Chapter 38

DISEASES SPREAD BY CLOSE PERSONAL CONTACT

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RESPIRATORY PATHOGENS

Introduction and Military Relevance

Respiratory pathogens have plagued military populations throughout US history. Records from the War of 1812, the Spanish American War, and World War I document the devastation respiratory pathogens have caused and the inability of public health officials to control them.[1–3] Especially well documented are the epidemics that occurred during the mobilization for World War I. In 1918, a 30-day epidemic of *Streptococcus pneumoniae* infections occurred at a military camp in Illinois, causing 2,349 hospital admissions for pneumonia and a 50% mortality rate.[4] During 1918, a 2-month military epidemic of influenza in Little Rock, Arkansas, affected 12,393 men and led to 1,499 cases of pneumonia, 31% of whom died during treatment.[5] Other reports record that hemolytic streptococci (*Streptococcus pyogenes*) were a continual cause of military epidemics of bronchopneumonia, empyema, and pharyngitis. In total, it was estimated that more than 1.4 million US Army personnel suffered from respiratory disease during World War I, accounting for more than 41% of all forms of disease and causing more than 77% (45,000) of Army disease deaths.[2]

Before antimicrobials were widely available, strategies to prevent military epidemics of respiratory disease were not very successful. Generally, military public health officers could do little more than attempt to isolate and treat the afflicted with various therapies against streptococci, which included digitalis, whiskey, strychnine, and various horse sera.[6–8] Following the success of researchers in South Africa, US military officials attempted to control *S pneumoniae* epidemics at select US Army camps during World War I with a crude vaccine,[9,10] but their efforts were unsuccessful.[3,11] Commenting on the trade-off between isolating the ill and compromising the mission, one military physician of 1917 wrote that "Exposure to infection and hardships which will result in deaths from pneumonia may be just as necessary as going into action with resulting deaths from gunshot wounds."[7]

Despite the limited effective interventions available to public health officials in the preantibiotic era, they made important observations regarding the types of acute respiratory diseases and their apparent bacterial causes. Those officials noted that crowding greatly contributed to respiratory epidemics[12,13] and that more important than reduced floor space in sleeping quarters was the number of men placed in the same room.[13] Southerners, blacks, and new military personnel from rural areas were thought to be at highest risk of developing pneumonia. Measles and influenza epidemics were observed to trigger epidemics of *S pneumoniae* and *S pyogenes* infections.[14,15]

Senior military officers were determined to reduce respiratory disease during the mass mobilization of personnel for World War II. Beginning in 1941, the US Department of War established the Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army. Later, this board assembled various commissions of scientific experts and established numerous public health and research facilities to study and prevent respiratory disease.[16] These joint military and university endeavors led to many of the antibiotic and vaccine prophylaxis interventions now used in military populations (Table 38-1).

As a result of these and subsequent research efforts, today most US military personnel receive enzathine penicillin (BPG) or oral erythromycin rophylaxis, adenovirus vaccines (when available), uberculosis screening, and influenza vaccine during their first military training. This is followed by nnual influenza vaccination and periodic tuberculosis screening throughout their military careers. he pathogens recognized to cause respiratory disease among these young adults are similar to those ausing community-acquired disease among the eneral US adult population.[17–20] Most frequently, he pathogens include *S pyogenes*, *Mycoplasma neumoniae*, *S pneumoniae*, *Chlamydia pneumoniae*, denoviruses, influenza viruses, and rhinoviruses. ess frequently, military personnel also suffer infections from *Haemophilus influenzae*, *H parainfluenzae*, *egionella pneumophila*, *Moraxella catarrhalis*, *Bordetella ertussis*, coxsackieviruses, respiratory syncytial irus, and parainfluenza viruses. The most significant pathogens to military populations are reviewed here in more detail.

Streptococcus pyogenes

S pyogenes is a leading cause of bacterial respiratory morbidity among US military personnel. New military trainees are at particularly high risk of clinically significant infection. During the late 1940s and the 1950s, dedicated scientific teams, sponsored by Army Board Commissions, worked at a number of Army, Navy, Air Force, and Marine Corps training centers and made much progress in understanding and controlling this pathogen.

