningococcal meningitis in New York City in the early 1900s led in 1907 to the introduction of intrathecal equine serum therapy for the treatment of meningococcal meningitis by Flexner.[17] Mortality was reduced to 40% from 75% to 85%. In 1908, Bruns and Hohn[18] noted a close relationship between the carrier rate in a population and the onset, rise, and decline of an epidemic. Serologically different meningococci were first recognized by Dopter[19] in 1909, and *N. meningitidis* was found to be distinct from the commensal *Neisseria lactamica.* Before and during World War I, the organism caused significant outbreaks. Glover[20] (1917) was the first to note that carrier rates in military recruit camps increased with periods of crowding, and Gordon and Murray[21] in 1915 developed the first meningococcal classification system (I, II, III, and IV). Later (1918), a similar system (A, B, C, D) was developed by Nicolle, Debains, and Jouan.[22] In 1928 to 1930 and in 1941, significant US and worldwide epidemics (serogroup A) occurred.[23–25] Rake[26] (1934) further defined the epidemiology of the meningococcal carrier state. In 1937, sulfonamide therapy radically altered the outcome of meningococcal infection and replaced serum as the initial treatment.[27] Beeson and Westerman[28] reported on 3575 cases in England and Wales in 1939 to 1941 managed with sulfonamides; mortality was 16%. In the 1940s and 1950s, Branhan further defined meningococcal serogroups based on differences in capsular polysaccharide and developed the internationally standardized nomenclature A, B, and C,[29,30] which was later expanded in the 1960s by the work of Slaterus and by the Walter Reed Institute of Medical Research to include serogroups E, X, Y, Z, and W.[31,32] Later work identified serogroups H, I, K, and L.[33,34] Meningococci that do not have the capacity to express capsules are commonly found as commensals in the pharynx.

Although *N. meningitidis* remains a devastating and worldwide cause of sepsis and meningitis, significant advances in control have been made in the past 2 decades, led by the introduction of new effective vaccines to prevent meningococcal disease.[6,7,35–37] Study of the meningococcus has also led to the discovery of important insights into bacterial pathogenesis and of pathogen evolution in humans.[38] The new meningococcal polysaccharide (MPS) conjugate vaccines against serogroups A, C, Y, X, and W (X in development), and new serogroup B vaccines, hold great promise for worldwide prevention in expanded human populations (e.g., infants and young children) and can (at least for the protein-polysaccharide conjugate vaccines) induce significant indirect effects and herd protection.[4,35,36,39] Major challenges are the global implementation of meningococcal conjugate vaccines (MCVs), the full introduction and breadth of coverage of vaccines against serogroup B, the duration of protection of meningococcal vaccines, increasing antibiotic resistance in meningococci, and the emergence or reemergence in the past 2 decades of serogroups (e.g., Y, W, X) and new invasive genotypes that now cause significant endemic and epidemic meningococcal disease.

MICROBIOLOGY

The meningococcus is a gram-negative diplococcus (0.6 × 0.8 μm), a β-proteobacterium, and a member of the bacterial family Neisseriaceae, which includes many commensal species (e.g., *N. lactamica*, *Neisseria subflava*, *Neisseria polysaccharea*) and also the human pathogen *Neisseria gonorrhoeae.*[40,41] The adjacent sides of the diplococcus are flattened to produce the typical biscuit or coffee bean shape. The meningococcus has a rapid autolytic rate. Lysis appears to be mediated by expression of lytic transglycosylase and cytoplasmic *N*-acetylmuramyl-L-alanine amidase genes and an outer membrane phospholipase,[42] which can result in considerable size and shape variation in older cultures. The organism may produce a polysaccharide capsule; structural differences in the capsular polysaccharide are the basis of the serogroup typing system.

Because the meningococcus is considered fastidious, appropriate media and growth conditions are necessary. On solid media, the meningococcus grows as a round, colorless-to-gray, nonpigmented, nonhemolytic colony that is 1 to 5 mm in diameter. Colonies are convex and, if large amounts of polysaccharide are present, can appear to be mucoid rather than smooth. Optimal growth conditions are achieved in a moist environment at 35°C to 37°C under an atmosphere of 5% to 10% carbon dioxide. The meningococcus will grow well on a number of medium bases, including blood agar base, trypticase soy agar, supplemented chocolate agar, and Mueller-Hinton agar. Classic confirmation of this organism in clinical specimens has depended on a positive oxidase test (the meningococcus contains cytochrome oxidase in its cell wall) and a series of carbohydrate fermentations. The meningococcus will metabolize glucose and maltose to acid without gas formation and fails to metabolize sucrose or lactose. The expanded use of molecular methods based on a variety of polymerase chain reaction (PCR) techniques[43,44] has confirmed and supplemented cultures in the diagnosis of patients infected with the meningococcus. This is particularly true for clinical specimens from patients treated with antibiotics before cultures are obtained.

BIOLOGY AND PATHOGENESIS

The dynamic pathobiology of *N. meningitidis* resembles the story of "Dr. Jekyll and Mr. Hyde." As an obligate human pathogen with no other reservoir, the organism is an ancient common human commensal that can be carried for months, most often in the human nasopharynx. Cross-sectional studies in multiple populations project an estimated 230 million to more than 1 billion meningococcal carriers worldwide (3%–25% of populations).[45,46] Carriage is an immunizing process, often resulting in natural protective immunity. In contrast, the meningococcus is a devastating human pathogen, historically causing approximately 500,000 cases of invasive meningococcal disease worldwide annually,[8] with high mortality and morbidity and with increased incidence in often otherwise healthy children and adolescents.

Meningococcal biology and pathogenesis can be defined by three interrelated components: (1) *N. meningitidis* human-to-human transmission, acquisition, and colonization; (2) virulence factors that facilitate these events and invasive meningococcal disease; and (3) human "host" susceptibility to invasive meningococcal disease. Each of these areas has implications for prevention strategies.

The potential *virulence* of *N. meningitidis* (defined as the ability to cause invasive disease) differs extensively among meningococcal strains. Unencapsulated strains rarely cause invasive disease, but even among

encapsulated strains there is considerable variability in virulence. Organism characteristics that facilitate survival during invasive disease and/or that also promote transmission and acquisition will increase disease incidence. Meningococcal disease patterns and incidence vary dramatically, both geographically and over time in populations. This is related to the appearance and disappearance in populations of invasive meningococci of specific genotypes designated as clonal complexes (CCs),[47] often but not exclusively associated with a specific capsular polysaccharide. Currently, 12 genomic CC types (see "Epidemiology") cause most endemic and epidemic invasive meningococcal disease worldwide.[47,48] The genomic population structure of colonizing meningococci is considerably more diverse.[49] One approach to the assessment of meningococcal virulence relates the number of cases in a population due to a specific clade or CC to the number of carriers of that clade or CC. This can range from much less than 1 case per 10,000 carriers to more than 1 case per 10 to 20 carriers for highly virulent CCs.[50,51] For example, the case-to-carrier ratio is much higher for serogroup A CCs or serogroup C, CC ST-11, than for serogroup X or serogroup Y meningococci, presumably reflecting a marked difference in meningococcal virulence.[52]

The meningococcus has a single chromosome of 2.1 to 2.3 megabases. The first whole-genomic sequences were from serogroup B and serogroup A strains and were reported in 2000.[53,54] With high-throughput whole-genome sequencing (WGS), the number of genomes as gap-closed, as finished genomes, or now more commonly as incomplete or draft genomes is rapidly increasing in available databases (http://neisseria.org/nm/genomes; http://patricbrc.org/portal/portal/patric/Home; http://PuBMLST.org). The *Neisseria* PubMLST database contains genetic data for a collection of over 50,000 isolates and over 19,000 genomes that represent the total known diversity of *Neisseria* species (http://PuBMLST.org). The core genome consists of 1300 to 1600 genes and differs by 3% to 5% from other sequenced strains, with the meningococcal "pan genome" estimated at more than 2500 genes.[55–58] The overall G and C content is 51%, but low G and C regions suggest horizontal transfer and contain genes that are important in pathogenesis. Work has identified a transcriptome of approximately 1100 transcribed open reading frames per strain with over 300 operons. The genome encodes core metabolic, fitness, and key virulence factors, including capsular polysaccharide, a requirement for virtually all invasive meningococcal disease and the basis for serogrouping; lipooligosaccharide (LOS), a lipopolysaccharide molecule without repeating *O* side chains and the basis for immunotyping; the pilus organelle complex that facilitates motility and initiates attachment; and other virulence-associated outer membrane proteins (PorA, PorB, Opc, Opa, NadA, FetA, FHbp), which are the basis for serotyping and serosubtyping (Fig. 211.1). Repetitive nucleotide sequences and polymorphic regions are present, usually in large heterogeneous arrays, suggesting active areas of genetic recombination. Transformation is the major means of horizontal gene transfer and a source of strain diversity. Over 1900 copies of the *Neisseria* uptake sequence (5′-GCCGTCTGAA-3′) ease *Neisseria* spp. DNA exchange by transformation and homologous recombination. Recombination events are recognized, including transfer of DNA including complete genes between meningococci, gonococci, and commensal *Neisseria* spp. and other bacteria.[57,58] The genome is modified and regulated at multiple levels. Genetic switches involved in gene regulation include small noncoding regulatory RNAs, CRISPR (clustered regularly interspaced short palindromic repeats), slipped-strand mispairing of repetitive nucleotides, global protein regulators of promoters (e.g., *fur*), intergenic recombination, IS (insertion sequence) element movement, methylation, hypermutator phenotypes, and two-component systems regulation. There are large genetic islands (e.g., IHT-A1 [8.5 kb], IHT-A2 [5.4 kb], IHT-B [17.1 kb], IHT-C [32.6 kb], IHT-E) in different meningococcal strains[55,58,59] containing bacteriophages, phage elements and remnants, and many restriction enzymes related to CC genomic structure virulence factors and other genes to encoding surface proteins. For example, the IHT-A2 locus encodes an ABC transporter homologue and a secreted protein and the IHT-C locus encodes 30 open reading frames, including toxin homologues, a bacteriophage, and potential virulence proteins.[50] Although one bacteriophage has been proposed as a marker of virulence,[59] the current evidence is that no specific virulence gene pool is exclusively present in all *N. meningitidis* strains from hyperinvasive lineages.[55,58]

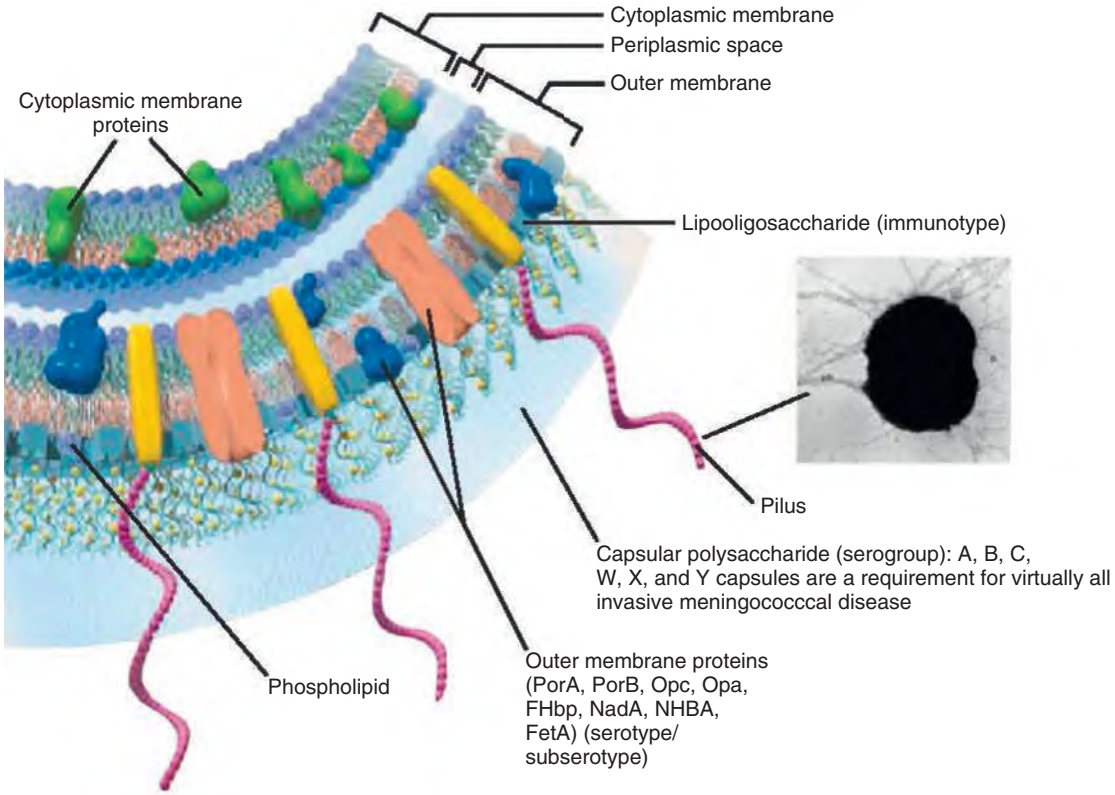

FIG. 211.1 Cross-sectional and scanning electron microscopic views of the meningococcus. *(Modified from Rosenstein NE, Perkins BA, Stephens DS, et al. Meningococcal disease.* N Engl J Med. *2001;344:1378–1388.)*

The major virulence factor for invasive disease produced by the meningococcal genome is capsular polysaccharide. Serologic typing and the biochemical composition of capsular polysaccharides have classified *N. meningitidis* capsular polysaccharides into a total of 13 serogroups (A, B, C, D, E, H, I, K, L, W, X, Y, and Z),[3] with A, B, C, E, H, I/K, L, W, X, Y, and Z now confirmed genetically.[60–62] However, six capsular serogroups (A, B, C, W, X, and Y) cause almost all invasive meningococcal disease. Serogroups B and C capsular polysaccharides are sialic acid homopolymers of (α2→8) and (α2→9) linkages, respectively, whereas serogroups Y and W are alternating units of D-glucose or D-galactose and sialic acid, respectively. Serogroup A *N. meningitidis* expresses a homopolymeric (α1→6) *N*-acetyl mannosamine-1-phosphate capsule, whereas serogroup X expresses (α1→4) linked *N*-acetyl-D-glucosamine-1-phosphate. Capsular polysaccharides provide antiadherent properties, thereby promoting meningococcal spread from mucosal surfaces, and provide protection in intracellular environments and against complement-mediated killing.

Capsule is produced by a 30-kb region containing the IHT-A1 genetic island with genes for capsule biosynthesis, assembly, and transport.[62–65] The island has been lost or never acquired in commensal *Neisseria* species, such as *N. lactamica,* the pathogen *N. gonorrhoeae,* and many commensal *N. meningitidis*[64]; but recent work shows evidence of a *cps* locus in some commensals such as *N. subflava*. The acquisition or reacquisition and evolution of this genetic island was a key to the emergence of invasive meningococcal disease. Capsule subunit and polymer biosynthesis, acetylation, assembly, protection from degradation, and transport to the cell surface are encoded by genes of the region. The region is related to capsule encoding islands in *Pasteurella* and other bacterial species. The different capsule structures are the result of evolutionary divergent biosynthesis, polymerization, or acetylation genes found in the capsule locus.

The serogroup B polysaccharide capsule ([α2→8]-linked polysialic acid) is similar to the capsular polysaccharides of *Escherichia coli* K1, *Pasteurella haemolytica* A2, *Moraxella nonliquefaciens,* and human polysialic acid structures, such as the neural cell adhesion molecule (NCAM).[66,67] Due to NCAM similarity, the serogroup B capsule is poorly immunogenic as an antigen in humans and animals.

Capsule, as with many other meningococcal virulence factors, is subject to genetic regulation. On↔off phase variation, regulation of amount of capsule expressed, and modifications to structure (e.g., capsule acetylation) are well described.[63–65,68] Thermoregulation of capsule expression (increased capsule expression at 37°C due to RNA thermosensors in the *cps* operon) is reported.[69] Meningococci "capsule switching" resulting in structural change also occurs, providing a mechanism of immune escape.[63,70–72] Gene conversion by transformation and homologous recombination of the capsule locus was first noted in a serogroup B outbreak in the United States in the 1990s[63]; otherwise identical serogroup C expressing strains appeared during the outbreak. Similarly, CC, ST-11 serogroup W *N. meningitidis* outbreaks associated first with the Hajj in 2000 and 2001 and more recently with other CC, ST-11 W clades were likely the result of distant capsule switching events from ST-11 serogroup C ancestors. In large meningococcal isolate collections, capsule switching events are detected in approximately 3% of isolates.[70]

Type IV pili (see Fig. 211.1) are complex surface appendages requiring at least 23 proteins (e.g., PilE, PilC, secretin, PilT, PilQ), either as structural components of the organelle or required for biogenesis. Pili are anchored in the outer membrane and radiate, through an oligomeric ring, several thousand nanometers from the meningococcal surface (see Fig. 211.1).[73–76] The major subunit may undergo *O*-linked glycosylation. Pili and accessory proteins (e.g., PilX) facilitate meningococcal aggregation and initial attachment and anchoring to human epithelial or endothelial cells.[77] Through cycles of polymerization and depolymerization that produce retraction and extension, pili are responsible for "twitching motility" (1–2 μm/sec). Pilus attachment to human cells initiates localized remolding of the human cell cytoskeleton. Pili also facilitate aggregation and microcolony formation but, when glycosylated, promote meningococcal disaggregation and dissemination. Pili are also necessary for DNA transformation.