TABLE 38-1

IMPORTANT EVENTS IN THE DEVELOPMENT OF MILITARY STRATEGIES TO PREVENT EPIDEMICS OF ACUTE RESPIRATORY DISEASE

Event	Year	Reference
Streptococcus pneumoniae vaccine is effective in South Africa	1911	Maynard[a]
First US Army troops receive an *S pneumoniae* vaccine—not effective	1918	Cecil[b]
Influenza virus discovered	1933	Smith[c]
First influenza vaccine with protective results	1936	Chenoweth[d]
Daily oral sulfonamide therapy found to prevent recurrences of rheumatic fever among civilian populations	1939	Coborn[e]
US Navy administers oral sulfonamide therapy as mass prophylaxis with good success to eight large training stations that have high *S pyogenes* disease rates, but therapy-induced sulfa resistance among endemic *S pyogenes* strains	1944	Coborn[f,g]
Eaton agent is identified (later it is called *Mycoplasma pneumoniae*) and is found to cause much respiratory morbidity among military trainees	1944	Eaton,[h] Chanock[i]
First US Navy personnel receive *S pyogenes* vaccines—ineffective	1944	EUNo-22[j]
Oral penicillin therapy found to prevent rheumatic fever in civilian populations	1948	Milzer[k]
Procaine penicillin G injection therapy found to prevent rheumatic fever in military personnel with *S pyogenes* pharyngitis	1950	Denny[l]
Oral penicillin first used in US military personnel with excellent prophylaxis success against *S pyogenes*	1951	NMRU–4[m]
Benzathine penicillin G first used among civilian populations to prevent *S pyogenes* infection	1951	Stollerman[n]
Adenovirus discovered and later found to cause much respiratory morbidity among military trainees	1954	Hilleman,[o] Davenport[p]
Benzathine penicillin G used prophylactically against *S pyogenes* among large populations of US military personnel	1956	Frank[q]
Inactivated adenovirus vaccine (types 4 and 7) found effective among US military trainees	1956	Hilleman[r]
A new chlamydial pathogen is recognized (later called *Chlamydia pneumoniae*) and found to cause epidemics of respiratory morbidity among military trainees	1965	Grayston,[s] Kleemola[t]
Oral adenovirus vaccines (types 4 and 7) found effective among military trainees	1971	Gaydos[u]
Long absent, acute rheumatic fever epidemics recur among US military personnel	1987	Wallace[v]

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Description of the Pathogen

S pyogenes is a Gram-positive coccus, or spherical bacteria, which, when grown on sheep blood agar, causes a clear zone of complete hemolysis (β-hemolysis). It is distinguished from other β-hemolytic streptococci by physiological and immunologic characteristics and by its implication as a cause of numerous acute clinical manifestations. *S pyogenes* strains are classified according to their capsular proteins, specifically T and M proteins. More than 90 unique M protein types have been identified. M types 1, 3, and 18 are associated with acute rheumatic fever, and M types 1, 3, 4, 12, and 25 are often associated with glomerulonephritis.

Epidemiology

The epidemiology of *S pyogenes* infection has been well described in military populations. Studies by military and university investigators in the 1950s demonstrate that transmission is most often by direct contact or large respiratory droplets and not commonly by fomites. The bacteria are thought to be endemic throughout the world, with perhaps some variation in the endemnicity of certain strains. Without prophylaxis, recent serologic evidence demonstrates that as many as 24% of military trainees may be infected over an 11-week period.[21]

Risk factors for serologic evidence of *S pyogenes* infection include being new to the military, crowding, lack of prophylaxis, close contact with an *S pyogenes* carrier, and close contact with a trainee not on prophylaxis.[22] A retrospective study of civilians with invasive *S pyogenes* infections suggested that Native Americans, and persons older than 65 years may be at higher risk of severe *S pyogenes* disease.[23] Active surveillance among Canadians have demonstrated that infection with human immunodeficiency virus, cancer, diabetes, alcohol abuse, and chickenpox are risk factors for invasive *S. pyogenes* disease.[24]

Pathogenesis and Clinical Findings

S pyogenes colonizes respiratory mucosal cells, causing pharyngitis and other clinical manifestations, such as fever and leukocytosis, in 36 to 72 hours. The complex interaction of cellular and extracellular *S pyogenes* products with the host immune system is not well understood, but it is recognized that immunity to *S pyogenes* is type-specific. Some patients progress to more invasive forms of infection, including streptococcal toxic shock syndrome, bacteremia, and necrotizing fasciitis. *S pyogenes* pyrogenic exotoxins A and B and other virulence factors have been implicated in severe infection. Numerous theories regarding the interaction of host immune response and *S pyogenes* virulence factors have been postulated; however, it remains unclear why one person is severely infected by a particular strain of *S pyogenes* and another person is merely colonized with the same *S pyogenes* strain and suffers no symptoms.

S pyogenes, unlike other β-hemolytic streptococci, is implicated as a cause of numerous acute clinical manifestations, such as pharyngitis, peritonsillar abscess, pneumonia, empyema, scarlet fever, necrotizing fasciitis, myositis, bacteremia, and streptococcal toxic shock syndrome. *S pyogenes* also causes the nonsuppurative manifestations of acute rheumatic fever and glomerulonephritis. The severity of *S pyogenes* infections has changed over time. In the late 1800s, epidemics of scarlet fever were common and associated with high mortality rates.[25] Today, epidemics of scarlet fever are relatively rare.[26] In a similar fashion, acute rheumatic fever was very common during the mobilization for World War II, with 21,000 cases recorded in the US Navy alone,[27] but, until the 1980s, few cases were detected among military populations.[28,29] Changes in disease rates have been attributed to changes in the prevalence of virulent strains of *S pyogenes*.[30]

Diagnostic Approaches

Even in high-prevalence situations such as epidemics, it is difficult to clinically distinguish *S pyogenes* pharyngitis from pharyngitis caused by other pathogens. Diagnosis is best made by culture or rapid antigen detection. Generally, a rapid antigen test is accepted if it is positive, but it should be confirmed by culture if it is negative. Because a high proportion of infected military persons may not seek medical attention despite symptoms, epidemiologic studies of *S pyogenes* generally are conducted by relying on serologic tests, particularly the antistreptolysin O test. A two-dilution rise in antistreptolysin O titer is considered evidence of infection. Generally, such a rise may be detected in paired sera drawn 2 to 3 weeks apart. Other serologic tests for *S pyogenes* infection include the antideoxyribonuclease B test, the antihyaluronidase test, and a hemagglutination test (Streptozyme). Some patients with glomerulonephritis or symptoms of acute rheumatic fever may not demonstrate a rise in antistreptolysin O titer and should be evaluated further with antideoxyribonuclease B or antihyaluronidase tests before *S pyogenes* is eliminated as a cause.

Recommendations for Control

Monthly BPG injections and twice-a-day oral erythromycin have an estimated efficacy of preventing serologic evidence of infection of 45%[22] and 56%,[31] respectively.

Advances in *S pyogenes* control were first made in civilian populations just before World War II, when it was discovered that continuous antimicrobial therapy prevented recurrence of rheumatic fever. After World War II, it was learned that administering antibiotics to US military personnel with pharyngitis could reduce the incidence of acute rheumatic fever. Eventually, healthy military populations at high risk for *S pyogenes* disease were studied while being given mass antimicrobial prophylaxis against acute rheumatic fever, and this successful intervention became standard practice for crowded training populations.[27,32]

Sulfonamides were among the first antibimicrobials available, and during the 1940s they were found to prevent military epidemics of acute respiratory disease.[27] Large field trials[33] of oral 0.5 to 1.0 g of sulfadiazine given daily to healthy US Navy personnel resulted in an 85% reduction in the incidence of streptococcal infections and rheumatic fever; however, daily prophylactic use caused exfoliative dermatitis and granulocytopenia in a small proportion of recipients. Bacteriostatic sulfonamide prophylaxis also often failed to eradicate *S pyogenes* from the nasopharynx of military personnel, and as soon as the therapy was discontinued, epidemics recurred. The most serious drawback occurred, however, when a Navy sulfonamide prophylaxis program reported that sulfonamide-resistant strains of *S pyogenes* had become endemic after only 1 year of routine prophylaxis.[27,34] After the failure of sulfonamides, other methods to reduce morbidity from *S pyogenes* were attempted. Military public health officials tried various environmental controls, including reductions in crowding,[13] dust suppression,[35] ultraviolet radiation,[36] and disinfectant vapors,[37] with varying degrees of success. Chlortetracycline also was tested as a mass prophylaxis agent, but it caused significant gastrointestinal side effects.[38] Military and university scientists also unsuccessfully attempted to control *S pyogenes* epidemics with inactivated, type-specific vaccines[39] (Figure 38-1).

Environmental controls, such as dust suppression by oiling floors and blankets, were largely abandoned when it was learned that penicillins were effective in the treatment and prevention of *S pyogenes* disease.[27] Oral penicillin therapy was first shown in 1948 as effective in preventing recurrent rheumatic fever in civilian populations.[40] Later, both oral and procaine penicillin G were shown to be effective in preventing rheumatic fever among healthy, high-risk military personnel; however, the drug's use in large military populations was logistically difficult because of the need for frequent dosing.[38,41,42] The development of BPG in 1951 led to its successful, large-scale testing as a prophylactic in a military population in 1956.[43] BPG's long-acting prophylactic effect, assurance of compliance, and few side effects soon made it the standard prophylactic intervention for the US Department of Defense (DoD) against *S pyogenes,* and it remains an effective intervention tool today.[27] BPG also has been used to combat epidemics of *S pneumoniae*,[44] and it seems to have a broader protective effect than can be explained by preventing *S pyogenes* disease alone.[45]

Despite the availability of antibiotic prophylaxis and surveillance programs among high-risk populations, military epidemics of *S pyogenes* continue to occur. In recent years, these epidemics have taken the form of pharyngitis and acute rheumatic fever.[22,27–29] An epidemic in 1989 of *S pyogenes* pharyngitis among Marine Corps trainees demonstrated that BPG prophylaxis for non–penicillin-allergic trainees alone might not be sufficient because unprotected penicillin-allergic recruits were shown to serve as an *S pyogenes* reservoir for reinfecting their peers.[22] This led to the Navy's adoption of oral erythromycin prophylactic therapy for penicillin-allergic recruits.[21,22]

Currently surveillance among trainees and preventive interventions vary among the military services. BPG (1.2 million units intramuscularly, once monthly) and oral erythromycin (250 mg orally, twice a day) interventions have been very effective in controlling *S pyogenes* epidemics. BPG remains effective for 2 to 4 weeks after injection. Oral erythromycin suffers from compliance problems due to its twice-daily dosing and gastrointestinal side effects. Oral azithromycin (500 mg weekly) has been shown to have an 84% efficacy in preventing *S pyogenes* infection and may be considered as an alternate therapy when an agent with a broader spectrum is desired.[31]

Reports of erythromycin-resistant *S pyogenes* isolates[46] and epidemics due to penicillin-tolerant *S pyogenes* strains[47,48] are causes for concern. Fortunately, thus far no penicillin-resistant *S pyogenes* isolates have been detected clinically; however, periodic surveillance of endemic strains among high-risk training populations should be conducted. This surveillance should contain antibiotic sensitivity testing of isolates, as well as strain typing.