The endotoxin of *N. meningitidis,* an LOS, lacks *O*-side chains and has a lipid A structure distinct from gram-negative enterics.[78,79] This LOS can mimic the i and I human blood group antigens.[80] LOS also is an important virulence factor, influencing cell damage, meningococcal attachment and invasion of host cells, and complement-mediated killing. Mass spectrometry analysis of the structure of LOS shows highly phosphorylated lipid A forms that influence innate immune responses and clinical outcomes.[81,82] The release of LOS during bloodstream or CSF invasion is a key factor in meningococcal sepsis and meningitis.[83] Serum or CSF levels of LOS are directly correlated with the severity of meningococcal sepsis and meningitis. For example, when LOS levels exceed 100 ng/L, septic shock and/or death are highly correlated.[84,85] LOS stimulates chemokine and cytokine release systemically by binding Toll-like receptor 4 (TLR4) on macrophages and other cells and stimulating MyD88-independent and MyD88-dependent pathways, resulting in tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein-3α (MIP-3α), IL-6, IL-8, IL-10, MCP-5, and release of other chemokines and cytokines.[79,83,85] LOS also downregulates genes involved in oxidative phosphorylation and mitochondrial function in human cells.[86] Non-LPS molecules can contribute to inflammation, but 10-fold to 100-fold higher concentrations are required to reach the same responses as those induced by LOS.[83]

Outer membrane porins are involved in host-cell interactions and are targets for bactericidal antibodies. PorB, which is the major outer membrane porin, inserts in membranes, induces Ca^{2+} influx, and activates Toll-like receptor 2 (TLR2) and cell apoptosis.[87] PorA is a second important porin and a major target of meningococcal outer membrane vesicle (OMV) vaccines including OMV in one of the new MenB vaccines. Meningococci also express variable proteins such as Opa and Opc, which are important in adherence and host cell interactions.[74] Another important outer membrane protein, a principal target for the new MenB meningococcal vaccines, is the factor H binding protein (FHbp), a lipoprotein involved in meningococcal resistance to complement-mediated killing. Other outer membrane vaccine-targeted proteins include neisserial adhesin A (NadA), a mediator of adhesion and cell invasion; and neisserial heparin binding antigen (NHBA), also involved in adhesion and in protection against complement-mediated killing.[37,88]

Iron is necessary for meningococcal survival, colonization, and infection. The meningococcus scavenges iron from the human proteins transferrin, lactoferrin, and hemoglobin through a series of highly evolved, surface-exposed receptors and TonB-derived energy.[1,61,75,89] More than 80 genes are regulated by the iron-responsive repressor Fur.[89] Meningococcal iron-acquiring proteins include HmbR (hemoglobin), TbpA and TbpB (transferrin), HbpA and HbpB (lactoferrin), and HpnA and HpnB (hemoglobin-haptoglobin complex) and FetA (ferric enterobactin receptor). Iron-loaded animals are more susceptible to fatal meningococcal infection.[90] New putative iron acquisition proteins, adhesion or invasion proteins, and toxin proteins have been identified in meningococcal genome searches.

Meningococcal Colonization and Transmission

The dynamic life cycle of *N. meningitidis* is shown in Fig. 211.2. The human nasopharynx is the most frequent site of meningococcal colonization and carriage and the major source of transmission to other humans.[46,51,74,76,91–95] The human nasopharynx, optimal for *N. meningitidis* growth, has a CO_2 content of 3% to 4%; high, 75% to 80%, humidity; and a temperature of 34°C. Colonization is a complex process of meningococcal interaction with upper respiratory mucosa. The initial adherence of meningococci is facilitated by type IV pili, which may recognize integrin α-chains or other receptors. Surface movement, proliferation, aggregation, and microcolony formation are facilitated on mucosal surfaces by type IV pili–induced twitching motility involving pilus retraction, and the phase variation of glycan decorations on pili. Meningococci attach to nonciliated nasopharyngeal epithelial cells and induce apical cortical plaques (see Figs. 211.2 and 211.3A), which anchor the organisms against loss by mucus and ciliary action and promote the formation of meningococcal microcolonies and biofilms (see Fig. 211.3A).[74–76] This process is mediated by close adherence involving the meningococcal outer membrane ligands (Opc, Opa, LOS, NadA, and others) and the human host receptors such as carcinoembryonic antigen–related cell adhesion molecules (CEACAMs) and integrins,

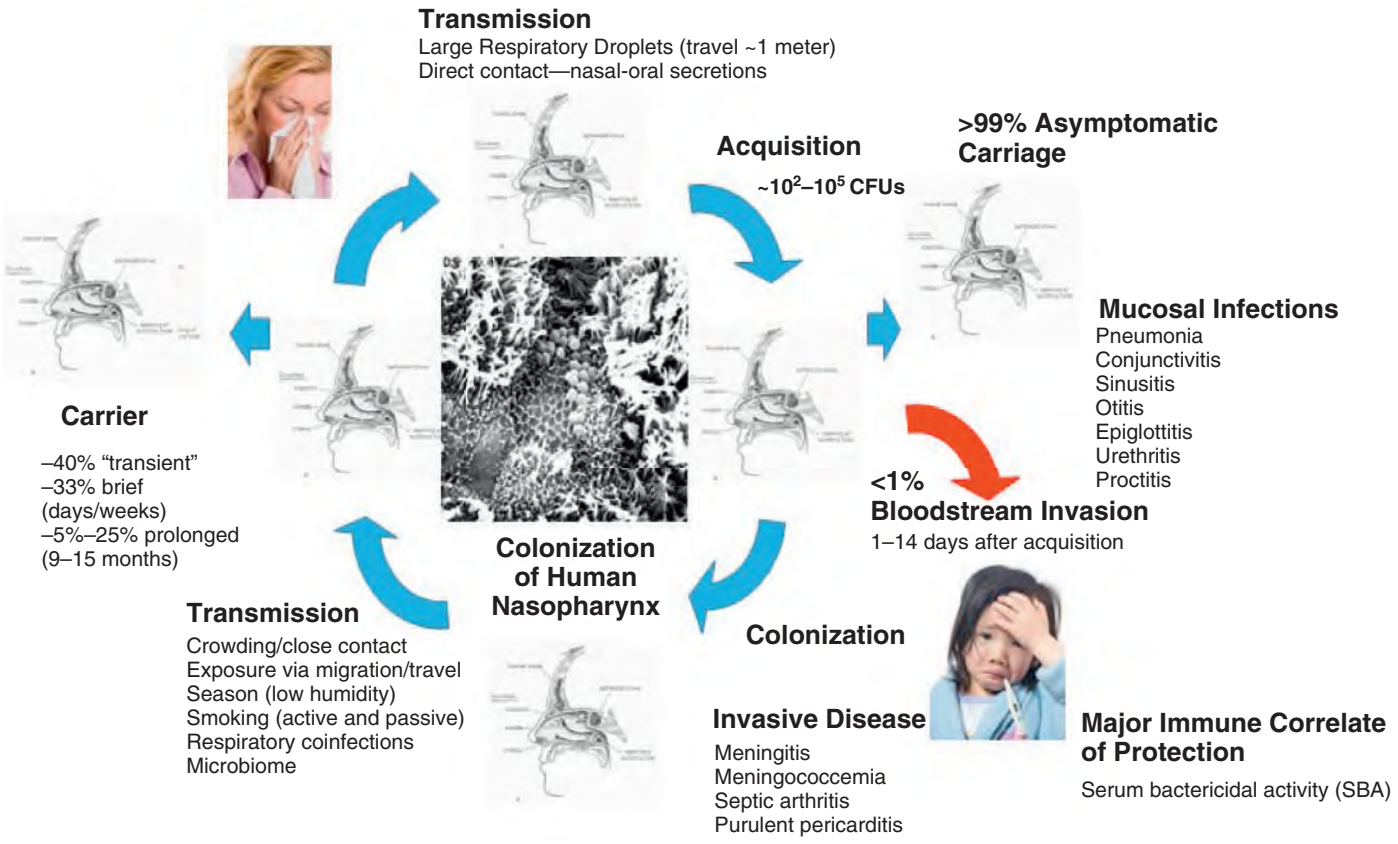

FIG. 211.2 **The life cycle of *Neisseria meningitidis.*** *CFUs,* Colony-forming units.

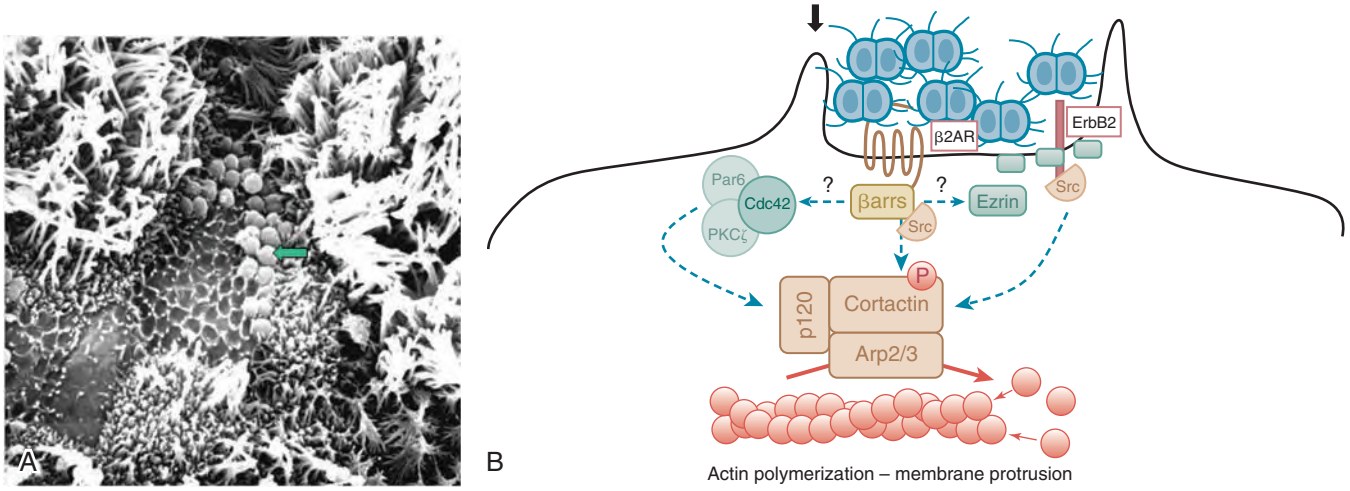

FIG. 211.3 **Dynamics of meningococcal attachment to human nasopharynx epithelial cells and human vascular endothelium.** (A) Electron micrograph of *Neisseria meningitidis (green arrow)* attaching to human nasopharyngeal mucosa. (B) Schematic of the molecular events occurring in (A). *(Modified from Stephens DS. Biology and pathogenesis of the evolutionarily successful, obligate human bacterium* Neisseria meningitidis. Vaccine. *2009;27(suppl 2):B71–B77; and Coureuil M, Join-Lambert O, Lécuyer H, et al. Mechanism of meningeal invasion by* Neisseria meningitidis. Virulence. *2012;3:164–172.)*

leading to cortical actin polymerization and plaque formation (see later). The induction of cortical plaques also leads to internalization of meningococci within epithelial cells, a site where capsule is advantageous for survival. Cell entry is a potential pathway to mucosal invasion and access to the bloodstream. Capsule expression and glycan expression on pili result in meningococcal disaggregation and spread along and from mucosal surfaces.

As previously noted, meningococci are common commensals, colonizing 3% to 25% of human populations worldwide.[50,51,92–94] Carriage rates are low in infants and young children and highest in adolescents and in closed populations, but there is considerable global diversity. Carriage may be transient or prolonged (e.g., months). Carriage does not directly predict an outbreak or the course of the outbreak, but "if there are no carriers, there are no cases."[96] Although usually less than 1% of persons exposed develop invasive disease, expanded transmission of meningococci with the capacity to cause disease will result in increased incidence. Transmission is by direct contact with respiratory secretions or by inhalation of large respiratory droplet nuclei that travel approximately 1 meter (3 feet); respiratory droplets may increase in low-humidity environments.[97] Meningococci are fastidious but can survive for hours

or more on innate surfaces.[96,98] Factors that influence meningococcal transmission and carriage include crowding or close contact, exposure through migration or travel (e.g., the Hajj), season, active and passive smoking, party or club attendance, male sex, and respiratory coinfections.[94,97,99–102] The human upper respiratory microbiome also influences meningococcal colonization (e.g., the presence of *N. lactamica* is negatively correlated with meningococcal carriage). A challenge in understanding the dynamics of meningococcal carriage has been the variable expression of capsule or other virulence factors detected with serologic technologies in colonizing isolates. WGS is a more accurate approach to characterizing meningococcal carriage isolates.[103]

The meningococcal inoculum required for nasopharyngeal colonization or needed to cause invasive disease is not known. However, data from experimental *N. gonorrhoeae* urethral infections in male subjects revealed a median infective dose (ID_{50}) of approximately 10^5 colony-forming units of gonococci, which could be further reduced to approximately 3×10^2 if gonococci obtained from the initial passage after infection were used.[104] In settings of very high exposure (e.g., military recruits), the acquisition of meningococci in the nasopharynx is transient (or not detected) in about 40% of individuals; in approximately 33%, the period of nasopharyngeal colonization and carriage is brief (i.e., days to weeks); and in approximately 25%, meningococcal carriage becomes fully established and can last 9 to 15 months or longer.[50,105] Meningococci that gain access to the bloodstream may cause a transient or mild bacteremia but also the clinical syndromes of septicemia and meningitis described later. Invasive meningococcal disease usually occurs 1 to 14 days after mucosal acquisition.[1,3] Cofactors associated with invasive meningococcal disease are respiratory tract infections (e.g., from mycoplasma, or influenza and other viral agents), active and passive smoking, and environmental damage to the upper respiratory tract (e.g., from low humidity, dusty winds of the Harmattan in Africa).[1,3,4,99,100] *N. meningitidis* also has the capacity to damage respiratory epithelial cells, can cause a pharyngitis, and can spread to adjacent mucosal surfaces of the upper respiratory tract to produce focal respiratory infections (e.g., pneumonia in up to 10% of presentations) but is an uncommon cause of otitis media or sinusitis. Meningococcal pneumonia and conjunctivitis are also recognized as portals of entry for systemic disease.

Once in the bloodstream, type IV pili facilitate meningococcal attachment to peripheral vascular endothelial cells. This results in the formation of microcolonies on vascular endothelium, the activation of signaling pathways in endothelial cells and formation of cortical plaques, and meningococcal entry into endothelial cells. A humanized mouse model shows meningococcal adherence only to human vessels.[101] Adherence results in extensive damage, inflammation, and development of a purpura at these sites. The specific steps in brain and other microvascular endothelial cortical plaque formation have been dissected[106–109] and involve the recruitment and activation of the β_2-adrenoreceptor and CD147 in hetero-oligomeric complexes, the accumulation of ezrin and ezrin-binding receptors, β-arrestins and β-arrestin–binding molecules such as Src and VE-cadherin, and the activation of the cortactin/Arp2/3 complex, leading to actin polymerization, membrane protrusions, and cortical plaque formation (see Fig. 211.3B). In brain microvascular endothelium there is also breakdown of tight junctions between endothelial cells, which also may allow meningococci to cross the blood-brain barrier and gain access to the subarachnoid space.[109]

Host Susceptibility

The absence of protective bactericidal activity (deficiency in bactericidal antibody or complement) is the most important single predisposing human factor for susceptibility to systemic meningococcal disease, but other genetic polymorphisms and other host cofactors contribute to invasive disease potential or severity.[110–112] Disappearance of maternal antibodies increases the risk for infants and young children. Congenital and acquired antibody deficiencies also increase risk.[110,111,113,114] Rapidly progressive, fatal meningococcemia can arise in patients deficient in properdin, and there is an increased risk for recurrent meningococcal infections for those with C3 deficiency and congenital or acquired defects (e.g., eculizumab therapy) in the terminal complement pathway (C5-C9).[115] Studies also have linked polymorphisms in complement factor H *(CFH)* and complement factor H related 3 *(CFHR3)* as contributing to meningococcal disease susceptibility.[116] However, opsonization and phagocytic function can also contribute to meningococcal host defense mechanisms, as suggested by disease reduction after meningococcal vaccination in individuals with congenital terminal complement deficiencies.[115] As detailed later, the risk of meningococcal disease in individuals receiving eculizumab, a potent inhibitor of C5, is >300 per 100,000 and opsonization and phagocyte function are also impaired in these patients.

Polymorphisms in genes coding for the Fcγ-receptor II *(CD32),* Fcγ-receptor III *(CD16),* mannose-binding lectin (MBL), TLR4, TNF, the collectin SP-A2, and the β_2-adrenocepter gene *(ADRB2)* have been associated with increased risk for meningococcal disease.[117–127] MBL is a plasma opsonin that initiates complement activation; specific polymorphisms in this gene have been identified more frequently in children with meningococcal disease than in controls[118] in some studies but not others.[119,120] Plasminogen activator inhibitor-1 (PAI-1) concentrations affect risk for severity and mortality of meningococcal sepsis, suggesting that impaired fibrinolysis is an important factor in the pathophysiology of meningococcal sepsis.[124] Genetic variation in the β_2-adrenoceptor has also been associated with susceptibility to meningococcal meningitis.[125]

Meningococcal disease is also linked to immunosuppressive disorders such as glomerulonephritis, hypogammaglobulinemia, splenectomy, and other chronic illnesses including human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) (i.e., an approximate 10-fold increased risk for sporadic meningococcal disease[126] versus about a 100-fold increased risk for infection with the pneumococcus in HIV/AIDS). In an outbreak in New York City of serogroup C meningococcal disease, the risk for disease was 12.6 per 100,000 in men who have sex with men (MSM), most of whom were infected with HIV, compared with 0.16 per 100,000 in non-MSM.[128] Serogroup C meningococcal outbreaks in MSM have also occurred in Chicago and Los Angeles.[129] However, there have been no well-documented increases in epidemic outbreaks of meningococcal disease in developing countries with high rates of HIV infection. Other chronic illnesses (e.g., chronic dialysis, diabetes mellitus, transplantation) in children and adults have been associated in case reports with susceptibility to meningococcal infections, due either to underlying disease or immunosuppressive therapy. Many of the meningococcal isolates from these patients are of low virulence, including capsule null *N. meningitidis.*[130]

EPIDEMIOLOGY

The epidemiology of meningococcal disease is dynamic. The rates of disease are influenced by the virulence of circulating strains, environmental and host factors influencing transmission, carriage and disease, population immunization, and other prevention strategies.[1,4,131,132] Meningococcal isolates have been historically classified by serologic typing based on the biochemical composition of the capsular polysaccharide. Serogroups A, B, C, E, H, I/K, L, W, X, Y, and Z are confirmed genetically[60]; however, six serogroups (A, B, C, W, X, and Y) currently cause almost all worldwide life-threatening disease.[1,4,48,60]

Outer membrane protein serotyping and serosubtyping and LOS immunotyping have also been used, especially for serogroup B meningococcal strains. Genomic typing (e.g., multilocus sequence typing [MLST]) and whole-genome comparisons have unlocked a broader understanding of the global epidemiology of meningococcal disease. With MLST,[133] meningococcal isolates are classified into different sequence types (STs) and CCs based on polymorphisms in seven housekeeping genes considered not to be under selective pressure. CCs ST-5 and ST-7 (serogroup A); ST-41/44, ST-32, ST-18, ST-269, ST-8, and ST-35 (serogroup B); ST-11 (serogroups C, W, or B); ST-23 and ST-167 (serogroup Y); and ST-181 (serogroup X) meningococci cause almost all invasive meningococcal disease[48,70,134]; but other new genotypes associated with disease continued to emerge (e.g., ST-10217, serogroup C in Africa[135,136]; ST-4821, serogroups C and B in China[136]). The emergence of rapid WGS as an epidemiologic technique and tool for better understanding pathogenesis has further defined meningococcal strain relatedness, diversity, and virulence.

Meningococcal disease is worldwide (Fig. 211.4), but with significant differences in serogroup/CC predominance. Incidence also varies in populations over time. Disease can be epidemic, endemic (sporadic),

FIG. 211.4 Global epidemiology of meningococcal disease by serogroup, 2018. Serogroups are linked to 12 major clonal complexes: ST-5 and ST-7 (serogroup A); ST-41/44, ST-32, ST-18, ST-269, ST-8, and ST-35 (serogroup B); ST-11 (serogroups C or W); ST-23 and ST-167 (serogroup Y); and ST-181 (serogroup X) meningococci currently cause almost all invasive meningococcal disease. *(Modified from Stephens DS, Greenwood B, Brandtzaeg P. Epidemic meningitis, meningococcaemia, and* Neisseria meningitidis. Lancet. *2007;369:2196–2210.)*

or hyperendemic. Meningococcal epidemiology is affected by the sequence types and serogroups circulating, by age and other host susceptibility (e.g., the frequency in the population of complement deficiencies), by the widespread use of antibiotics that eradicate the meningococcal carrier state, and by vaccines. The introduction of polysaccharide vaccines in the 1970s decreased the incidence of meningococcal disease through widespread use in the military, in sub-Saharan Africa, in China, and in countries associated with the Hajj and Umrah pilgrimages. More recently, the A, C, W, Y MCVs that both induce individual protection and interfere with transmission resulting in herd protection have had greater impact.[70] Other changes in populations (e.g., in strain- or clonal group–specific immunity) and other environmental factors (e.g., crowding, smoking, humidity, dust, viral, or mycoplasmal coinfections) also influence the incidence of meningococcal transmission and disease.[1,4,131,132]

Meningococcal disease epidemiology dramatically changed in industrialized nations after World War II.[a] Before and during this war, large serogroup A outbreaks occurred in the United States, Europe, Asia, South America, and Africa that were cyclical, having peaks and troughs every 5 to 12 years. These large serogroup A outbreaks dominated meningococcal disease throughout the world in the 19th and first half of the 20th centuries; disappeared from the United States, Western Europe, and Japan after World War II; but continued in parts of Asia, South America, and sub-Saharan Africa. For example, before and during World War II the incidence of meningococcal disease in the United States was 3 to 4 per 100,000 population, with episodic serogroup A outbreaks raising the incidence to 8 to 17 per 100,000.[137] With the disappearance of serogroup A outbreaks and serogroup A carriage for reasons that are not well understood, overall attack rates in the United States declined to 1.7 per 100,000 population by the mid-1990s, but with periodic "hyperendemic" fluctuations in the incidence of B, C, or Y meningococcal disease. In the United Kingdom, incidence decreased from more than 5 per 100,000 population in the 1990s to less than 3 per 100,000 population after the virtual elimination of serogroup C disease as a result of the introduction of C specific conjugate vaccines (see later).[138] However, in 2010 the rates of serogroup W ST-11 disease began to increase in the United Kingdom.[139] The increase is associated with the emergence of new ST-11 serogroup W sublineages with severe disease, often in adolescents and older adults, and clinical presentations that include pneumonia, gastroenteritis (nausea, vomiting, diarrhea), septic arthritis, and epiglottitis or supraglottitis. The W:CC 11 lineages have appeared globally, causing increased disease in South America, Canada, Europe, China, Australia, and sub-Saharan Africa.[139,140] These events have led to the increasing use of A, C, W, Y conjugate vaccines in many countries.

Although increases in W:CC 11 disease have occurred, the overall meningococcal disease incidence and carriage rates in many industrialized countries' populations have continue to decline[b] (in the United States in 2015 the invasive meningococcal disease incidence was 0.12 per 100,000). In Japan, rates of disease are now <0.04 per 100,000 (and carriage rates are 0.4%), with a high percentage of the remaining meningococcal disease occurring in complement-deficient individuals.[115,141,143]

In the United States, serogroups B (ST-41/44, ST-32), Y (ST-23), and C (ST-11), although declining in incidence, continue to cause most (87%) of the meningococcal disease.[4] The United States saw the emergence in the early 1970s and again in the mid-1990s into the 2000s of serogroup Y (ST-23) disease. Serogroup Y disease incidence peaked in 1997, accounting for approximately 50% of reported cases, in contrast to approximately 2% in the early 1990s.[2–4] Almost all of the serogroup Y meningococcal disease in the United States in the 1990s was caused by ST-23 CC strains.[48,70] In 1998, a carriage study of high school students from counties in the metropolitan area of Atlanta, Georgia, found the rate of meningococcal carriage to be 7.7%; and of these isolates, 48% were serogroup Y.[146] However, in 2006–07, a similar carriage study in high school students found a much lower carriage rate of less than 3% and a much lower proportion of serogroup Y carriage.[48,147] The lower frequency of serogroup Y and overall meningococcal carriage correlated with the decline in invasive serogroup Y cases after 1998. However, serogroup Y continues to cause disease in the US population and is seen globally.

The overall declines in disease also continue to be interrupted by localized serogroup C outbreaks in the United States and Europe, such as in MSM[142,148,149]; or by serogroup B outbreaks in communities and institutions such as on college campuses.[150] The increased serogroup C rates in MSM compared with non-MSM populations led to specific targeting of educational and vaccination efforts in New York City and in other locations.[129]

In South and Latin America (in particular, Brazil and Chile), serogroup W:CC 11 is currently a major cause of disease, followed by serogroups B and C.[151] In Europe, serogroups B (ST-41/44, ST-32, ST-18, ST-269, ST-8), W (ST-11), C (ST-11),[144] and Y (ST-23) currently predominate; in Russia, serogroups B, C, A, W, and Y; in China and Mongolia, serogroups C, W, B, and A; in India and Nepal, serogroups A, C, and B[152,153]; in Oceania, serogroups W, B, Y, and C; in the Middle East and North Africa,[154] serogroups W, B, A, and Y; and in sub-Saharan Africa, serogroups C (ST-10217), W (ST-11), and X (ST-181).[52] Serogroup Y CC ST-11 and ST-167 have been increasingly reported in South Africa, Israel, parts of Europe, and Japan.

Serogroup A is historically associated with the highest incidence and largest epidemics of meningococcal disease,[1,11,131,155,156] especially meningitis. Serogroup A global pandemics in the 20th century were caused by five major ST CCs (e.g., ST-5, ST-7). Three pandemic waves arising in China and spreading to Russia, the Middle East, Africa, and globally were recorded in the 1960s to 1970s, 1980s, and into the 1990s. Serogroup A strains are genetically distinct from other meningococci and appear to have evolved from a common ancestor in the 19th century.[12] In sub-Saharan countries of Africa, extending from Senegal and The Gambia in the west to Ethiopia, Eritrea, and northern Kenya in the east, a region known as the African meningitis belt, large periodic epidemics of serogroup A meningococcal disease occurred every 5 to 12 years from the late 1800s to 2010.[11,157] Virulent meningococci may have been first introduced into the region by returning Hajj pilgrims. The size of these epidemics was enormous. In major African epidemics, the attack rate ranged from 100 to 800 per 100,000 population during epidemics, and individual communities have reported rates as high as 1 per 100.[c] Between 1988 and 1997, 704,000 cases and more than 100,000 deaths were reported; from 1996 to 1997, more than 300,000 cases and 30,000 deaths, the largest serogroup A epidemic year ever recorded, with spread to countries south of the meningitis belt (e.g., Rwanda, Burundi, Tanzania, Zambia, and the Central African Republic); between

[a]References 1, 3, 4, 131, 137, 539.

[b]References 1, 4, 131, 132, 138, 141–145.

[c]References 11, 17, 155, 156, 158, 159.

1998 and 2002, 224,000 cases; and, in 2009, 88,199 meningococcal meningitis cases occurred in the belt.[158]

The CCs, ST-5 and ST-7, were responsible for these global serogroup A pandemics, the African meningitis belt outbreaks, endemic serogroup A meningococcal disease in the belt, and the worldwide cases of serogroup A disease.[157] The epidemics in the meningitis belt have been linked to environmental factors, such as climatic changes (dry season, "dust" and winds of the Harmattan), coinfections, poor living conditions, overcrowded housing, travel and population displacements, and specific population immunologic susceptibility.[d] Disease in this region predominantly occurs in the dry season (December to June), ending during the intervening rainy season. Respiratory droplets that facilitate meningococcal transmission have higher density in the dry season.[97] Although serogroup W, X, and rarely C had had caused epidemic outbreaks in sub-Saharan populations, serogroup A epidemic meningococcal disease was a major public health threat in the meningitis belt and other areas of the developing world. Over the past 2 decades, great strides have been made in development and implementation of serogroup A–directed MCVs. The successful introduction beginning in 2010 of a new serogroup A MCV, MenAfriVac (Serum Institute of India, Pune, India), in sub-Saharan Africa[160] (see "Meningococcal Conjugate Vaccines") has radically altered meningococcal disease in this region. The serogroup A conjugate vaccine has been introduced into the 26 countries in the African meningitis belt, resulting in a remarkable decline in the burden of disease. However, the region does continue to see serogroup C meningococcal disease, with two large outbreaks in Nigeria and Niger,[161] serogroup W in Ghana[162] and Burkina Faso, and serogroup X in Burkina Faso, Chad and Togo. This is a consequence of bacterial evolution rather than serogroup replacement.[162] The cost of vaccination remains a primary obstacle to further progress against other serogroups in the African belt, but a low-cost pentavalent meningococcal conjugate A, C, W, X,Y is in development, projected for implementation in 2020 or 2021.

The epidemiology of meningococcal disease in parts of Africa outside the meningitis belt is not as well defined. In a report from rural Mozambique, the average incidence of endemic meningococcal disease was 11.6 per 100,000, with both sepsis and meningitis identified and with W (ST-11) as a major cause.[163] It is important to note that epidemics of *S. pneumoniae* meningitis (serotype 1, ST 217 CC) are also reported in the meningitis belt,[164,165] and febrile encephalopathy due to malaria can mimic meningococcal meningitis.[166] More longitudinal and laboratory-based surveillance is needed in Africa.

As noted, serogroup W has emerged in the past 2 decades as a cause of global epidemic outbreaks of considerable size.[139,167–169] In 2000 and 2001 several hundred pilgrims attending the Hajj in Saudi Arabia were infected with *N. meningitidis* serogroup W. Then in 2002, serogroup W emerged in Burkina Faso, striking 13,000 people and killing 1500. Global spread with secondary cases from these epidemics was also observed. The outbreaks were caused by W (ST-11) strains closely related to ST-11 serogroup C strains. Serogroup X (ST-181) has caused localized outbreaks in certain African countries, including Kenya, Niger, and Ghana, but has rarely been a cause of meningococcal disease outside Africa.[52,170] Curiously, serogroup B disease is quite rare in sub-Saharan Africa but does cause significant disease in South Africa.

Serogroup B is the major cause of prolonged outbreaks, hyperendemic disease, and endemic (sporadic) meningococcal disease, especially in infants and young children in developed countries.[1,4,131,171–174] Serogroup B epidemic outbreaks have also occurred worldwide and are usually of lower overall incidence compared with serogroup A outbreaks, but can reach levels of 20 to 45 per 100,000 in highly affected populations, as was seen in Pacific Islanders and Maoris in New Zealand and in infants. Serogroup B outbreaks can persist over many years. The serogroup B (ST-32) outbreaks of meningococcal disease in the US Pacific Northwest[171] from 1988 to approximately 2007 and in New Zealand[173] in 1992 to 2003 are examples. Recently in the United States, college campuses have been sites of a series of serogroup B meningococcal outbreaks (13 from 2008 to 2017).

There is greater genetic diversity, and thus antigenic diversity, in serogroup B strains that cause meningococcal disease. Most serogroup B disease is caused by seven major ST CCs: ST-41/44, ST-32 (members of these first two complexes account for over two-thirds of serogroup B disease), ST-18, ST-35, ST-269, ST-8, and ST-11.[48] However, several other STs are found in collections of serogroup B isolates, and novel serogroup B strains can cause disease worldwide. The diversity of CCs causing serogroup B disease has presented a challenge to control through vaccination, because the B capsule structure has identity to human polysialic acid determinants.[67] Also, ST-11 isolates, a CC usually associated with serogroup C, can express the serogroup B capsule as a result of "capsule switching,"[63,70,71] allowing escape from vaccine-induced or natural protective immunity. This escape mechanism has raised concerns about serogroup B replacement as a threat to the effectiveness of meningococcal A, C, Y, and W conjugate vaccines.

Vaccines have only recently become available for the routine prevention of serogroup B disease. OMV vaccines were initially developed for control of serogroup B clonal outbreaks (see "Serogroup B Vaccines") such as in 2004 in the New Zealand serogroup B outbreak. A serogroup B outer membrane protein–containing vaccine, VA-MenGOC-BC (Finlay Institute, Havana, Cuba), was also extensively used in Cuba and Latin America.[175–178] New approaches to serogroup B vaccines based on conserved outer membrane proteins are now approved and in use in Europe, Canada, Australia, the United States, and other countries (see "Serogroup B Vaccines").[37,179]

Serogroup C (predominantly CC ST-11) continues to account for significant meningococcal disease, especially in older children and adolescents and young adults throughout the world.[48,153,180–182] Increases in serogroup C meningococcal disease were seen in the United States and Europe in the 1980s and 1990s. In response, the meningococcal serogroup C conjugate vaccines were developed and first introduced in the United Kingdom in 1999. After serogroup C conjugate vaccine introduction, serogroup C invasive disease rapidly declined in the United Kingdom[35,36,138,183] and in other European countries,[184] but it has not been eliminated.

In the United States, surveillance including Active Bacterial Core surveillance (ABCs), a prospective laboratory- and population-based surveillance system, has tracked invasive bacterial pathogens, including *N. meningitidis*.[4,132] This surveillance has documented the contribution of the *Haemophilus influenzae* type b capsular conjugate vaccines, the pneumococcal conjugate vaccines, and the MCVs to the marked decline in bacterial meningitis in the United States. However, *N. meningitidis* remains an important cause of bacterial meningitis and septicemia in infants, children, and adults. In the United States, it has been the second most common cause of community-acquired adult bacterial meningitis.[185]

Based on this recent detailed surveillance, the incidence of meningococcal disease in the United States in the last quarter-century peaked at 1.7 per 100,000 population in the mid-1990s and since has continually declined; it was 0.35 per 100,000 in 2007,[3] and in 2015 it was at a historic low of 0.12 per 100,000 population,[4] a decrease of greater than 92%. From 2006 to 2015,[4] a total of 7924 cases of meningococcal disease were reported in the United States; 14.9% of these cases were fatal. "Sporadic" cases accounted for 98% of cases, but molecular typing is better defining invasive isolate relatedness in communities.[186] The incidence of meningococcal disease varies by season, with more cases occurring during January through March (34.7 % of cases) and the fewest cases occurring during August and September (11.2% of cases). The incidence of meningococcal disease in 2006 through 2015 by state ranged from 0.13 cases per 100,000 population to 0.79 cases per 100,000 population (median, 0.25 per 100,000). The incidence was highest in Oregon (0.79 cases per 100,000 population), reflecting the persistence of the longstanding serogroup B ST-32 strains in the region. The incidence of serogroup B–specific meningococcal disease was 0.31 cases per 100,000 population in Oregon, compared with 0.07 cases per 100,000 population in the other states.

Although the highest attack rates occur in the very young (<1 year old, 2.45 per 100,000), 73% of cases of invasive meningococcal disease in the United States occur in adolescents and adults. The rates of meningococcal disease have declined in all age groups in the United States since the mid-to-late 1990s.[3,4] Male patients accounted for 50.6% of cases. Female patients were significantly older than male patients (median age, 35 years in female patients compared with 22 years in

[d]References 1, 11, 99, 100, 102, 155, 159.

male patients). The incidence of meningococcal disease among black persons was 0.27 cases per 100,000 population, compared with 0.20 cases per 100,000 population among white persons and 0.20 cases per 100,000 population among other race categories combined. The distribution of serogroups causing disease has also shifted in the United States.[3,4,187] From 2006 to 2015, serogroup B caused 35.8% of all meningococcal disease, serogroup C was responsible for approximately 22.8% of endemic disease, and case clusters and local outbreaks and serogroup Y caused 28.5% of cases. The case-fatality rates of serogroups C (20.2%) and W (20.9%) were higher than those of serogroup B (11.5%) or serogroup Y (13.7%).

CLINICAL MANIFESTATIONS AND PATHOPHYSIOLOGY

The common presentations of invasive meningococcal disease are *meningococcemia* and acute *meningitis*. In several large series of cases, predominantly of serogroup B or C disease[4,83,188–192] in industrialized settings, 40% to 65% of patients presented with meningitis, 10% to 20% had fulminant meningococcemia with shock but without meningitis, 7% to 12% had both meningitis and fulminant meningococcemia, and 18% to 33% had bacteremia without shock or meningitis. Less common presentations are *primary pneumonia* (up to 10%, especially with serogroup Y), *septic arthritis* (2%), *purulent pericarditis, chronic meningococcemia, gastroenteritis, conjunctivitis, epiglottitis, sinusitis, otitis, urethritis,* and *proctitis*.[4,83,188–191] Rare presentations include necrotizing fasciitis.[193] Invasive disease often occurs in otherwise healthy individuals and is difficult to identify early. In part, this is because sporadic meningococcal disease is not common and the classic clinical features of disease (e.g., petechial or purpuric rash, meningismus, and impaired consciousness) often appear late in the illness.