The best hope for preventing *S pyogenes* disease

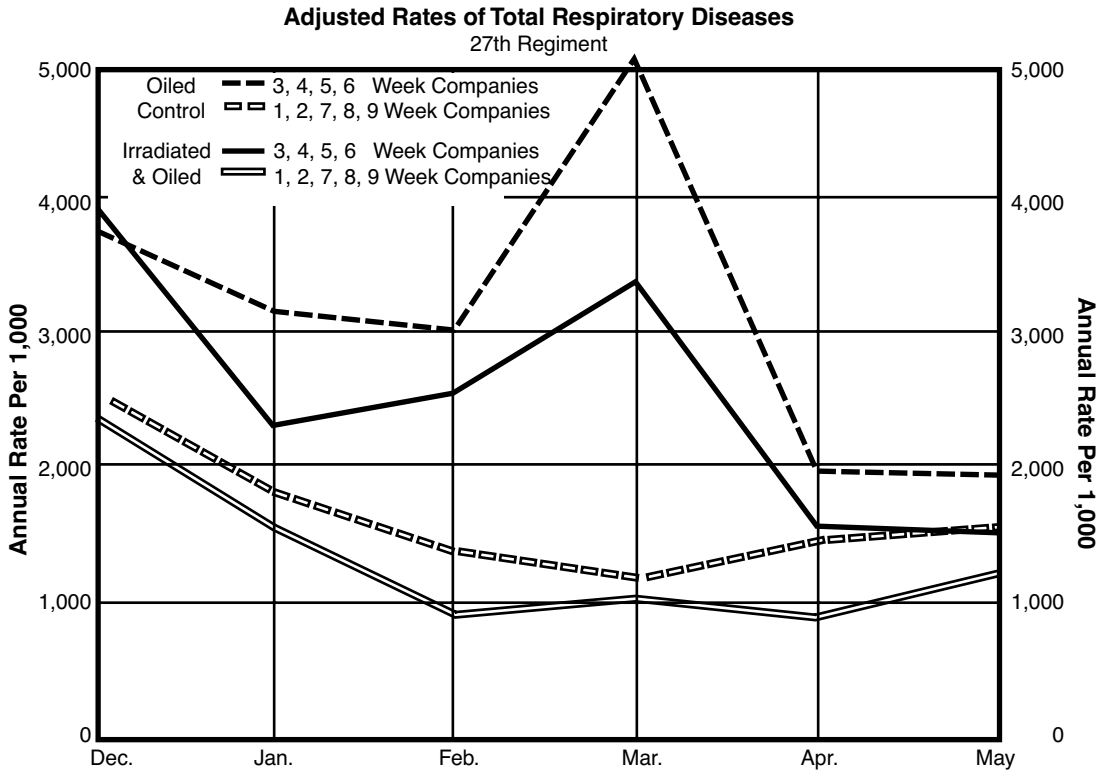

Fig. 38-1. Respiratory disease hospital admission rates by week of training and treatment groups. Dust in barracks was controlled by oiling floors and bed blankets; irradiated barracks indicates that ultraviolet radiation lamps were hung from ceilings and placed on floors. Lamps were on for 24 hours each day.
Reprinted, with permission from the *Journal of Infectious Diseases* from Miller WR, Jarrett ET, Willmone TL, Alexander H, Brown EW, et al. Evaluation of ultraviolet radiation and dust control measures in control of respiratory disease at a naval training center. *J Infect Dis*. 1948;82:86–100.

among military populations lies with the development of vaccines. Several approaches are being considered, including immunologic presentations of shared epitopes of various capsular M proteins. Vaccines, however, most likely will not be available for a number of years.

Streptococcus pneumoniae

A frequent cause of pneumonia in adults, *S pneumoniae* (pneumococcus) infections cause significant morbidity among US military populations. In the preantibiotic era, *S pneumoniae* infections could lead to large epidemics exceeding several hundred cases, particularly after influenza outbreaks. Today, epidemics caused by infection with *S pneumoniae* occur less often, but they remain a threat. Recently, an epidemic of pneumonia (128 hospitalizations) was recorded among Marine Corps trainees in southern California, triggering mass BPG and pneumococcal vaccine injections[44] (Figure 38-2).

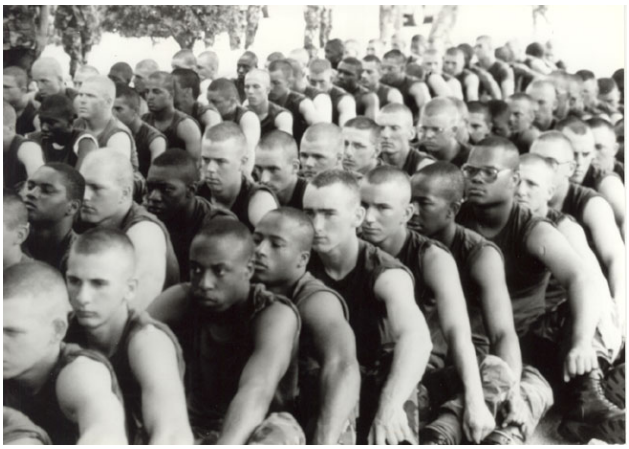

Fig. 38-2. The close and frequent person-to-person contact of trainees make military recruit training a very efficient time for respiratory pathogen transmission.
Photograph: Courtesy of Captain Gregory C. Gray, US Navy.