In fulminant meningococcemia, the time window between the progression from initial symptoms to death can be narrow (hours). In a study by Thompson and colleagues,[191] nonspecific symptoms, such as fever, loss of appetite, nausea and vomiting, and sometimes diarrhea (which may have been preceded by a coryza and pharyngitis), occur in the first 4 to 6 hours, with more severe symptoms developing by 8 hours, such as leg pains, cold hands and feet, labored breathing, abnormal skin color, and rash; the median time to hospital admission was 19 hours, and by 24 hours, individuals can be dead or moribund.[188] Physicians and health care providers should be alert to the concern of parents or relatives about the abrupt or rapid deterioration of a patient.[194,195] Major complications of meningococcemia and/or meningococcal meningitis are necrosis and limb or digit loss, scarring, cranial nerve palsies (mostly commonly eighth nerve loss resulting in deafness), postinfectious immune complex–mediated polyarticular arthritis or pericarditis, long-term learning and cognitive disabilities, seizures, motor deficits, and chronic renal dysfunction. The overall case-fatality rate, despite antibiotics and aggressive support, remains at approximately 10% to 15% in developed countries.

Although the clinical features of meningococcal disease are similar in all epidemiologic situations, the number of patients who have a specific clinical presentation can vary from outbreak to outbreak for reasons that are not well understood. For example, meningitis is the major presentation, and septicemia is recorded less frequently during serogroup A epidemics in the African meningitis belt in comparison with patients in industrialized countries.

Meningococcemia

In 10% to 20% of cases, septicemia with shock is the dominant clinical picture and presentation is acute, with sudden-onset fever, generalized malaise, weakness, cold extremities and skin pallor, leukocytosis or leukopenia, rash, headache and/or drowsiness, and hypotension.[5,196] A petechial or purpuric rash, a classic sign of meningococcal septicemia, is seen in 40% to 80% of cases of meningococcemia but may be difficult to detect initially. A maculopapular blanching rash can also be an early sign in the disease, can progress to a petechial or purpuric rash, or can persist in 13%.[197] Median time from onset to admission for meningococcemia in two studies was 13 hours and 12 hours, which is less than half the time recorded for patients with meningitis.[85,198] Generalized muscle tenderness may also be an important differential sign. Occasionally the pain from these myalgias is quite intense and causes the patient considerable discomfort. Clinical signs of meningeal irritation are usually absent, few meningococci are present in CSF, and CSF pleocytosis is negligible.[1]

A rapid proliferation of meningococci in the circulation characterizes meningococcal septicemia (including the classic Waterhouse-Friderichsen syndrome[199] with adrenal hemorrhage) (Figs. 211.5 to 211.7), resulting in very high concentrations of bacteria (10^5–10^8/mL) and meningococcal endotoxin (10^1–10^3 endotoxin units [EU]/mL).[1] Cases with fatal outcome have higher concentrations of meningococcal endotoxin in plasma than mild cases, and these patients are sicker than survivors.[1] The adherence of intact meningococci and/or OMVs to the microvasculature and association with macrophages and mononuclear cells in fulminant meningococcemia is striking.[200] Expression of human CD46 by macrophages may accelerate inflammatory responses on meningococcal infection or LOS stimulation.[201] The rapid bacterial growth in the bloodstream causes an exaggerated and destructive intravascular inflammatory response, leading to progressive circulatory collapse and severe coagulopathy.[1] There is also evidence of meningococcal proliferation and massive local inflammatory response in specific organs.[202,203] Shock all too frequently dominates the clinical picture. Patients can present with severe, persistent shock that lasts more than 24 hours or until death. The patient is poorly responsive, and peripheral vasoconstriction is present, with cyanotic, poorly perfused extremities. Arterial blood gas analysis demonstrates evidence of acidosis in the range of pH 7.25 to 7.3, and, depending on the degree of shock, anoxia may manifest with an arterial oxygen pressure below 70 mm Hg.

Patients develop impaired renal, adrenal, and pulmonary function and disseminated intravascular coagulation (DIC), with thrombotic lesions in the skin, limbs, kidneys, adrenals, choroid plexus, heart, and occasionally the lungs. Clinical evidence of DIC includes increasing petechiae within prescribed areas, gastric or gingival bleeding, or oozing at sites of venipuncture or intravenous infusions. Myocardial dysfunction is also well described in adults and children with meningococcemia.[204–206] Postmortem studies by Hardman[207] and by Gore and Saphir[208] indicated that myocarditis of varying degrees of severity is present in more than half the patients who die of meningococcal disease. The hypotension and vascular complications can lead to extensive scarring and loss of digits or limbs, and survivors can be severely handicapped.[196]

Mild or transient bacteremia without sepsis is a presentation in less than 5% of cases. Admission or emergency evaluation is often for an upper respiratory tract illness, fever, or presumed viral exanthema. After recovery in 2 to 5 days and frequently after release without specific antimicrobial therapy, the unexpected results of blood cultures are reported as positive for *N. meningitidis*. In one study, Sullivan and LaScolea[209] reported that the levels of bacteremia in this presentation were low, from 22 to 325 organisms per milliliter of blood. Meningococcal disease in terminal complement-deficient patients is also often milder and associated with a lower mortality for reasons that are not well understood (see "Complement Deficiency and Meningococcal Disease").[115] Also, patients with isolates with LOS lipid A mutations have less rash and coagulopathy.[210]

Meningitis

Meningitis is the most common presentation of invasive meningococcal disease and is seen in 40% to 65% of cases,[e] reflecting the meningeal tropism of *N. meningitidis*. In older children, adolescents, and adults, sudden-onset headache, fever, vomiting, myalgias, photophobia, irritability, decreased ability to concentrate, agitation, drowsiness, and meningeal signs (neck stiffness, Kernig or Brudzinski sign), and cloudy CSF, with or without a rash, are seen.[211–224] Uncommonly, the conus medullaris syndrome,[216] or more frequently cranial nerve dysfunction (particularly of the sixth, seventh, and eighth cranial nerves), can complicate meningococcal meningitis.[217] Although focal neurologic signs and seizures may be less common in meningococcal meningitis than in pneumococcal meningitis or in meningitis caused by *H. influenzae* type b,[217] van de Beek and associates[224] reported that 33% of 257 adult patients with meningococcal meningitis had focal neurologic deficits and 5% had

[e]References 1, 4, 5, 188–192, 194, 196.

FIG. 211.5 Fulminant meningococcal septicemia. (A) Ecchymoses. (B) Hemorrhagic adrenals. (C) Thrombosis and gangrene of the fingers of a child. *(From Stephens DS, Greenwood B, Brandtzaeg P. Epidemic meningitis, meningococcaemia, and* Neisseria meningitidis*.* Lancet*. 2007;369:2196–2210.)*

FIG. 211.6 Rashes of meningococcal disease. (A) Rubella-like rash seen early in meningococcal sepsis. Macular (B) and nonblanching petechial (C–E) rashes in meningococcal disease. *(From Stephens DS, Greenwood B, Brandtzaeg P. Epidemic meningitis, meningococcaemia, and* Neisseria meningitidis*.* Lancet*. 2007;369:2196–2210.)*

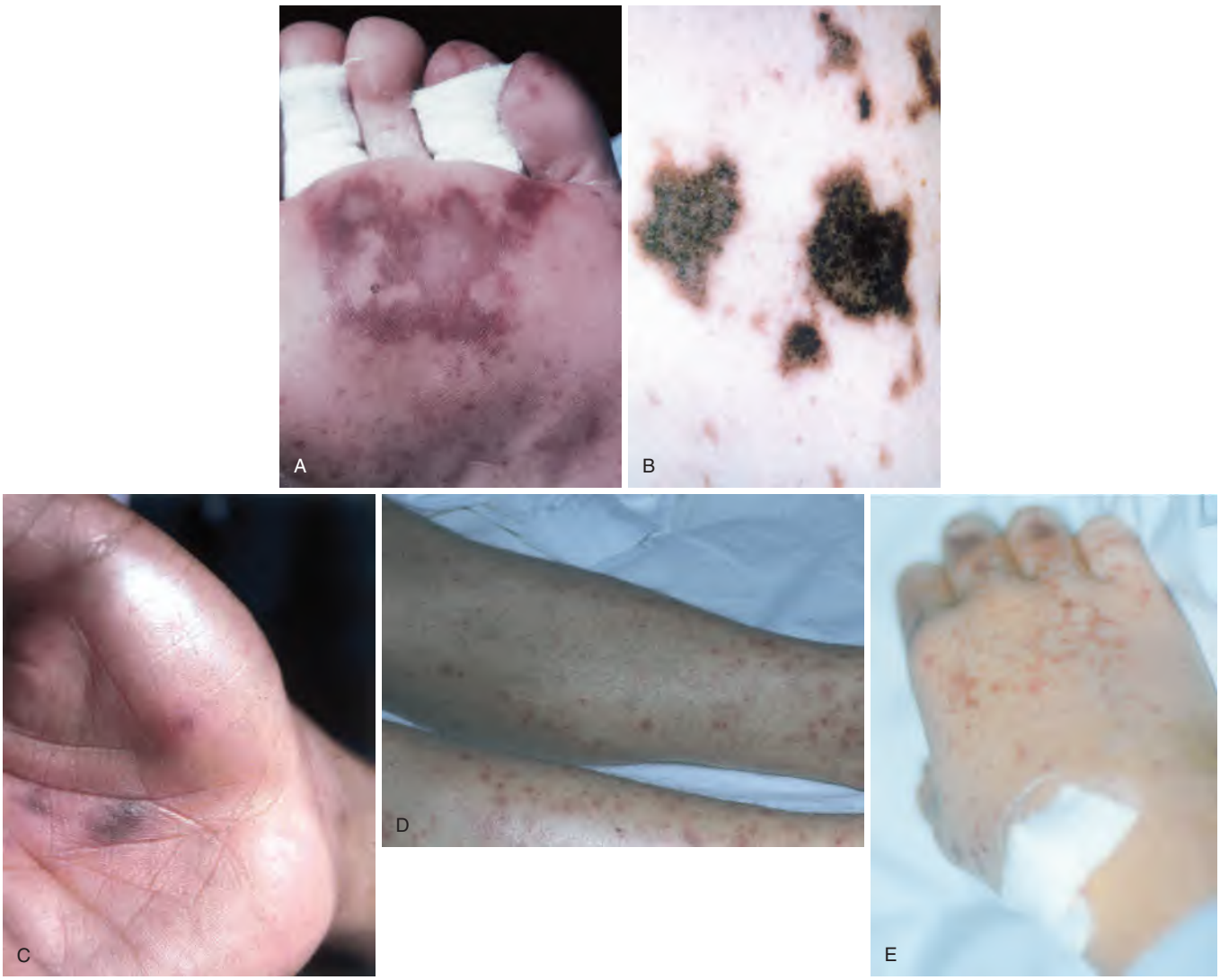

FIG. 211.7 Subcutaneous ecchymoses, embolic lesions, and petechiae of meningococcal disease. (A) Subcutaneous ecchymoses on a sole resulting from meningococcal sepsis. (B) Subcutaneous ecchymoses on the back resulting from meningococcal sepsis. (C) Embolic lesions on a palm secondary to meningococcal sepsis. (D) Petechial lesions on legs in meningococcal disease. (E) Petechiae on the dorsum of a hand resulting from meningococcal sepsis. *(Courtesy Dr. Peter Densen.)*

seizures during their clinical course and that seizures may increase to one-third in children.[5,218] Subdural empyema, in contrast to *Streptococcus pneumoniae* meningitis, is a rare complication of meningococcal meningitis. Some patients with meningococcal meningitis are comatose with an encephalitic picture and pathologic reflexes.

The inflammatory response triggered within the subarachnoid space by replicating meningococci is responsible for the symptoms and signs of meningitis.[219] A rash may be present in 26% to 62% of patients with meningococcal meningitis[220,221] and is commonly petechial but may have fewer lesions than seen in meningococcal septicemia, and/or atypical lesions. In a prospective observational cohort study, the classic meningitis triad of fever, neck stiffness, and altered mental status was present in 70 of the 258 patients (27%) with meningococcal meningitis; when rash was added, 89% of patients had at least two of these four signs.[223] The classic triad is much more common in pneumococcal meningitis (58% in the same cohort study).[224] As reviewed by Pace and Pollard,[5] children younger than 5 years with meningococcal meningitis may present with irritability or lethargy, fever, vomiting, impairment in consciousness, or seizures[211,225] as predominant features without signs of meningeal irritation.[211,225,226] Infants may have inconsolable crying, poor feeding, and a bulging fontanelle.[225,227]

Patients with meningococcal meningitis usually have a low concentration of meningococci (<10^3/mL) and endotoxin (<3 EU/mL) in plasma but high concentrations in CSF,[85,198,228–232] leading to a large compartmentalized inflammatory response in the subarachnoid space, with pronounced increase in concentrations of TNF-α, interleukins (IL-1β, IL-6, IL-8, and IL-10), different chemokines, and other inflammatory mediators. The inflammatory response in the systemic vasculature, as shown by cytokines and complement activation, is modest.[85,198] Raised intracranial pressure, caused by cerebral inflammation and edema, in meningococcal meningitis may lead to cerebral herniation and death. Thomas[233] found that focal cerebral involvement in meningococcal meningitis was rare. The cause of death in meningococcal meningitis was related to cerebral edema and to secondary effects on the vital centers in the midbrain region. Meningococcal meningitis has a mortality of 5% to 18%.[4,189,224] Although either meningococcemia or meningitis usually predominates, about 12% of patients have features of both.[188]

Brandtzaeg and coworkers have made major contributions to our understanding of the physiologic effects of LOS during sepsis and meningitis caused by *N. meningitidis*.[f] These studies have placed a pathogenetic rationale for the clinical states of infection described by Wolfe and Birbara[192] and others, have demonstrated the ability to measure LOS in the plasma and CSF of infected patients, and have shown a

[f]References 83, 85, 198, 219, 228, 230, 232.

close correlation between plasma LOS levels and prognosis. The compartmentalization of LOS production correlates with the clinical findings in meningococcal infections.[230] LOS levels in patients defined as having septicemia were high in plasma (median, 3500 ng) and low in CSF, whereas in patients with meningitis, LOS was detectable in the plasma of 3 of 19 patients and in the CSF of 18 of 19 patients with median levels of 2500 ng. The release of LOS from the surface of the meningococcus in the form of membrane blebs[231] is now considered to be the principal factor associated with the high endotoxin levels in meningococcal sepsis or meningitis. Meningococci covered with multiple, long membrane protrusions, thus indicating surplus outer membrane (blebbing), occurs in both the blood and CSF in vivo.[228,229] Mass spectrometric analysis of the endotoxin from patients with meningococcal sepsis indicated that the endotoxin was of meningococcal origin rather than arising from the gastrointestinal tract as a result of increased permeability during infection.[234]

Rash of Meningococcal Disease

In endemic and epidemic disease outbreaks in industrialized countries, skin lesions are present in 28% to 77% of patients with invasive meningococcal disease on admission[235–237] but can be more difficult to see in patients with dark skin.[238] The classic petechial rash manifests as discrete lesions 1 to 2 mm in diameter, most frequently on the trunk and lower portions of the body (see Fig. 211.6) but also on mucosal membranes and sclera. Lesions are commonly seen in clusters in areas where pressure may be applied to the skin by elastic in underwear or stockings. Petechiae of meningococcemia are usually larger and bluer than pinpoint petechiae caused by thrombocytopenia, leukocytoclastic vasculitis induced by other infections, or those induced by vomiting or coughing. The petechial lesions can coalesce and form larger lesions that appear ecchymotic. Ecchymoses (diameter >10 mm) or purpura are mainly noted in patients with severe DIC.[198,235] Ecchymosis are secondary to subcutaneous hemorrhage, can occasionally be vesicular, and can desquamate as the patients recover. Petechiae correlate with the degree of thrombocytopenia and are clinically important as an indicator in the evolution of bleeding complications secondary to the DIC. Early and aggressive intervention with antimicrobial agents and support of vascular perfusion are keys. At times, surgical débridement of lesions and skin grafting may be necessary. Deep necrosis of limbs or digits may call for amputation. Biopsy samples from dermis show that meningococci are present in and around the microvascular endothelial cells.[200,239,240] Meningococci in these lesions express the polysaccharide capsule, pili, and PorA and can be cultured up to 12 hours after effective antibiotic treatment is started.[200,239,240]

Petechial lesions are a common harbinger of systemic meningococcal infections, but occasionally if the patient is not completely undressed when examined or if examination of mucous surfaces such as the palpebral conjunctiva is omitted, these important telltale lesions or other rash can be missed (see Fig. 211.6C–D). Differential diagnosis of the rash of meningococcal disease includes Henoch-Schönlein purpura (leukocytoclastic vasculitis), Rocky Mountain spotted fever, typhus, viral infections, idiopathic thrombocytopenic purpura, and thrombotic thrombocytopenic purpura; a petechial purpuric rash can also be seen in sepsis due to *S. pneumoniae, H. influenzae, Staphylococcus aureus,* and other bacterial pathogens. In two studies of children with a nonblanching rash,[221,222] 11% and 15% were caused by *N. meningitidis*. Clinical signs such as fever greater than 38.5°C (101.3°F), purpura, slow capillary refill time, circulatory collapse, and signs of meningitis increase the likelihood of meningococcal disease for patients with a nonblanching rash. Children with a nonblanching rash confined to the distribution of the superior vena cava are very unlikely to have meningococcal infection.[221]

A number of authors have described a maculopapular blanching eruption in invasive meningococcal disease that can vary somewhat in hue and can be mistaken for a wide variety of viral exanthems, particularly rubella (see Fig. 211.6).[192,241,242] This eruption is not initially purpuric or pruritic but may progress to petechiae or purpura or be transient. In some patients, red maculae with a diameter greater than 1 cm are the only signs of meningococcemia (see Figs. 211.6 and 211.7).[198]

COMPLEMENT DEFICIENCY AND MENINGOCOCCAL DISEASE (See also Chapter 9)

The importance of the human complement system in protection against meningococcal infections is well recognized, in particular the risk for C5 to C9 deficiencies of the terminal pathway complement pathway, properdin (factor P, a promoter of the alternative pathway of complement and link to innate NK cell activity) deficiency, and C3 deficiency.[243–253] Up to 39% of individuals with late complement deficiency and 6% with properdin deficiency develop systemic meningococcal infections. Terminal complement deficiency is associated with a 1400- to 10,000-fold increase in development of meningococcal disease, and 40% to 50% of patients have recurrent infections.[243,244] Vaccinating individuals deficient in late complement components may shift the burden of host defense from serum bactericidal activity (SBA) to opsonophagocytosis and confer protection.[251,252]

Studies by Lim and coworkers first demonstrated an absence of the sixth complement component as a risk factor for meningococcal disease,[246] and Alper and associates noted that a patient with recurrent meningococcal disease lacked C3.[247] Human deficiency of C8 was found in persons with meningococcal infections, disseminated gonococcal infection,[248] and gonococcal meningitis.[249] Ellison and coworkers[250] evaluated the complement system in 20 patients with first episodes of serious systemic meningococcal infection. Six of 20 (30%) had a complement deficiency. Three had deficiencies in a terminal complement protein or proteins, and three had deficiencies of multiple factors associated with underlying disease states. Densen and coworkers studied a family with properdin deficiency whose members had a high rate of fatal meningococcal disease[251]; about 50% of properdin-deficient individuals develop invasive meningococcal disease.[244]

Complement deficiency is also a factor in the risk for meningococcal disease associated with systemic lupus erythematous and C3 and C4 nephritic factor (autoantibody) states,[245] such as in glomerulonephritis and in patients in whom the complement inhibitor eculizumab is used.[254] The role of complement in meningococcal infections has been reviewed by Densen[243] and by Ram and colleagues.[244] The role of the lectin complement activation pathway in meningococcal disease is controversial. Data have supported the hypothesis that MBL polymorphisms may play a role in susceptibility to meningococcal disease in early childhood[2] or even colonization, but data from large case-control studies revealed that MBL2 structural polymorphisms do not predispose children or adults to invasive meningococcal disease.[120,255]

Chronic Meningococcemia

Chronic meningococcemia is an uncommon meningococcal infection that can last from weeks to months.[256–260] The symptoms are intermittent fever (often low grade), migratory arthralgias or arthritis, and a nonspecific, often maculopapular rash; however, petechial, purpuric, and vesicular rashes are also reported. Symptoms might completely disappear for days before they return with fever, joint pain, and signs of vasculitis. The distribution and appearance of the cutaneous lesions can resemble those seen in disseminated gonococcal infection, for which it can be mistaken.[261] Systemic meningococcal infection should be in the differential diagnosis of the acute arthritis-dermatitis syndrome. Chronic meningococcemia can progress to meningitis and death. Recently, meningococcal isolates with a mutation in the *lpx*L1 gene that results in an underacylated LOS, a less potent endotoxin inducer of proinflammatory cytokines and tissue factor,[210,262] have been associated with chronic meningococcemia.[263]

Primary (Purulent) Pericarditis

Meningococcal bacteremia can result in pericardial infection, sometimes presenting as a massive pericardial effusion and tamponade.[264–270] Primary meningococcal pericarditis is described more in adolescents and adults and has been predominantly caused by serogroup C and W, especially CC ST-11 strains.[267,268] With appropriate antibiotic treatment and drainage of pericardial fluid, patients can do well. Sterile pericarditis is also a postinfectious complication of meningococcal disease.

Septic Arthritis

Primary (purulent) meningococcal arthritis[5,261,268,271–273] is often monoarticular, with the knee and ankle being the joints most frequently affected,[5,272] often occurs in adolescents and young adults (mean age of 21 years), and has been associated with hyperinvasive strains (serogroup C or W) of the ST-11 CC.[5,268] Meningococcal septic arthritis can also resemble the arthritis-dermatitis syndrome caused also by *N. gonorrhoeae.*[3] Response to antibiotics is excellent, and a prolonged course or drainage is usually not required. Septic arthritis should be distinguished from postinfectious immune complex–mediated arthritis,[273] which occurs during convalescence after meningococcal disease (see "Complications").

Respiratory Tract Infections

Meningococcal pneumonia has been recognized as a clinical syndrome for more than 80 years.[4,268,274–276] Of all meningococcal cases, 5% to 10% manifest as pneumonia, and approximately 10% of patients with invasive meningococcal disease have an infiltrate evident on a chest radiograph. Primary meningococcal pneumonia is a more common presentation in adults and especially older adults (>50 years). In patients from whom *N. meningitidis* was isolated, serogroup Y has been the most prevalent single serogroup causing pneumonia (44%), followed by W (16%), B (17%), and C (15%).[4,268,274] In a study of the etiology of community-acquired pneumonia in Finland, *N. meningitidis* was implicated as the etiologic agent in 6 of 162 cases.[277] In the US surveillance of meningococcal cases in patients older than age 65 years, approximately 35% manifested as pneumonia.[4] Because of the nasopharyngeal carriage of the meningococcus, establishing the diagnosis by sputum culture or stain alone is difficult. Koppes and associates used transtracheal cultures to establish the diagnosis in Air Force recruits with group Y meningococcal pneumonia.[275] In that series, a history of cough, chest pain, chills, and previous upper respiratory tract infection occurred in more than half the patients. Rales and fever occurred in almost all patients, and evidence of pharyngitis was present in more than 80%. The disease involved more than one lobe in 40%, with the right lower and middle lobes involved most frequently. The prognosis was good, with no deaths occurring in the 68 recruits with pneumonia. In the elderly, however, the picture is different, with significant mortality of 15.9% with meningococcal pneumonia.[4] One difficulty in the interpretation of infiltrates is the association of invasive meningococcal infections with preceding viral respiratory tract infections. Young and coworkers investigated an outbreak of meningococcal infection in an aged population, most of whom had serologic evidence of influenza.[276]

Meningococcal sinusitis and otitis are described,[238] but in contrast to *S. pneumoniae, H. influenzae, or Moraxella catarrhalis,* the meningococcus is an uncommon cause of these focal respiratory tract infections. However, in one study, *N. meningitidis* was found in 4.7% of persistent middle ear effusions.[278] Meningococcal upper respiratory tract infection (pharyngitis) associated with contacts of cases and as a prior manifestation in cases of serious meningococcal disease has also been described.[279] Meningococcal supraglottitis is a rare presentation of meningococcal infection. Supraglottitis was first reported as a syndrome in 1995; since then, multiple case reports have been published including recent presentations of serogroup W (CC:ST-11). The diagnosis should be considered with the patient's clinical picture of sore throat, dysphagia, fever, muffled voice, and swollen supraglottic tissues, as seen on plain radiography, fiberoptic laryngoscopy, and cervical computed tomography.[280]

Conjunctivitis

Meningococcal conjunctivitis, typically manifesting with a unilateral hyperacute purulent exudate with hyperemia and edema, has been reported in all age groups, including neonates, but is more common in childhood (mean age, approximately 8 years).[5,281,282] *N. meningitidis* accounts for approximately 2% of cases of bacterial conjunctivitis reported.[282] Direct inoculations of secretions or airborne droplet spread is the presumed mode of transmission. Meningococcal conjunctivitis may progress to panophthalmitis or to invasive disease (10%–40% of patients) or both; thus, systemic therapy with intravenous antibiotics and contact chemoprophylaxis is the preferred method of treatment.[282] Conjunctivitis and endophthalmitis are also reported as complications of meningococcal bacteremia.

Meningococcal Urethritis and Proctitis

Meningococci can be isolated from the urethra and can be the etiologic agent of urethritis. Recently, increased cases of meningococcal urethritis have been reported from sexually transmitted infection clinics in the United States.[283] An association between orogenital sex and acquisition of the organism has been suggested.[284,285] The US urethritis outbreak is due to a specific CC ST-11.2 clade.[286] The clade has acquired gonococcal genes important for anaerobic growth. In MSM, the meningococcus can be frequently isolated from the oropharynx, rectum, and urethra.[284] The meningococcus can be carried asymptomatically in the rectum of both men and women and has been linked to approximately 3% of symptomatic proctitis in homosexual men.[287–289]

Complications

Immune complex–mediated complications such as arthritis, cutaneous vasculitis, iritis, episcleritis, pleuritis, and pericarditis can first appear several days to 2 to 3 weeks after onset of invasive meningococcal disease, when the patient is otherwise improving. These complications are due to the deposition of antigen–antibody complexes composed of meningococcal capsular polysaccharide or other antigens, meningococcal-specific immunoglobulins and C3; they complicate 6% to 15% of meningococcal meningitis or septicemia.[5,290,291] The subject has been reviewed by Pace and Pollard.[5] These inflammatory complications may be associated with reemergence of fever and an increase in the number of leukocytes and in C-reactive protein (CRP) levels; and it is more commonly seen after severe disease, following serogroup C infections, and in adolescents and adults.[5] The most common manifestation, an aseptic monoarticular arthritis in 7% to 14% of patients, tends to affect the knees, ankles, or elbows, although polyarthritis may also occur.[291] Cutaneous vasculitis in 2% to 8% has a diverse presentation varying from a maculopapular rash, which may be mistaken as a drug-induced rash, to vesicular-bullous lesions, ulcers, and nodules.[291,292] Pleuritis and pericarditis may be associated with an effusion, which rarely requires drainage.[291,292] Treatment is with aspirin or nonsteroidal antiinflammatory drugs, and resolution is complete, usually within 14 days from the onset and usually without residual sequelae.[5] A case report noted excellent response with intravenous immunoglobulin to an immune complex reaction after meningococcal sepsis.[293]

Long-term sequelae and morbidity after meningococcal disease are significant. Neurologic impairment occurs in 7% to 10% of patients with meningococcal meningitis.[294] Palsies of cranial nerves VI, VII, and VIII and hemiparesis and quadriparesis occur. Unilateral or bilateral sensorineural hearing loss occurs in 2% to 9% of patients,[292,294,295] which is profound in 2% of affected persons[8] and necessitates cochlear implantation in 0.4%.[295] A formal audiologic assessment should be performed as soon as possible after discharge. Neurodevelopmental impairment, including behavioral and psychological problems, learning difficulties, memory deficits, executive function problems, decreased academic performance, spasticity, seizures, and focal neurologic signs, is also seen in approximately 10% of patients.[292–294,296–300] Visual difficulties, seizures, and motor deficits are reported in 2% to 3%, with multiple neurologic disabilities occurring in 1% to 2% of affected individuals; reported incidence of the latter is twice as high in Africans and Southeast Asians.[294,301] Survivors of meningococcal sepsis and meningitis in childhood have, in 5% to 37% as young adults, long-term behavioral and emotional problems, problems with intellectual functioning, and illness-related physical or social consequences.[302,303]

Headache and lower limb pain are also frequent chronic symptoms observed in children after meningococcal septicemia, although data on the incidence of chronic pain are limited. Scarring of the skin, secondary to necrotic purpura, may vary from unnoticeable to requiring skin grafting.[304] Multiple areas may be involved, with the lower limbs being most frequently affected, followed by the arms, chest, and face.[305] Amputations of the digits or limbs are frequently multiple, result from necrosis of the skin,[306] muscle, and bone of the affected parts (see Fig. 211.5), and, depending on the site and extent, prostheses may be required in order to improve function or appearance.[307] Bone growth disturbances, stump overgrowth, scar contractures, and soft tissue and bone infections may complicate amputations.[308] Limb-length discrepancies, which may result from the growth plate infarction, often necessitate further surgical

intervention.[305] After acute renal failure at presentation, renal function recovers in the majority of individuals; however, evidence of renal dysfunction may persist for more than 4 years in both children[309] and adults,[310] with the risk being higher in those who required renal replacement therapy.

Family and Community Impact

Meningococcal disease and its complications, often occurring rapidly in otherwise healthy individuals, have significant individual, family, community, health care, and public health impact.[311–320] The physical and emotional toll on individuals who survive[312] and of the families of those with meningococcal disease in intensive care units, of those who survive with complications, and of those who die is considerable and a global phenomenon.[311–315] In communities, meningococcal disease may also create considerable fear and anxiety.[316] Posttraumatic stress disorder (PTSD) occurs at a higher frequency in both patients and families, often months after the illness.[314–316] In one study, PTSD was present in 15% of children, in half of the mothers, and in 19% of fathers[314] at 3 months. Meningococcal disease and its complications also result in substantial hospital and long-term health care costs.[318,319] Furthermore, delay in the diagnosis of meningococcal sepsis and meningitis and septicemia is a common reason for successful litigation.[320,321]

DIAGNOSIS

Confirming the cause as *N. meningitidis* is important in order to initiate prevention of secondary cases, anticipate complications, and have cultures or DNA for antibiotic susceptibility testing and epidemiology. Meningococci with increasing resistance to the penicillins, and rarely resistance to chloramphenicol or quinolones, have been reported (see "Treatment").

The definitive diagnosis of invasive meningococcal disease is based on bacteriologic isolation of *N. meningitidis* antigen or DNA identification of *N. meningitidis* in a usually sterile body fluid such as blood, CSF, synovial fluid, pleural fluid, urine, or pericardial fluid; or detection of *N. meningitidis* in formalin-fixed tissue by immunohistochemistry.[1,3,322–324] Blood and CSF are the most fruitful sources of positive cultures and for DNA identification via the PCR assay, but urine and skin lesions can also yield results in systemic meningococcal disease. The diagnosis of meningococcal meningitis is confirmed through CSF pleocytosis and Gram stain showing gram-negative diplococci (often inside neutrophils) and/or CSF culture, latex agglutination (LA) tests detecting meningococcal capsular polysaccharide in CSF, or PCR assay identifying *N. meningitidis* in CSF. In patients considered to have meningococcemia without clinical evidence of meningitis, CSF cultures are also often positive.[325]

In an analysis of 727 cases of meningococcal disease, Hoyne and Brown described the results of 400 blood cultures, of which 51.4% were positive for meningococci.[326] CSF examination of 423 patients from the same series found 94% positive for gram-negative diplococci by either CSF Gram stain or culture for the meningococci from CSF. Carpenter and Petersdorf indicated that 46% of their cases of meningococcal meningitis were positive by CSF culture.[327] In an additional 12% of the cases, the diagnosis was aided by Gram stain of CSF. Levin and Painter studied 28 patients with culture-proven meningococcal disease; and in 22 of 27 patients tested, the CSF was positive, whereas 15 of 28 had positive blood cultures.[325] In 8 of 12 patients considered to have meningococcemia without clinical evidence of meningitis, the CSF cultures were positive. Feldman has quantitated the bacterial counts of meningococcal meningitis in CSF and reported a mean of 1.27×10^5 (1.5×10^2 to 6×10^7) organisms per milliliter.[328] In cases of meningococcal and pneumococcal meningitis in adults, the Gram stain of CSF has a sensitivity of 40% to 80% and a specificity of over 95%.

Carpenter and Petersdorf[327] examined the CSF of 58 patients with meningococcal meningitis. The median leukocyte count was about 1200, with a range of less than 10 to 65,000/mm.[3] About 75% had CSF glucose levels below 40 mg/dL. CSF protein levels ranged from 25 to more than 800 mg/dL, with a median value of about 150 mg/dL. Although studies have shown higher CSF pleocytosis and protein levels and a lower glucose concentration in the CSF of patients with bacterial meningitis compared with those with nonbacterial, aseptic, or viral meningitis,[329] no clinically reliable threshold can discriminate between bacterial and other forms of meningitis.[330] Early in the course of meningococcal meningitis, CSF findings may be minimal although cultures are positive. Appropriate antibiotics should be given if there is clinical suspicion of the infection and if the cell count is abnormal (>20 cells/μL in neonates and >5 cells/μL in older children).[330]

The ability to see or to culture meningococci in petechial skin and mucosal lesions varies. Hoyne and Brown[326] reported identification in 69.8% of the petechial smears examined. In a prospective study of the use of Gram stain and culture from biopsy specimens from skin lesions in patients with suspected meningococcal infection and controls,[331,332] the sensitivities of culture of the aspiration and skin specimens were 44% and 36%, respectively, and with the combination of Gram stain and culture the sensitivities were 62% and 56%, respectively. Patients with meningococcal disease at presentation can have peripheral leukocytosis and high CRP levels.[329,330,333] However, there is no useful white blood cell threshold; and although in one study[330] a CRP level greater than 6 was 100% sensitive in detecting children with meningococcal disease, it had very poor specificity.

LA tests for meningococcal capsular polysaccharides have been used for detection of *N. meningitidis* in CSF, serum, and also urine samples, especially in patients who received prior antibiotics. LA is less sensitive than a PCR assay, especially for serogroup B. LA assays can cross-react with K1 *E. coli* capsular polysaccharide, but LA can be used in laboratories or epidemiologic settings (e.g., sub-Saharan Africa)[334,335] where a PCR assay is not readily available.

PCR assays are rapid, sensitive, and specific and are increasingly used as the major test for the diagnosis of meningococcal disease. The assay can also determine serogroup and MLST and has the potential for detecting antibiotic resistance determinants.[44,323,324] PCR techniques include real-time PCR testing of CSF, blood, and other sterile specimens, and multiplex assays for other meningitis pathogens. Urine is a less sensitive fluid for PCR assay. An increasing number of patients are now diagnosed by means of PCR testing without culture.[336] The sensitivity and specificity of the PCR assay for the diagnosis of meningococcal meningitis are greater than 90% to 95%; in contrast, the sensitivity of CSF or blood culture is less than 65%.

The PCR assay is particularly useful in diagnosis in situations in which culture has little value because of prior antibiotic administration.[336] Sensitivity is not affected by prior antibiotic administration, which can sterilize the CSF within 4 hours. Multiplex PCR assays permit simultaneous testing for meningococci, pneumococci, and *H. influenzae* type b in establishing the diagnosis of disease.[32,337] PCR assay also has the capability of rapidly genetically typing strains, which is a useful adjunct in situations that appear to be an evolving epidemic.[44] Although the PCR assay has not replaced traditional culture methods, it is more sensitive than culture or antigen detection and is established as a very important tool in the rapid diagnosis of invasive meningococcal infections. However, a negative PCR test result does not rule out meningococcal disease.