Description of the Pathogen

S pneumoniae is an ovoid, Gram-positive coccus that often forms distinctive pairs and chains. It grows well on sheep blood agar, causing partial hemolysis β-hemolysis), and it is distinguished from other streptococci by chemical growth inhibition and immunologic reaction. Eighty-four recognized strains or types are classified by their distinct capsular polysaccharides.

Epidemiology

S pneumoniae is spread by respiratory droplets or person-to-person contact. It is thought not to have geographical limitations, but data are sparse regarding the geographical distribution of capsular types. The incidence of disease among military personnel has not been well studied. US Navy data from 1981 to 1991 suggest that *S pneumoniae* causes approximately 12% of Navy and Marine Corps pneumonia hospitalizations, which occur at a rate of 9.5 per 100,000 person-years.[49] Because the incidence of outpatient disease is unknown and there are diagnostic difficulties identifying this pathogen, these estimates greatly underestimate its impact. Personnel at increased risk include individuals who are immunocompromised; are asplenic; or have sickle cell disease, renal disease, or diabetes mellitus. Military recruits are at high risk of *S pneumoniae* infection.

Pathogenesis and Clinical Findings

S pneumoniae is often found on the epithelium of healthy nasopharynx tissue, and its pathogenesis is not well understood. Other respiratory pathogens, especially viruses, may serve as a cofactor for invasion of local tissue by *S pneumoniae*, which if unchecked, may lead to clinical disease. Immunity is capsular, type-specific, and thought to last for years.

S pneumoniae causes various forms of pneumonia, meningitis, empyema, bacteremia, conjunctivitis, sinusitis, and arthritis.

Diagnostic Approaches

Because *S pneumoniae* is considered normal, oral bacterial flora, it is difficult to confidently diagnose infection from the oral pharynx. The accepted clinical diagnostic gold standard is bacterial culture from a normally sterile site. Blood cultures from patients with pneumonia caused by *S pneumoniae*, if studied before antibiotic administration, should be positive 20% of the time. A clinically expedient and alternative diagnostic tool for *S pneumoniae* pulmonary infection is a well-prepared sputum specimen. Gram-stained sputum specimens should contain few to no squamous cells per low-powered microscopic field. The numerous serologic techniques available to assess *S pneumoniae* infection generally are confined to research institutions and involve detecting antibody to pneumococcal proteins or capsular polysaccharides. Generally, a rise in antibody titer from acute to convalescent sera is considered evidence of recent infection. Latex agglutination tests for pneumococcal antigens in urine has been found to have poor sensitivity but good specificity and are valuable when positive.[50]

Recommendations for Control

For military personnel, the 23-valent polysaccharide pneumococcal vaccine is the best protection against *S pneumoniae* infection. In 1991, the Armed Forces Epidemiological Board recommended a single dose of this vaccine be given to asplenic individuals and military personnel at bases with high prevalence of pneumonia. It is used routinely in high-risk Marine Corps trainee populations during the winter months. BPG, 1.2 million units intramuscularly, has been used to combat pneumococcal pneumonia epidemics, but it has never been evaluated for efficacy.[44] A study[31] of oral azithromycin (500 mg weekly) demonstrated an 80% efficacy of preventing serologic evidence of pneumococcal infection.

The recent rapid spread of clinically important, penicillin-resistant *S pneumoniae* strains throughout the United States and other developed countries has frustrated clinicians.[51,52] National US surveillance has demonstrated increasing prevalence of penicillin-resistant strains and increasing numbers of strains and serotypes resistant to multiple antibiotics. National public health panels have called for increased surveillance for antibiotic resistance among *S pneumoniae* isolates, careful use of antibiotics, and increased use of pneumococcal vaccine among high-risk populations.[53]

Mycoplasma pneumoniae

Long before microbiologists had distinguished agents causing acute respiratory disease, differences were noted in the clinical manifestations of pneumonias. Military personnel frequently suffered from acute pneumonia, which was milder than lobar pneumonia. Although this atypical pneumonia demonstrated significant pulmonary involvement on chest radiographs, patients lacked the high fever, pleuritic chest pain, and rigor associated with lobar pneumonia caused by *S pneumoniae*. In some

US Army camps, 85% to 90% of pneumonias were of the atypical variety.[54] The agents (or agent) causing this atypical pneumonia or primary atypical pneumonia were a matter of some debate. Often, patients with atypical pneumonia had positive cold agglutinin tests. In 1944, Eaton described his DoD-funded research, which demonstrated that a filterable agent (later named *Mycoplasma pneumoniae*) taken from patients with atypical pneumonia could cause pulmonary lesions in rats.[55] In 1961, Chanock[56] reported that *M pneumoniae* was responsible for 68% of atypical pneumonias among Marine Corps trainees and that as many as 41% of recruits had serologic evidence of infection during a 3-month training period.