TREATMENT

Before passive immune or antibiotic treatment was available, the mortality of invasive meningococcal disease was 70% to 90%.[17] Although the introduction of antibiotics dramatically improved the prognosis of meningococcal disease, current mortality remains 10% to 15% in developed countries (this has not changed significantly in the last 50 years[338]), and is higher in the developing world.[1,4,8,297,339] The value of early diagnosis in lowering the mortality rate is exemplified by the historical results at Fort Dix, New Jersey,[340] where an intense surveillance program was established between 1968 and 1969 and the mortality was less than 5%. An analysis of 7924 cases of meningococcal disease in the United States from 2006 to 2015[4] found that the overall mortality was 14.9%; case-fatality ratios were highest among adults 65 years or older (22%) and decreased with lower age (8.6% in infants younger than 1 year). Isolated bacteremia and meningococcal pneumonia have higher case-fatality ratios (13.2% and 15.9%, respectively) than meningococcal meningitis (9.0%).[4] The case-fatality ratio is highest among cases caused by serogroup W (20.9%) and serogroup C (20.2%) and lower among cases caused by serogroup B strains (11.5%) and serogroup Y (13.7%).[4]

Early recognition by parents and health care professionals of the importance of fever and headache with a rash, prehospital antibiotic treatment, rapid transportation to a local hospital, early effective antibiotics, and stabilization in an intensive care unit can reduce the case-fatality rate. In addition to the early use of antibiotics, the application of supportive care to treat the problems of DIC, shock, heart failure, prolonged mental obtundation, pericarditis, and pneumonia, which complicate this infection, can affect individual cases. For patients in intensive care, recognition of the different pathophysiologic processes associated with meningococcal meningitis (which causes death predominantly by cerebral edema) and meningococcal septic shock (which causes death predominantly through hypovolemia, capillary leak, myocardial dysfunction, and multiorgan failure) results in distinct treatment and management strategies for these two different forms of the disease. Management of shock using volume expansion, intensive care unit monitoring, inotropic support, management of raised intracranial pressure, and the correction of hemostatic metabolic abnormalities can reduce rates of mortality in fulminant meningococcemia.[1]

Antibiotic Therapy

Invasive meningococcal disease is a medical emergency, and early antibiotic treatment should be the primary goal,[341] because effective antibiotics immediately stop the proliferation of *N. meningitidis*.[228,342] Meningococci in CSF are killed within 3 to 4 hours after intravenous treatment with an adequate dose,[343] and concentrations of endotoxin in plasma fall by 50% within 2 hours.[228,342] The concentrations of key cytokines and chemokines fall in parallel.[344,345] Antibiotic treatment does not induce a large release of meningococcal endotoxin or lead to an increased inflammatory response (Herxheimer reaction).[228,346–348] Traditionally, patients have been treated for 7 to 14 days,[349] depending on the clinical syndrome and response of the patient, but 3 or 4 days of intravenous treatment has been shown to cure patients with meningococcal meningitis without relapse.[350–352] However, the duration of antibiotic therapy will vary with the manifestation of the disease and with the response of the patient.

The recommendations for antibiotic treatment of meningococcal meningitis and meningococcemia are summarized in Table 211.1. A goal of antibiotic therapy for meningitis is to establish concentrations of antibiotics in the CSF that approximate 10 times the minimal inhibitory concentration (MIC) of the organism for that agent.[353] Patients with suspected bacterial meningitis of unknown etiology are usually given ceftriaxone or cefotaxime initially, often combined with vancomycin (and sometimes ampicillin in adults older than 50 years) until the causative agent has been identified.[354–356] When *N. meningitidis* is identified, antibiotic treatment should be continued with a third-generation cephalosporin (e.g., ceftriaxone or cefotaxime). Meropenem is also highly active clinically and bacteriologically in the treatment of meningococcal meningitis. If patients are allergic to penicillin and cephalosporin, moxifloxacin and chloramphenicol are potential choices. Fluoroquinolones such as moxifloxacin (used in suspected pneumococcal-resistant meningitis) have excellent in vitro activity against *N. meningitidis,* but clinical data are limited and fluoroquinolone resistance (mutations in *gyr*A) of meningococcal isolates (e.g., CC ST-4821 in China, Japan, and Canada), although rare, has emerged.[356–359]

TABLE 211.1 Antibiotic Treatment of Meningococcal Meningitis and Meningococcemia in Adults With Normal Renal Function

Ceftriaxone, 2 g IV every 12 hours
or
Cefotaxime, 2 g IV every 4–6 hours
or
Meropenem, 2 g IV every 8 hours, 6 g/day
or
If patient has severe allergy to β-lactams (e.g., anaphylaxis), moxifloxacin 400 mg IV once daily; or chloramphenicol, 25 mg/kg IV every 6 hours up to 1 g every 6 hours

Originally modified from Shin SH, Kwang Kim SK. Treatment of bacterial meningitis: an update. Exp Opin Pharmacother. *2012;13:2189–2206.*

The era of chemotherapy for meningococcal infection began with a report of Schwentker and associates in 1937 that demonstrated that sulfonamides could be successfully used in the treatment of meningococcal meningitis and meningococcemia,[360] resulting in a dramatic change in the prognosis. However, studies by Schoenback and Phair[361] and by Love and Finland[362] revealed small populations of sulfonamide-resistant meningococci; and in 1963, an epidemic of group B meningococcal infection occurred at Ford Ord, California, in which the infecting strain was resistant to sulfonamides.[363,364] The majority of *N. meningitidis* isolates are now resistant to sulfadiazine.[365] Thus, sulfonamides now are no longer used in the treatment of meningococcal infections.

Early studies of penicillin given in relatively low doses (120,000 units/day IM) indicated that it was not as effective as sulfonamides.[366] Using larger amounts of the drug, Kinsman and D'Alonzo demonstrated that treatment results with penicillin were identical to those with sulfonamides.[367] Historically, high-dose penicillin therapy, using an intravenous dose of 300,000 units/kg/day with an upper limit of 24 million units/day administered as 2 million units every 2 hours, was effective for meningococcal infections. Although the majority of *N. meningitidis* isolates have remained susceptible to penicillin, 3% to 26% of isolates (approximately 10% in the United States) now have MICs in the intermediate susceptibility range (0.12–1 μg/mL), and sensitivity of meningococci to penicillin has been decreasing worldwide.[368–376] Relative resistance to penicillin is due to a reduced affinity of penicillin-binding proteins 2 and *penA* gene polymorphisms. CSF levels of penicillin averaged 0.8 μg/mL on the first day of therapy. This concentration approximates the MIC for penicillin G for the most intermediate-resistance isolates. Intermediate-resistance strains are also relatively resistant to cefuroxime, but cefotaxime, ceftriaxone, and meropenem generally remain very active against these strains in vitro. The MICs of cefotaxime, ceftriaxone, and meropenem are generally not affected by the presence of most *penA* polymorphisms (see later). Penicillin-insensitive *N. meningitidis* strains, with MICs greater than 1.0 μg/mL, have been reported from Great Britain, Spain, and, less commonly, the United States and other countries.[372] High-level resistance due to β-lactamase–producing strains of *N. meningitidis* was reported in the 1980s[377] but has not been subsequently confirmed.

An important issue is that antimicrobial susceptibility testing is not routinely performed in many practice settings, and rapid assays used for other organisms (e.g., Etests, disk diffusion, and automated systems) are not standardized or approved for *N. meningitidis*.[378] Also, broth microdilution and agar diffusion reference methods are impractical for clinical laboratories that do not regularly isolate *N. meningitidis*.[378] Cost and episodic limited availability of aqueous penicillin G have also lessened enthusiasm for this agent as the first-line drug in therapy for meningococcal disease.

The therapeutic efficacy of first-generation cephalosporins was studied in the 1960s and produced variable results[379]; and first generation cephalosporin use is contraindicated in treating meningococcal infections. In contrast, third-generation cephalosporins (e.g., ceftriaxone, cefotaxime) have demonstrated excellent in vitro and in vivo effectiveness against the meningococcus and achieve excellent central nervous system concentrations to treat meningococcal infections.[380,381] With the recommended doses of third-generation cephalosporins, CSF concentrations of these antibiotics obtained at a second lumbar puncture are 45-fold to 8750-fold higher than are the MICs (up to .012 μg/mL) for most isolated meningococci.[382] The ability to administer ceftriaxone twice daily makes this drug particularly attractive as the most cost-effective regimen, and ceftriaxone is the first-line recommendation in infants older than 3 months, children, and adults (see Table 211.1).[383–385] In younger infants, cefotaxime is preferred.

Of concern is a recent report from France indicating that 2% of invasive meningococcal isolates from 2012 to 2015 demonstrated reduced susceptibility (0.125 μg/mL, a 10-fold increase in MICs) to third-generation cephalosporins.[386] These isolates harbored a novel *penA327* allele also detected in meningococcal isolates from urethritis and in gonococci. However, the MICs of these isolates remained below the breakpoint (0.250 μg/mL) for resistance, and third-generation cephalosporins remain effective.

The efficacy of chloramphenicol as a therapeutic agent was demonstrated by McCrumb and coworkers.[387] Chloramphenicol is bactericidal for *N. meningitidis* and penetrates the blood-brain barrier effectively. Chloramphenicol has been an effective substitute in patients with immediate reactions (e.g., anaphylaxis) or other severely penicillin-allergic patients[388] but potential toxicity has limited its use. Chloramphenicol-resistant strains have been reported but remain rare in the United States and in most countries.[1,389,390]

Prehospital antibiotic treatment is now advocated[348,391–393] as soon as the diagnosis is suspected and has led to a significantly more favorable outcome. In one study, a single death occurred in 119 patients treated for meningococcal disease with antibiotics before admission, compared with 15 deaths in 329 similar patients ($P = .04$) who were not given prehospitalization therapy. The primary goal is to reduce the case-fatality rate for patients with fulminant meningococcal septicemia with rapidly increasing concentrations of meningococci and endotoxin in the circulation.[85,394] In view of the unimpeded growth of meningococci in the vasculature of some patients with an estimated doubling time of bacteria of 30 to 45 minutes, the window of opportunity closes rapidly. In one study of 51 patients, the chance of surviving the shock was 75% with admission plasma concentrations of endotoxin in the range of 10 to 50 EU/mL, 15% for those with concentrations of 50 to 250 EU/mL, and zero for those with concentrations above 250 EU/mL; 50% of nonsurviving patients with shock die within the first 12 hours of hospital admission.[85,198,345]

If antibiotic treatment is initiated before admission, ceftriaxone or another effective antibiotic should be injected intravenously or intramuscularly in adults and intramuscularly in children. The recommended site for intramuscular injection is the quadriceps muscle. During epidemics in developing countries, a single injection of ceftriaxone injected intramuscularly is as effective as a single injection of long-acting chloramphenicol injected intramuscularly; ceftriaxone has become the preferred treatment for epidemic meningitis in developing countries.[395]

Adjunctive Therapy and Supportive Care

Common complications of meningococcemia are vascular collapse and shock, primarily caused by the effects of meningococcal LOS, a potent toxin. There is also evidence of organ-specific inflammation including the heart, leading to acute myocarditis. The levels of meningococcal LOS in blood from patients with meningococcal disease are closely associated with the clinical presentation and outcome. The cytokine and chemokine cascade induced by LOS and other meningococcal components from endothelial and mononuclear cells leads to vascular collapse and shock. TNF-α released in large quantities by LOS is a mediator of endotoxic shock.[396,397] Girardin and coworkers demonstrated that serum levels of TNF-α, IL-1, and interferon-γ correlated with the severity of meningococcemia in children.[398] Brandtzaeg and coworkers have extensively studied the host responses in meningococcemia and meningococcal meningitis in patients in Norway.[g] These investigators found that IL-6, IL-1, and the antiinflammatory cytokine IL-10 are released into the serum and coexist with TNF-α and LOS in the systemic circulation during the initial phases of meningococcal septic shock. High levels of IL-6, IL-1, and notably IL-10 are associated with a fatal outcome.[399] LOS was compartmentalized in the plasma and in tissues such as heart and lungs in patients[202] with meningococcemia, whereas patients with meningitis had high levels in CSF and low or undetectable levels in plasma. LOS also is a potent inducer of tissue factor mRNA in human monocytes.[85] Tissue factor is the main initiator of blood coagulation and is known to be essential in the development of coagulopathy in meningococcal disease. This group has also shown that extensive complement activation due at least in part to LOS occurs in fulminant cases of meningococcemia, suggesting that complement-activating products in concert with other mediators may contribute to the multiple-organ failure and death occurring in the most severe cases.[400] Based on the pathophysiology, many adjuvant therapies have been tried in efforts to affect meningococcal sepsis and meningitis,[1,341,401–414] with no or marginal success.

[g]References 85, 198, 228, 230, 234, 349, 396, 400, 541-543.

Although initial clinical studies in patients with septic shock treated with recombinant activated protein C substitution (drotrecogin alfa [Xigris]) indicated efficacy, the incidence of serious bleeding was increased.[402–405] In 2011, recombinant activated protein C was withdrawn from the market after the failure of a worldwide trial that did not demonstrate improved outcomes in sepsis.[406] Randomized clinical controlled trials using hyperimmune serum, antibodies, or recombinant bactericidal or permeability-increasing protein ($rBPI_{21}$) designed to inactivate *N. meningitidis* endotoxin have been done, without beneficial effect on survival.[407–409]

Plasmapheresis, blood exchange, extracorporeal membrane oxygenation, and intraaortic balloon counter pulsation have been used in meningococcal purpura fulminans and shock.[411–414] However, no controlled trials have been done. Plasmapheresis and blood exchange have little additive effect to the endogenous clearance of LOS and cytokines from the circulation,[1,411,412] and low concentrations of protein C and antithrombin are not corrected. Extracorporeal membrane oxygenation has been used in several centers,[413,414] with better results for children with acute pulmonary failure than for those with refractory septic shock.[414]

The management of shock and its therapy are best accomplished in an intensive care unit. Circulatory collapse, which is the primary cause of death from meningococcemia in industrialized countries, is a result of an altered endothelial barrier function leading to the capillary leak syndrome, vasodilation, and a pronounced reduction in myocardial function.[1,85,198,204–206] The rapidly rising levels of meningococci in the circulation trigger exaggerated release of cytokine (IL-6, for example, is linked to myocardial dysfunction[206]), bradykinin, and presumably nitric oxide.[1,85] At a later stage, very substantial complement activation contributes to the altered endothelial barrier function and relaxation of the smooth muscles in the vessel wall through large generation of anaphylatoxins (C3a and C5a). The capillary leak syndrome results in increased flux of albumin and water across the altered capillary wall to the extravascular space. The magnitude of this flux can be judged by the volumes of fluids needed to combat insufficient tissue perfusion and hypotension. The patient accumulates a large amount of fluid in the extravascular tissue. Plasma concentration of albumin falls and rises only temporarily after intravenous infusion of albumin. The concentration of albumin in the urine increases and equals the concentration recorded in patients with nephrotic syndrome.[83]

The primary goal in fluid management is to increase the circulating blood volume by means of aggressive fluid treatment.[1,5,198] Both colloids and crystalloids (saline 0.9%) are used,[1] without a demonstrated difference in effectiveness. The volume infused seems to be more important than the type of fluid. Patients with persistent shock need large volumes of fluid. The total fluid volume needed per 24 hours is decided by the response to the treatment (e.g., tissue perfusion, blood pressure, urine output, and evidence of intravascular volume overload). Detailed treatment recommendations for the administration of fluids in fulminant meningococcemia have been reported.[198,349,384,415–419] The volume treatment is usually combined with vasopressor therapy, including dopamine, norepinephrine, epinephrine, or dobutamine.[420,421] Fluid treatment in patients with shock may be complicated by reduced renal function. Patients may need dialysis or hemofiltration to compensate for the failing kidney and to reduce the substantial edema that accumulates. Hyperglycemia is also seen in patients admitted with meningococcal sepsis and septic shock but usually resolves without insulin.[422] Myocarditis will resolve if effective antibiotic therapy is administered early enough.

Patients with meningitis or mild meningococcemia should be given the normal daily requirement of fluid intravenously supplemented with the volume lost before admission unless there was evidence of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Excessive volume treatment in patients with meningitis can contribute to fatal brain edema and herniation, but fluid restriction is not of value in meningitis unless there is evidence of raised intracranial pressure or SIADH.[384]

The use of corticosteroids in meningococcal sepsis, particularly in patients with evidence of purpura fulminans and concomitant adrenal hemorrhage (Waterhouse-Friderichsen syndrome), remains controversial.

In the 1950s, several investigators recommended the use of corticosteroid replacement therapy. However, the studies of Belsey and colleagues were inconclusive in demonstrating a beneficial effect of the application of low-dose corticosteroid in meningococcal infections.[423] Patients with fulminant meningococcal septicemia often develop adrenal hemorrhage (see Fig. 211.5). The corticotropin concentration is higher, the cortisol concentration is lower, and the corticotropin-to-cortisol ratio is higher in patients with fatal meningococcal shock than in survivors.[1,424,425] Dexamethasone along with appropriate antibiotic therapy has a beneficial effect on meningococcal sepsis in transgenic mice expressing human transferrin.[426] Adults with septic shock and indications of inadequate adrenal function are often given low doses of corticosteroids.[1,427] A benefit has not been documented in children, although intensive care specialists use low doses of corticosteroids in children with shock caused by *N. meningitidis*.[1]

Dexamethasone has been shown to reduce morbidity (e.g., especially hearing loss) in pneumococcal and *H. influenzae* type b meningitis in industrialized countries[354,355,428,429] and Vietnam,[430] but a benefit has not been established in Africa.[431,432] The evidence for reduction in morbidity in *N. meningitidis* meningitis is also less clear. Randomized controlled clinical trials have not demonstrated that dexamethasone significantly reduces death or sequelae from meningococcal meningitis. However, the numbers of patients in these studies were limited. In one study done from 1998 to 2011 from The Netherlands of adults with meningococcal meningitis, unfavorable outcome was similar in those who received or did not receive dexamethasone.[223] The rate of hearing loss was 3 of 96 (3%) and of death was 4 of 100 (4%) in those who received dexamethasone versus 30 of 258 (12%) and 19 of 256 (7%) in those who did not ($P = .67$ and $P = .24$, respectively).[223] There was no evidence of harm, and the rate of arthritis was significantly decreased in the group receiving dexamethasone.[433] Many now recommend that dexamethasone (10 mg every 6 hours for the first 4 days, and in children at a dose of 0.15 mg/kg every 6 hours for 4 days beginning before or with the first dose of antibiotics) be given early in suspected or confirmed bacterial meningitis.[223,384,433–438] Glycerol has been used to reduce intracranial pressure in bacterial meningitis,[439–441] but its value is not proven.

As pointed out earlier, the problem of DIC is ominous. Petechiae are frequent accompaniments of meningococcal sepsis. The development of increasing petechial lesions, confluent ecchymoses, persistently bleeding venipuncture sites, and bleeding gums despite adequate antimicrobial therapy and supportive care is indicative of DIC. Heparin treatment of this complication of meningococcal disease[1,442] is probably not indicated because as many patients can be harmed by the inappropriate treatment of DIC, as by DIC itself. To complicate matters, in severe DIC the problem of plasmin activation with fibrinolysis becomes a clinical reality. It appears that impairment of the protein C anticoagulation pathway is critical to the thrombosis associated with sepsis and to the development of purpura fulminans in meningococcemia. This occurs because protein C activation is impaired, a finding consistent with the downregulation of the thrombomodulin–endothelial protein C receptor pathway.[443]

Anticoagulant treatment has frequently been given to patients with invasive meningococcal disease and DIC but has not been documented to improve outcome.[198,349,444] Patients with fulminant meningococcal septicemia have retained the capacity of the endothelium to convert protein C to activated protein C,[445] and infusion of protein C concentrate restored the plasma concentration in patients with meningococcemia.[446] As noted earlier, initial reports[403,404,446] with concentrated protein C suggested a beneficial effect with bleeding risks,[405] but there were no adequate control groups, and a phase III study of recombinant activated protein C in children with severe sepsis of all causes (26% meningococcal sepsis) was stopped because no benefit was noted.[406,447] The use of recombinant human tissue plasminogen activator to ease thrombolysis is not lifesaving, increases the risk for cerebral hemorrhage, and is not recommended.[448] Other major life-threatening complications necessitating therapy include adult respiratory distress syndrome, neurologic sequelae ranging from coma to diabetes insipidus, pneumonia that is not necessarily meningococcal but may be secondary to aspiration during the obtunded state, and pericarditis.

PREVENTION

Chemoprophylaxis

Chemoprophylaxis eliminates meningococci from close contacts of confirmed or presumptive cases, protects susceptible individuals, and disrupts the further transmission of meningococci. The occurrence of meningococcal disease in individuals in the same household, especially children and individuals in other close contact settings (e.g., daycare or preschool centers, playmates, teammates, military recruits, closed environments such as college dormitories, residential schools, prisons, other institutions), or anyone else directly exposed to an infected patient's oral or nasal secretions (e.g., via kissing, close social contact, sharing of eating or drinking containers, mouth-to-mouth resuscitation) is 100-fold or greater (e.g., 500- to 800-fold in households) than in the normal population.[3,449,450] The recommended therapy for meningococcal prophylaxis is rifampin, ceftriaxone, ciprofloxacin, or azithromycin (Table 211.2), all of which have activity against meningococci in the nasopharynx, but each agent has caveats regarding use. Chemoprophylaxis with the agents recommended is 90% to 95% effective.[322]

Shortly after the clinical use of sulfonamides for the treatment of meningococcal disease in the 1940s, it became apparent that short courses of the sulfadiazine resulted in the disappearance of meningococcal carriage for prolonged periods.[451,452] With the recognition of widespread sulfonamide-resistant meningococci and the failure of sulfadiazine to have an impact on an epidemic in 1963 at Fort Ord, California,[453–455] these agents were abandoned for meningococcal chemoprophylaxis except in instances in which the meningococcal case strains were known to be sulfa sensitive. Over half of meningococcal strains remain sulfonamide resistant (owing to mutations in *folP*, which encodes dihydropteroate synthase[365,456,457]), and thus sulfonamides, once highly effective, are rarely used now for chemoprophylaxis.

The search for new agents for chemoprophylaxis has been extensive. Penicillin has proved ineffective: penicillins may suppress but do not eradicate nasopharyngeal carriage.[458] Minocycline and rifampin were found to eradicate the carrier state rapidly, and this eradication persists for up to 6 to 10 weeks after treatment[459]; however, the use of minocycline is not recommended because of vertigo, and the effect on the vestibular system. Rifampin treatment can result in the rapid emergence of rifampin-resistant meningococci in 10% to 27% of patients treated.[460] In addition, rifampin causes red urine and other secretions, which can stain contact lenses and be quite disconcerting unless the patient is forewarned. Rifampin should be avoided in pregnant women and may reduce the efficacy of oral contraceptives. Studies by Pugsley and coworkers[461] demonstrated that ciprofloxacin, 500 mg every 12 hours for 5 days, eradicated the meningococcus from the nasopharynx in 100% of individuals for up to 13 days after the completion of therapy. Gilja and coworkers[462] used a single dose of 400 mg of ofloxacin in a controlled study and showed that it can eradicate nasopharyngeal carriage for up to 33 days in 97% of subjects. A single dose of ceftriaxone (250 mg IM for adults and 125 mg IM for children <15 years) has also been shown to eradicate nasopharyngeal carriage for 14 days.[463] Furthermore, a single 500-mg dose of azithromycin has been found to be as effective as rifampin in eradicating meningococci from the nasopharynx of asymptomatic carriers.[464]

A number of other agents active against meningococci in vitro have been tested but have failed to provide prophylaxis. These agents include erythromycin, trimethoprim, cephalexin, oxytetracycline, and nalidixic acid. Hoeprich[465] studied a number of these drugs and found that the primary factor determining effectiveness as a meningococcal prophylactic agent is the ability to achieve bactericidal levels in tears and saliva.

The question of who should receive prophylaxis has concerned public health officials since the advent of effective chemoprophylaxis. Initially sulfonamides were used, little discrimination between high-risk and low-risk populations was attempted, and the drugs were administered very widely to people without an increased risk for disease. With the clinical emergence of sulfa resistance and the problem of finding agents that are safe and effective, attention focused on the populations at greatest risk. The definition of "close contact" includes persons who have had prolonged contact while in close proximity (3 feet is the general limit for large-droplet spread) to the patient or who have been directly exposed to the patient's oral or nasal secretions.[322] As noted earlier, during

TABLE 211.2 Antibiotic Chemoprophylaxis for Household or Intimate Contacts

ANTIBIOTIC	DOSAGE	COMMENT
Rifampin	Adults: 600 mg q12h orally for 2 days Children <1 mo: 5 mg/kg q12h orally for 2 days Children >1 mo: 10 mg/kg q12h (maximum, 600 mg) orally for 2 days	Rifampin can interfere with efficacy of oral contraceptives and some seizure prevention and anticoagulant medications; may stain soft contact lenses. Not recommended for pregnant women.
Ceftriaxone	Children <15 yr: 125 mg, single IM dose Children >15 yr and adults: 250 mg, single IM dose	Ceftriaxone is recommended for prophylaxis in pregnant women.
Ciprofloxacin	Adults: 500 mg, single oral dose	Not recommended routinely for persons <18 yr, but use in infants and children (20 mg/kg) may be justified after careful assessment of the risks and benefits. Not recommended for pregnant or lactating women. Cases of ciprofloxacin resistance have been reported,[538] but it remains rare.
Azithromycin	10 mg/kg (maximum, 500 mg) single oral dose	Equivalent to rifampin for eradication of meningococci from nasopharynx, but data are limited.

[a]Recommended groups for chemoprophylaxis,[322,469,470] based on exposure to the index patient in the week before onset of illness:

- Household contacts and persons sharing the same living quarters, particularly young children; the attack rate for household contacts exposed to patients who have meningococcal disease is estimated to be four cases per 1000 persons exposed, which is 500–800 times greater than the rate for the total population.
- Daycare center, nursery school or child care contacts, frequent playmates of young children.
- Close social contacts who were exposed to oral secretions in week before onset, such as by kissing or sharing eating or drinking utensils or toothbrushes.
- For airline travel lasting more than 8 hours, passengers who are seated near an infected person should receive prophylaxis.
- Prophylaxis is recommended for health care professionals who have had intimate exposure (e.g., management of airway or contact with respiratory secretions) to an infected person. Vaccination is recommended for microbiologists who may handle *Neisseria meningitidis* isolates.
- Because the risk for secondary cases is highest during the first few days after exposure, chemoprophylaxis should be initiated as soon as possible, ideally <24 hours after identification of the index patient.
- If more than 14 days have passed since the last contact with the index patient, chemoprophylaxis is not likely to be of benefit.
- Pharyngeal cultures are not helpful in determining the need for chemoprophylaxis and may unnecessarily delay the use of effective chemoprophylaxis.
- Chemoprophylaxis has also been recommended for patients given penicillin or chloramphenicol for treatment, because pharyngeal carriage may not be eliminated with these antibiotics and the patient could remain colonized with a virulent strain.
- Ceftriaxone is recommended for pregnant women.
- May want to avoid ciprofloxacin or azithromycin in individuals at risk of QT prolongation.

epidemics and in endemic situations in civilian populations, household contacts have been shown to be at increased risk for infection. Analysis by the meningococcal surveillance group of the Centers for Disease Control and Prevention (CDC) showed that the attack rate in this group was 500 to 800 times greater than that determined for the general population studied.[466] Similar high-risk situations exist in closed populations such as in some college dormitories, long-term care hospitals, nursery schools, and military barracks.[467,468] Recently, close contact of individuals during air travel was identified as a risk factor. In the community, chemoprophylaxis is recommended for household contacts, daycare center members, and anyone exposed to oral secretions but not usually school, transportation, or office contacts unless they meet the criteria for close contact.[322,469,470]

Secondary cases usually occur within 1 to 14 days of the primary case. Close surveillance of this group for at least 14 days would ensure prompt treatment of secondary cases that might arise in the absence of effective chemoprophylaxis. Beginning chemoprophylaxis more than 2 weeks after exposure to the index case is likely too late to prevent secondary cases. Most hospital personnel are not at increased risk and in general should not receive chemoprophylaxis; however, medical staff who have intimate exposures such as mouth-to-mouth resuscitation or endotracheal intubation should receive prophylaxis.[449,469–471] Nosocomial transmission of meningococcal disease between patients has been reported.[472,473] For hospitalized patients, in addition to standard precautions, droplet precautions are recommended until 24 hours after initiation of effective antimicrobial therapy. Laboratory personnel handling cultures also should be vaccinated.[471] The index patient should also be treated before leaving the hospital if penicillin, ampicillin, or chloramphenicol was used because these antibiotics do not reliably eradicate the carrier state.

Immunoprophylaxis

Immune Correlates of Protection and Meningococcal Polysaccharide Vaccines

Simon Flexner, in 1907, demonstrated that a passive immune-based approach using meningococcal antiserum raised in horses and given intrathecally reduced the death rate (>75%) of meningococcal meningitis by one-half.[17] The first meningococcal vaccine candidates based on heat-killed bacterial cultures were developed in 1912 but were ineffective and highly reactogenic. George D. Heist first demonstrated differences in bactericidal activity of human blood against the meningococcus.[474] Unfortunately, Dr. Heist's own sera was a negative control and he died at age 36 (1920) of meningococcal meningitis. In 1935, Henry Scherp and Geoffrey Rake first identified meningococcal capsular material of serogroup A meningococci as a polysaccharide.[475] The introduction of effective therapy and chemoprophylaxis in the 1940s with sulfonamides, penicillin, and other antibiotics put meningococcal vaccine approaches on a slower trajectory. However, with outbreaks of meningococcal disease in military recruits and the appearance of sulfonamide resistance in the meningococcus, renewed interest in meningococcal vaccines began in earnest in the 1960s.

The importance of human SBA as the correlate of protection against meningococcal disease was further defined by Goldschneider, Gotschlich, and Artenstein of Walter Reed Army Institute of Research in a 1969 study of military recruits.[110] Depending on the assay, SBA titers greater than or equal to 4, or greater than or equal to 8, indicate protection against meningococcal disease when human or baby rabbit complement sources, respectively, are used. A greater than or equal to fourfold rise in the SBA titer also indicates protection. Strain selection, complement source, and assay standardization are critical for the interpretation of the SBA. As the validated correlate of protection in efficacy trials of MPS vaccines, SBA has become an accepted basis of new meningococcal vaccine (conjugate, MenB) licensure without efficacy trials.

Work at the Walter Reed Army Institute of Research in the 1960s identified high-molecular-weight meningococcal capsular polysaccharide of serogroups A and C as vaccine antigens inducing protective SBA responses. Artenstein and coworkers[476] then demonstrated the effectiveness of a capsular polysaccharide group C vaccine in studies of US Army recruits; and Makela and associates[477] showed that administration of group A polysaccharide to Finnish military recruits significantly lowered the incidence of meningococcal disease caused by that serogroup when compared with an unvaccinated control population. The work led to the introduction of MPS vaccines for serogroups A, C, and later Y and W in the 1970s and 1980s in military and civilian populations and for control of disease outbreaks.[478] The MPS vaccines were safe (reactions usually limited to local erythema of the vaccine recipients). Millions of doses have been used worldwide; MPS vaccines have excellent efficacy (>85%) in older children and adults. But these vaccines are poorly immunogenic (C>A) in children younger than 18 to 24 months; induce protective SBA titers of limited duration (around 3–5 years of protection); create at best a transient herd protection effect; do not generate immunologic memory responses or antibody affinity maturation; and demonstrate immunologic hyporesponsiveness to repeat vaccinations of the polysaccharides.

Meningococcal Conjugate Vaccines

The successful introduction of capsular polysaccharide-protein conjugate vaccines for *H. influenzae* type b in 1990, led by efforts of David Smith, Porter Anderson, John Robbins, and Rachel Schneerson,[479] fueled the development of the MCVs in the 1990s. Covalent linkage of a saccharide to immunogenic carrier protein to create a glycoconjugate had been first investigated in 1929 by Avery and Goebel.[480] In contrast to a T-cell–independent antigen of the saccharide alone, conjugation leads to a T-cell–dependent antigen recruitment of T-cell help by the carrier protein. The two MCVs licensed in the United States use diphtheria proteins. Menveo uses CRM197, a nontoxic variant of diphtheria toxin, and Menactra uses diphtheria toxoid.

MCVs[35,183] are safe, have excellent immunogenicity, induce immune memory responses and amnestic antibody levels with repeated doses in contrast to the hyporesponsiveness seen with MPS vaccines, have equal efficacy to the polysaccharides, and provide prevention in expanded human populations (infants, young children). They have now largely replaced MPS vaccines in the vaccine prevention of meningococcal disease. Unlike the MPS vaccines, MCVs have long-term effects in reducing transmission, resulting in significant herd protection at modest levels of vaccine coverage (due to a low R_0 of *N. meningitidis*; see "Herd Protection and Vaccine Strategies").[481] Special populations, such as solid-organ transplant recipients, still represent a vulnerable population with poor responses to both polysaccharide nonconjugate and conjugate vaccines.[482]

In response to a significant burden of serogroup C meningococcal disease, the first MCVs used were serogroup C conjugates and were introduced in the United Kingdom in 1999 to 2000 as a broad catch-up campaign for those younger than 19 years of age; the highest meningococcal carriage rates are in adolescents. These vaccines were then incorporated in the routine vaccination program for infants and young children.[483,484] Serogroup C disease decreased dramatically in the first 2 years after vaccine introduction and virtually disappeared by 2005.[138] A major contributor (approximately 50% of effectiveness) to this rapid decline was herd protection created by the generation of mucosal immunity by these vaccines and the interference with transmission of serogroup C expressing meningococci.[485–487] Vaccine effectiveness for reducing nasopharyngeal carriage of serogroup C in adolescents was more than 75% (serogroup C specific carriage declined from 0.42% to 0.09%),[487] and reduction in serogroup C meningococcal disease due to herd protection has persisted now for almost 2 decades. No significant change in serogroup B disease (serogroup replacement) was observed. The introduction of serogroup C conjugate vaccines in other countries in Europe has been the driving force behind the reductions in serogroup C disease across the continent.[184]

This success led to the rapid development of MCVs by major vaccine manufacturers, a public-private partnership (Meningitis Vaccine Program for the African meningitis belt), and multiple formulations and conjugation approaches for C, A, A/Y, X, and A/C/Y/W, sometimes in combination with other antigens (e.g., *H. influenzae* type b conjugate). A tetravalent conjugate vaccine (MCV4, Menactra; A, C, Y, W) was first approved for use in the United States in 2005 in adolescents, and now two MCV4s are available (Table 211.3).[488,489] Recent data suggest an impact of the US MVC4 program in reducing incidence of A, C, Y, and W disease in this age group.[490]

An important example of a cost-effective approach to conjugate and other vaccine development was the Meningitis Vaccine Program, a partnership among PATH, the World Health Organization, and the GAVI Alliance, for the development of a group A MCV for Africa,[160,491] designated MenAfriVac. At less than 50 cents a dose, MenAfriVac is produced at the Serum Institute of India, Ltd. Because of the huge impact of herd protection of the serogroup C conjugate vaccine introduction in the United Kingdom, MenAfriVac was introduced as a mass vaccination strategy for those aged 1 to 29 years. The MenAfriVac vaccination campaign began in Burkina Faso in December 2010[160,492] and was extended to Mali, Chad, Niger, Nigeria, Benin, Ghana, Senegal, Cameroon, Sudan, and other regions of the African meningitis belt. Over 280 million doses in 26 African countries have been administered. Vaccine effectiveness through the elimination of serogroup A carriage has been demonstrated through the African Meningococcal Carriage Consortium (MenAfriCar) and other surveillance efforts (MenAfriNet).[159,493,494] Results show the virtual elimination of serogroup A meningococcal disease in the countries in which vaccination was performed in the first 7 years after the mass campaigns began.