Description of the Pathogen

M pneumoniae lacks a rigid cell wall and is much smaller than other bacteria. It grows very slowly on special nutrient agar, and isolation techniques most often are performed by reference laboratories. *M pneumoniae* grows on the surface of the epithelial cells that line the respiratory tract. Generally, it is not considered an agent of the nasopharyngeal flora. Due to its extracellular existence, however, it may be found in respiratory excretions weeks after clinical disease has resolved.

Epidemiology

M pneumoniae is transmitted by respiratory droplet inhalation or person-to-person contact and has a worldwide geographical distribution. Among US military populations, infection risk increases in late summer,[57] and females may be at higher risk of infection than males.[49,58,59] Certainly, crowding contributes to infection risk. Antibody to this pathogen is common among young adults. A recent study[60] demonstrated that on entry into the service, 58% of Marine trainees had evidence of previous infection with *M pneumoniae*. The prevalence and incidence of infection among US military training populations as measured by serologic antibody titer change is high, especially during outbreaks. One study[56] demonstrated seroconversion in as many as 57% of recruits during an 11-week period. Routine incidence in military training centers is more likely similar to the 6% to 8% detected among recent Marine Corps training populations during 3-month periods.[31,60]

Pathogenesis and Clinical Findings

Because of the low mortality and diagnostic difficulties, the pathogenesis of *M pneumoniae* infections has not been well determined. The pathogen adheres to epithelial cell receptors. After infection, antibodies to *M pneumoniae* surface antigens are formed, which offer protection from further infection. Many *M pneumoniae* infections evoke immunoglobulin M (IgM) autoantibody, which agglutinates human erythrocytes (cold agglutinins) and, in some cases, may trigger an autoimmunogenic mycoplasma-receptor complex.[36]

M pneumoniae infections are noted for their gradual onset of symptoms, dry cough, malaise, headache, and chills. Although some infections may be asymptomatic, *M pneumoniae* commonly causes a pharyngitis and may cause bronchopneumonia with patchy pulmonary infiltrates radiating from hilar areas. Occasionally, *M pneumoniae* may cause severe pneumonia or severe disease of the central nervous system, including meningoencephalitis, aseptic meningitis, ascending paralysis, and transverse myelitis. *M pneumoniae* also has been reported to cause various forms of cardiac disease, and numerous dermatological conditions.[61]

Diagnostic Approaches

M pneumoniae may be isolated from the nasopharynx after several weeks of incubation on special nutrient agar. For the best yield, a pharyngeal culture should be inoculated immediately into nutrient agar broth for incubation. Reference laboratories will need several weeks to isolate and identify *M pneumoniae* from clinical specimens. It is distinguished from other mycoplasmas by colony morphology, growth, and metabolic inhibition. Identification may be confirmed with serologic or molecular methods.

Clinically, the diagnosis of *M pneumoniae* infection may be presumed if the symptom complex is consistent with disease and the patient has a positive cold agglutinin test (titer ≥ 1:32 in convalescent sera). A positive test is more common with severe pneumonia. However, this test lacks sensitivity in that approximately 50% of infected patients may have a negative cold agglutinin test. The cold agglutinin test is additionally problematic in that it may be falsely positive in the presence of hematologic and hepatic diseases. Alternatively, acute *M pneumoniae* infection may be diagnosed by detecting high IgM titers specific for *M pneumoniae*[62] or by detecting *M pneumoniae*–specific nucleic acid with polymerase chain reaction assay (PCR).[63,64] Although several commercial diagnostic kits have been marketed for rapid diagnostic use in the clinical laboratory, their sensitivity and specificity have not approached that of reference laboratory serologic assays.

Two serologic tests, complement fixation assay and enzyme-linked immunosorbent assay (ELISA), have been used effectively to detect *M pneumoniae* in epidemiologic studies. Generally, these tests are performed by a reference laboratory, and a 4-fold rise in antibody titer by either method (acute symptom sera to 3- to 4-week convalescent sera) is accepted as evidence of recent infection.[62,65]

The DoD conducts no specific surveillance for *M pneumoniae* infection among military populations. The US Army's surveillance program for acute respiratory disease[45] includes morbidity from *M pneumoniae,* but only in the aggregate with that from other pathogens. At present, the DoD has no sustained *M pneumoniae* research program and no *M pneumoniae* reference laboratory. Military investigators must rely on other academic or federal laboratories for diagnostic assistance.

Recommendations for Control

Few options are available for combating *M pneumoniae* epidemics. Although several studies[66,67] have demonstrated that preexisting antibody titers against *M pneumoniae* may prevent infection and vaccine candidates were tested in the 1960s and 1970s with mixed success,[68–70] no vaccine is available. In 1965, a 10-day course of oxytetracycline was used to prevent disease in family members of patients.[59] This four-times-a-day regimen was reported to have had a prophylactic effect. This result, however, has never been validated. Navy researchers have demonstrated that weekly oral azithromycin (500 mg) has a 64% protective serologic efficacy against *M pneumoniae* among Marines, and this strategy may hold some promise.[31]

Chlamydia pneumoniae

First accepted as a new species in 1989, *Chlamydia pneumoniae* has been found to be a frequent cause of acute respiratory disease in military personnel. In Norway and Finland, *C pneumoniae* has been shown to infect as many as 56% of military recruits.[19] The agent is thought to cause approximately 8% of pneumonias in the United States.[71]

Description of the Pathogen

Like all *Chlamydia*, *C pneumoniae* is an obligate intracellular parasite, depending on its host cell for nutrients. It grows poorly on special media and is sensitive to freeze–thaw cycling.

Epidemiology

Recently recognized and difficult to diagnose, *C pneumoniae* has not been exhaustively studied. The pathogen is transmitted by person-to-person contact and respiratory droplets.[72] It has been found in many parts of the world and is thought to be both endemic and epidemic in some populations, with outbreaks lasting from 4 months to 3 years.[73] No seasonal variation in risk is apparent.[74] The prevalence of antibodies in adults is thought to average about 50%,[75,76] with a higher proportion of men having antibodies than women.[77] The pathogen is considered responsible for about 10% of pneumonias worldwide, with seroconversion peaking during teenage years, at about 10% per year.[78] Military training populations may suffer higher rates of infection. A 1989 study[60] of US Marine Corps recruits demonstrated seroconversion in 3.9% of them during an 11-week training period. Another trainee study[31] conducted in 1994 found evidence of seroconversions in 8% during a 63-day training period. Risk factors for *C pneumoniae* infection are not well defined. As military recruits seem to be at higher risk, crowding probably plays a role in transmission.

Pathogenesis and Clinical Findings

Limited data are available regarding pathogenesis caused by *C pneumoniae*. The pathogen multiplies in macrophages, various connective tissues, and smooth muscle cells.[79] A 1989 study[60] of Marines suggested that a preexisting antibody is protective against serologic evidence of infection. Evidence exists, however, that humans may be reinfected with *C pneumoniae*. Generally, reinfection results in milder disease, but among the elderly, reinfections may lead to severe disease.[80,81]

Many infections may be asymptomatic, and clinical manifestations are often insidious. *C pneumoniae* has been implicated in causing pharyngitis (often with hoarseness),[74] sinusitis, bronchitis, and lower respiratory tract infections. *C pneumoniae*–infected patients often do not have a marked fever or an elevated white blood count. Some evidence shows that *C pneumoniae* may be associated with coronary artery disease,[82] reactive airway disease,[83,84] and chronic pharyngitis.[85]

Diagnostic Approaches

Difficulties in diagnosing *C pneumoniae* infection are numerous. The pathogen is difficult to culture

(sensitivity ~50%),[79] and, because of evidence of an asymptomatic carriage,[86,87] some authors argue that isolation apart from other evidence of infection may be misleading. Two serologic methods have been used to diagnose *C pneumoniae* infection among young adults: complement fixation and micro-immunofluorescence. Generally, a 4-fold rise in titer from acute to convalescent sera is considered evidence of recent infection. A high acute microimmunofluorescence IgM titer also is accepted.[88] Complement fixation is less sensitive than the microimmunofluorescence method, but the latter is technically more difficult and subject to significant reader error.[79] Neither method is widely available, and investigators must rely on reference laboratories for support. Both serologic methods may be confounded by *C trachomatis* infections, which may cause cross reactions.[79,89] Several different PCR diagnostic methods have been developed.[90,91] Dacron swabs are recommended, because other swab types may inhibit PCR technique.

Recommendations for Control

The only evidence of an effective intervention has been the data suggesting that weekly oral azithromycin (500 mg) has a 58% efficacy in preventing serologic evidence of infection.[31] Because effective diagnostic tests are not commercially available, the DoD does not conduct routine surveillance for *C pneumoniae*. No vaccine is available.

Influenza

Before vaccines were available, influenza outbreaks could devastate a military population in a matter of weeks. A 1919 report of a 2-week outbreak of influenza in an Arkansas military camp recorded that the camp hospital received 188 to 486 influenza admissions per day, overwhelming hospital staff, who themselves had a 25% incidence of disease.[92] Despite the availability and annual use of influenza vaccine, epidemics still occur among US military populations. During 1996, a Navy ship with a 551-person crew had a 42% attack rate, although 95% of the men had recently received influenza vaccine (G.C.G., unpublished data, 2000). Viral isolates indicated that the epidemic strain was not covered by that year's vaccine (Figure 38-3).

Description of the Pathogen

Some of the most studied viruses, influenza viruses are recognized for their antigenic variation