TABLE 211.3 Vaccines for *Neisseria meningitidis*: United States, 2018

Menveo (GlaxoSmithKline)	Meningococcal (groups A, C, Y, and W) Oligosaccharide Diphtheria CRM197 Conjugate
Menactra (Sanofi Pasteur)	Meningococcal (groups A, C, Y, and W) Polysaccharide Diphtheria Toxoid Conjugate Vaccine
Bexsero (GlaxoSmithKline)	Meningococcal group B directed Recombinant Protein Vaccine
Trumenba (Pfizer)	Meningococcal group B directed Recombinant Protein Vaccine

Serogroup B Vaccines

The successful development and use of the effective polysaccharide-protein glycoconjugate vaccines for serogroups A, C, Y, and W focused attention on serogroup B *N. meningitidis* (expressing an [α2→8]-linked polysialic acid capsule), a leading cause of meningococcal disease, especially in infants, young children, and adolescents, in many countries. Because the serogroup B polysaccharide resembles the human NCAM and other human antigens, the molecule is poorly immunogenic and carries a theoretical risk for autoimmunity. Serogroup B vaccines based on OMV proteins (especially the PorA protein) were successful in the control of clonal outbreaks of serogroup B disease in Norway, New Zealand, Cuba, France, Brazil, and Chile.[175,495–497] However, due to meningococcal surface structure heterogeneity, difficulties in the consistency of manufacture and composition, limited duration (approximately 2 years) of protection, and lack of evidence of herd protection, these vaccines have not been candidates for routine prevention of endemic serogroup B disease. The use of meningococcal OMV vaccines in infants and young children is also limited, requiring multiple doses, and is associated with higher reactogenicity.

New serogroup B vaccines based on semiconserved surface-protein antigens identified by "reverse vaccinology" have now been introduced. The first of these, MenB-4C (Bexsero), licensed in Europe in 2013 and in the United States in 2015, contains semiconserved surface-protein antigens—(1) a member of the FHbp family, (2) NadA, and (3) NHBA—and a meningococcal serogroup B PorA-containing OMV preparation previously used to control the serogroup B clonal outbreak in New Zealand.[498,499] Alum is the adjuvant. The second serogroup B vaccine licensed in the United States in 2014 and in Europe in 2017, MenB-FHbp (Trumenba), is based on two distinct members of the FHbp family. MenB-FHbp has been used in a college outbreak in several states.[500] Initial evaluations of the immunogenicity and safety of these vaccines have been excellent.[498,501–504] Both vaccines have a higher incidence of pain at the injection site. Both have been approved for the prevention of invasive meningococcal disease in persons aged 10 through 25 years and have been used in response to control of college campus outbreaks in the United States. In the United Kingdom, MenB-4C has been introduced in infants and young children as part of the routine immunization program and has been used to control a serogroup B outbreak in Quebec.[503,504]

In the United States, the Advisory Committee on Immunization Practices (ACIP) recommends that adolescents and young adults aged 16 to 23 years (the age of greatest risk) may be vaccinated with a serogroup B vaccine.[502] Important evaluation continues regarding the use of these vaccines, such as effectiveness in different countries and regions, reactogenicity in infants and children, whether herd protection will be generated, and the length of persistence of the protective immune responses. However, the prevention of serogroup B disease is a significant step closer with these vaccines.[179] There is also evidence of cross-protection against other meningococcal serogroups that share related outer membrane protein epitopes. For example, serum from MenB-vaccinated children demonstrate SBA against the hypervirulent W CC:11 strain circulating in England (see "Epidemiology" earlier).[139,492,503–505]

Whether MenB vaccines have a herd protection effect remains controversial.[506–508] There is limited evidence to support an effect,[506] and in other studies MenB-FHbp did not rapidly reduce or prevent serogroup B carriage.[508] Persistence after the initial priming series for both MenB vaccines is also an important issue. Data in several vaccinated populations show an approximately 50% decline in hSBAs 12 to 18 months after the priming series.[509–512] A booster is amnestic, indicating immunologic memory with hSBA titers rising quickly to high levels and possibly persisting for longer, although the duration of this booster response is not known. If the risk of MenB disease persists or recurs (e.g., college outbreak) a booster is needed.

Of interest, retrospective case-control and cohort studies of the OMV MenB vaccine used in New Zealand (MeNZB) and of Bexsero used in an outbreak in Canada have suggested that these vaccines may have activity against *N. gonorrheae*.[513] Estimated vaccine effectiveness of MeNZB against gonorrhea in 15- to 30-year-olds was 31%.[513] The advances in meningococcal vaccinology now suggest the possibility of worldwide control and even the potential eradication of *N. meningitidis* as a human pathogen.[514,515] However, important issues remain to be addressed with the new meningococcal vaccines.

Duration of Protection

The older MPS vaccines in adults induced 3 to 5 years of protection. It was initially anticipated that MCVs that induce memory responses and higher antibody levels would provide protection of more than 8 years. However, data suggest that the protection provided after a single dose of MCVs may not be much longer than with the polysaccharide vaccines.[4] The ACIP recommends that persons aged 2 to 55 years who remain at increased risk for meningococcal disease 5 years after vaccination with an MCV should be revaccinated and that a booster dose should be given to adolescents (routine vaccination at age 11, with a booster at age 16).[488] The duration of protection after the new serogroup B vaccines after the initial series is also a concern, and boosters may be required.[509]

Immunologic Memory and Interference

In the absence of protective anticapsular antibody concentrations (human SBT ≥1 : 4), immunologic memory alone is insufficient for protection against *H. influenzae* type b or meningococcal disease.[488,516–518] Four to 7 days are required for an immunologic memory response to develop, and the time from exposure to disease is often less than 7 days. Immune interference and concurrent administration with other vaccines is another important consideration with conjugate vaccines.[519] For example, although immune enhancement can be seen with the coadministration of two tetanus toxoid (TT) vaccines, CRM197 and TT together induce bystander interference, and CRM197 and TT produce carrier-induced epitopic suppression.[520] One example of interference is the coadministration of MenACWY-D and PCV7, which results in lower geometric mean concentrations of immunoglobulin G (IgG) antibodies to some pneumococcal serotypes when compared with corresponding IgG geometric mean concentrations at PCV7 administered alone.[488]

Vaccine Population Coverage and Effectiveness

Given the ever-changing epidemiology of meningococcal disease, effective coverage of the population against circulating strains is an essential determinant in decisions about new meningococcal vaccines. Thus, accurate and ongoing laboratory-based surveillance and assessment of the epidemiology and of the strains causing meningococcal disease remain essential. For example, the coverage of serogroup B isolates by new serogroup B vaccines is an important consideration in decisions about the introduction and use of these vaccines.[179] The population effectiveness over individual efficacy (e.g., through herd protection) is also an increasingly important factor in meningococcal vaccine strategies.

Herd Protection and Vaccine Strategies

Protection against the bacterial meningitis pathogens through herd protection is remarkable and powerful, and was an unanticipated, effect of bacterial polysaccharide-protein conjugate vaccines.[39] Herd protection can account for approximately one-half of the MCV effectiveness at preventing meningococcal disease. Herd protection is an important strategy in planning for meningococcal vaccine introduction, implementation, and evaluation. As noted, in 1999 to 2000 the meningococcal serogroup C conjugate vaccines were introduced in the United Kingdom as a broad catch-up campaign for those younger than 19 years. This approach reduced nasopharyngeal carriage of serogroup C in adolescents by more than 75%, and created herd protection that has persisted for almost 2 decades.[483,487] The remarkable herd protection effect is related to the low R_0 (basic reproduction number, or the average number of secondary infectious cases that are produced by a single index case in a completely susceptible population), estimated at 1.3, for meningococcal disease. Thus, herd protection is achieved with 17% to 26% MCV coverage of a population.[39,521] In contrast, measles, mumps, pertussis, polio, and rubella have an R_0 greater than 5 and require much higher thresholds (i.e., >80% vaccine coverage for herd protection).[481,514] The immunologic basis of mucosal (herd) protection with conjugate vaccines, however, remains poorly defined. Generation of capsule-specific mucosal immunoglobulins, transudation of high-avidity serum IgG to mucosal surfaces, and Th17-induced immunity via macrophage clearance are proposed as mechanisms.[39] Cost-effectiveness, measured as a quality-adjusted life-year (QALY) score, is an important consideration of vaccine recommendations in public health, and herd protection significantly enhances benefit-cost analyses.[489]

Meningococcal Vaccine Recommendations

Two meningococcal quadrivalent polysaccharide-protein conjugate vaccines (MCV4s) that provide protection against meningococcal serogroups A, C, W, and Y (MenACWY-D [Menactra; Sanofi Pasteur, Swiftwater, PA] and MenACWY-CRM [Menveo, Novartis Vaccines, Cambridge, MA]) are licensed in the United States and other countries. MenACWY-CRM is licensed in the United States for infants ages 2 through 23 months. MenACWY-D is licensed as a two-dose series for infants and toddlers aged 9 through 23 months. MenACWY-D and MenACWY-CRM are licensed for persons aged 2 through 55 years as a single dose. Two serogroup B vaccines (MenB-4C [Bexsero; GlaxoSmithKline, Research Triangle Park, NC] and MenBFHbp [Trumenba; Pfizer, Philadelphia, PA]) have been licensed in the United States for persons aged 10 through 25 years, Bexsero as a two-dose series and Trumenba as a two-dose or three-dose series.[502,522]

Adolescents and Adults

The ACIP recommends routine vaccination with a quadrivalent (MenACWY, MCV4) MCV (MenACWY-D or MenACWY-CRM) for adolescents aged 11 or 12 years, with a booster dose at age 16 years as an effective strategy to reduce meningococcal disease among adolescents and young adults.[488,523] Vaccination is also recommended for adults at risk for meningococcal disease. The following adult populations are at risk for meningococcal disease: college freshmen living in dormitories who were not previously immunized; microbiologists who are routinely exposed to *N. meningitidis*; military recruits; persons who travel to or reside in countries in which *N. meningitidis* is hyperendemic or epidemic; persons who have complement component deficiencies (e.g., C3, C5-9, properdin, factor H, factor D) or those taking eculizumab (Soliris); persons who have functional or anatomic asplenia; and persons at risk because of an A, C, W, or Y outbreak. Adults who have HIV type 1 infection are at increased risk for meningococcal infection, and vaccination is now also recommended for this group. Use of an MCV4 is preferred for persons aged 11 to 55 years and may be administered to older individuals. A two-dose primary series with an MCV4 is recommended for adults with asplenia, for those with persistent complement component deficiency, and for persons with HIV infection; otherwise, an initial single dose is indicated. Booster doses of an MCV4 administered every 5 years are recommended for persons who remain at increased risk for meningococcal disease. Individuals at risk who previously received an MCV4 conjugate vaccine also should get an MCV after they reach 55 years of age.

MenACWY-D or MenACWY-CRM is administered as a single 0.5-mL intramuscular dose. Protective levels of antibodies are usually achieved

within 7 to 10 days after vaccination. In persons aged 2 through 55 years, MCV4 vaccines can be administered concomitantly with other vaccines but at a different anatomic site. Providers administering vaccinations should be aware of the potential for syncope after vaccination, especially among adolescents, and should take appropriate measures to prevent potential injuries. Two studies have provided evidence that the risk for Guillain-Barré syndrome (GBS) is not increased over the background risk in adolescents after MCVs.[488] The ACIP has recommended removing the precaution against use of MCVs for persons with a history of GBS, although it remains a listed precaution in the US Food and Drug Administration (FDA) package insert for MenACWY-D.

MenB vaccines, either as a two- or a three-dose series (Trumenba, MenB-FHbp) or as a two-dose series (Bexsero, MenB-4C), may be administered to adolescents and young adults aged 16-23[502,522,524–526] to provide short-term protection against serogroup B disease. The preferred age for MenB vaccination is 16 to 18 years of age. The two available MenB vaccines are not interchangeable. Trumenba or Bexsero may be administered concurrently with other vaccines indicated for patients of this age but at a different anatomic site, if feasible. The choice of the dosing series for MenB-FHbp is based on the patient's risk for exposure and susceptibility to serogroup B meningococcal disease.[526]

MenB vaccines are also recommended for persons 10 years of age or older who are at increased risk for serogroup B meningococcal disease.[524] This includes persons with persistent complement component deficiencies including those taking eculizumab, persons with anatomic or functional asplenia, microbiologists exposed to isolates of *N. meningitidis,* and persons identified as at increased risk because of a serogroup B meningococcal disease outbreak such as on college campuses. Adults who have HIV type 1 infection are also at increased risk for serogroup B meningococcal infection, and vaccination should also be considered for this group.

Infants and Young Children

In the United States, routine meningococcal vaccination of infants and children 2 months to 10 years of age is not currently recommended. The current low burden of disease limits the potential impact of a routine meningococcal vaccination program for infants and children. A targeted approach is recommended to protect infants and children who are at increased risk for meningococcal disease. This contrasts with the routine vaccination program for infants and children in the United Kingdom, where the incidence of meningococcal disease is higher. In the United States the approach includes MenACWY-CRM vaccination for children aged 2 months to 10 years or MenACWY-D for children aged 9 months to 10 years who are at increased risk for meningococcal disease—for example, children who have complement deficiencies (C3, C5-9, factor P or properdin, factor H, or those taking eculizumab), those with anatomic or functional asplenia including sickle cell anemia, and those with HIV infection.[524] Certain infants with congenital heart disease have asplenia, and infants with sickle cell disease may initially have functional spleens but develop functional asplenia during childhood. So as not to interfere with the immune response to the pneumococcal conjugate vaccine (PCV) series, MenACWY-D should not be used until age 2 in children with asplenia (including those with sickle cell or HIV, and not until at least 2 weeks after completion of all PCV 13 doses). MenACWY-CRM is preferred. The MCV4 vaccines are also used in children in communities with a meningococcal disease outbreak for which vaccination is recommended, and travelers to or residents of countries in which meningococcal disease is hyperendemic or epidemic. Infants at risk are recommended to receive a four-dose vaccination series with MenACWY-CRM with doses at ages 2, 4, 6, and 12 months. A two-dose primary series is recommended for children aged 7 to 23 months, with the second dose at ≥12 months of age and ≥3 months after the first dose, and a two-dose primary series also for all persons with asplenia, persistent complement component deficiency, or HIV infection of any age who are at increased risk for meningococcal disease; otherwise, an initial single dose is indicated. Booster doses of MCV4 administered every 5 years are recommended for persons who remain at increased risk for meningococcal disease except for children who received their previous dose before their sixth birthday; these children should receive a booster dose 3 years after their previous dose.

Hib-MenCY-TT (MenHibrix), previously available for children aged 2 through 18 months for prevention of *H. influenzae* type b infection and serogroups C and Y meningococcal disease, has been withdrawn from the US market. MenB vaccines are recommended in the United States for children ≥10 years of age[522] at high risk for serogroup B disease (e.g., those with complement deficiencies including those on eculizumab, asplenia, HIV infection).

Outbreak Immunoprophylaxis

Cases of invasive meningococcal disease can occur in communities or organizations (e.g., college campuses) several days, weeks, or months after onset of the disease in an index cases. Thus, meningococcal vaccination is an adjunct to expanded chemoprophylaxis when an outbreak is caused by a vaccine-preventable serogroup. Guidelines for evaluation, management, and reevaluation of outbreaks of meningococcal disease, either organizational or community based, recently revised by the CDC, are available[525] and include decision making about vaccination, chemoprophylaxis, the population at risk, and the importance of molecular typing including WGS of isolates. Both MCV4 or MenB vaccines are used in outbreak control.

Hajj and Umrah Pilgrimages

The occurrence of meningococcal outbreaks during the Hajj and Umrah pilgrimages has been related to high meningococcal transmission and carriage in pilgrims.[527] Three million participate in the annual Hajj pilgrimage. In one historic study from Mecca, meningococcal carriage rates were as high as 80%.[528] Owing to the previous serogroup A and C meningococcal outbreaks associated with the Hajj, the A and C MPS vaccine became a requirement for the attendance of the Hajj in 1986. In 2000 and 2001, two large outbreaks caused by meningococcal serogroup W[529,530] resulted in the inclusion of a quadrivalent (A, C, Y, W) vaccine, either polysaccharide within 3 years or conjugate vaccine within 5 years, as a requirement for a Hajj or Umrah visa.[527,531,532] In addition, visitors arriving from countries in the African meningitis belt except pregnant women receive chemoprophylaxis with ciprofloxacin at entry to lower the rates of meningococcal carriage.[532] It is estimated that 400,000 to 460,000 pilgrims receive the recommended doses at the port of entry in Saudi Arabia.[528] Compliance with meningococcal vaccination among arriving international pilgrims is 97% to 100%.[533] Carriage rates in pilgrims are now <5%, and 0% to 0.6% in returning pilgrims.

Eculizumab (Solaris)

Prevention of meningococcal disease in those receiving eculizumab is a special concern. Eculizumab is a humanized monoclonal antibody that binds C5 and inhibits the terminal complement pathway. Eculizumab is approved for use in complement-mediated thrombotic microangiopathies such as paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic-uremic syndrome, and its use is now extending to a variety of other conditions.[534] The risk of meningococcal disease in individuals receiving eculizumab is >300 per 100,000. Both ACWY and MenB vaccines are recommended before individuals receive eculizumab, but vaccine-induced protection is incomplete,[534–536] possibly because of eculizumab's inhibition of complement-mediated opsonic and phagocytic functions.[537] Over half of cases in those receiving eculizumab are due to nongroupable strains. Antibiotic chemoprophylaxis is recommended, but development of resistance to oral penicillin regimens has been reported.[536] Heightened awareness, early care seeking, vaccination of close contacts, and administration of ceftriaxone or other effective antibiotic agents at first signs of symptoms are recommended.

Future Meningococcal Disease Vaccine Prevention Strategies

Vaccines that provide long-term protection early in life, through adolescence, and into adulthood against the major meningococcal serogroups and CCs that cause meningococcal disease are now available and have the potential to greatly reduce the global burden of

meningococcal disease. Challenges are the costs and other barriers to worldwide implementation of the meningococcal conjugate and MenB vaccines, gaps in vaccine coverage (e.g., certain serogroup B serotypes, serogroup X), the need for periodic boosters for meningococcal vaccines, and the introduction of meningococcal vaccines in conjunction with routine vaccination regimens. In addition, the continuing evolution and adaptability of *N. meningitidis* result in a dynamic disease epidemiology, and the emergence of new CCs and serogroups that can result in vaccine escape. Of note, meningococcal vaccine work may provide potential new insights into gonococcal vaccine strategies.

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The complete reference list is available online at Expert Consult.

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