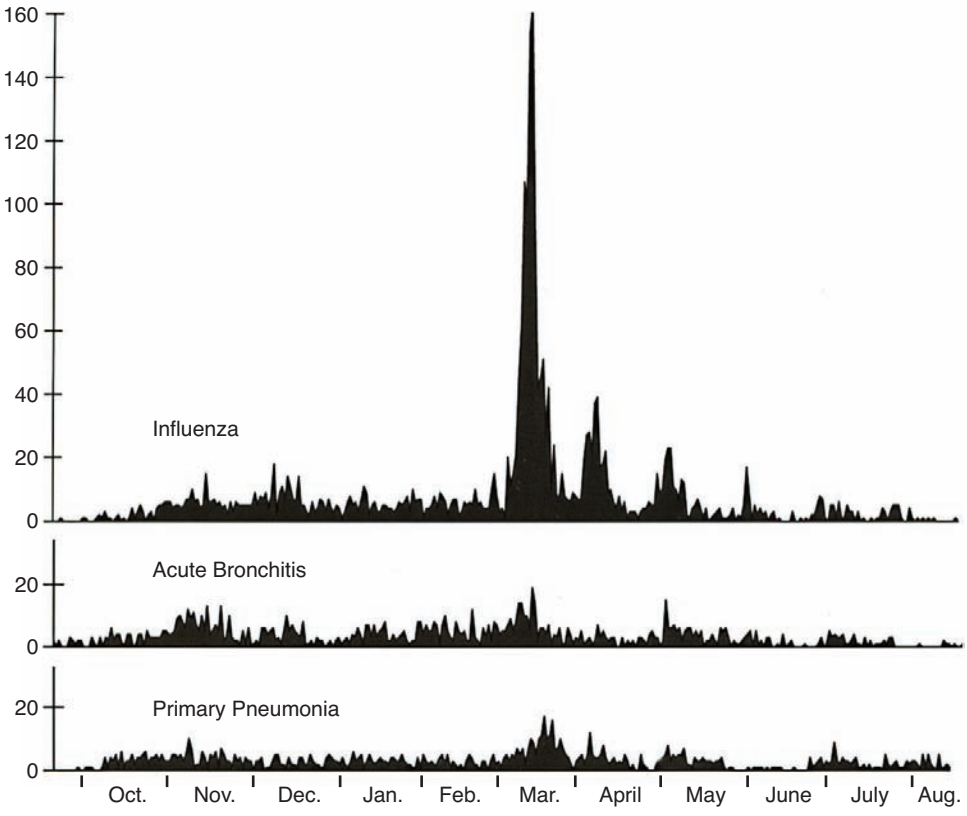

Fig. 38-3. Respiratory disease hospitalizations for influenza, acute bronchitis, and primary pneumonia at Army Camp Funston in Fort Riley, Kansas, from 20 September 1917 to 20 August 1918.
Adapted by Phil Larkins with permission from: Opie EL, Freeman AW, Blake FG, Small JC, Rivers TM. Pneumonia at Camp Funston. *JAMA*. 1919;72:114. Copyright 1919, American Medical Association.

and classified into 3 types: A, B, and C. The viruses, especially types A and B, vary their antigenic presentation and cause cyclical pandemics. Type A influenza virus is classified by the antigenic presentation of its surface glycoproteins—hemagglutinin and neuraminidase. Mutations in the genes for these glycoproteins have caused pandemics throughout recent history (1889, 1918, 1957, and 1968). A major change in glycoproteins is known as an antigenic shift, minor changes as antigenic drift. Type B influenza virus also is recognized for antigenic drift, but its antigenic variation is less than that of type A. Type C influenza virus causes sporadic disease and varies its antigenic presentation to a lesser extent than do types A and B.

Epidemiology

The influenza viruses generally are transmitted by person-to-person contact or through droplet spread from sneezing or coughing. Influenza viruses vary geographically in their antigenic makeup, and surveillance for type A variants is conducted worldwide. Surveillance information is used to anticipate epidemics and select antigenic components for vaccine production.

Influenza epidemics often are explosive and result in high mortality. The 1918–1919 influenza pandemic resulted in an estimated 20 million deaths.[93] During epidemics, more than 40% of a military population may be affected during a brief period.[94] Persons at highest risk of experiencing severe clinical symptoms from influenza infection are those with chronic cardiac, pulmonary, or renal conditions; those with diabetes mellitus or immunosuppression; pregnant women; and the elderly.

Pathogenesis and Clinical Findings

The influenza virus invades the host via the upper respiratory tract. Viral particles penetrate host respiratory epithelial cells, replicate, and infect neighboring cells. Peak viral loads are reached within 24 hours. Influenza virus is thought to remain largely in the respiratory tract. Both secretory and serum antibodies are involved in host defense against influenza virus invasion. After natural infection, immunity to influenza virus with those antigens wanes after several years.

Clinically, influenza viral infection may range in manifestations from asymptomatic or cold-like symptoms to severe pneumonia leading to death. The viruses may cause chills, fever, headache, myalgia, sore throat, backache, sneezing, anorexia, nausea, vomiting, and cough. Pneumonia is a serious complication and is often associated with concomitant secondary bacterial infections.

Diagnostic Approaches

Influenza is diagnosed by viral culture, antigen detection, or association with other laboratory-proven clinical cases. Diagnoses also may be made retrospectively in epidemiological studies by serologic assay.

Recommendations for Control

DoD-sponsored research[95,96] demonstrated the safety and effectiveness of using amantadine prophylactically to prevent influenza infection among close contacts of those infected. Today, both amantadine and rimantadine are still so used, but recent evidence suggests that viruses resistant to both drugs may emerge.[97,98]

Although vaccine work began shortly after the discovery of the influenza virus (see Table 38-1), progress was slow due to viral antigenic variation. An article on the first attempt at human influenza vaccination was published in 1936.[99] Early influenza A vaccines contained contaminants from the embryonated egg culture and caused considerable reactions. Additionally, the varying antigenic makeup of influenza isolates was not well understood, and results from early vaccine studies were mixed.

In 1943, the DoD sponsored some of the first influenza vaccine testing among military students at several US sites.[100,101] One of the earliest combined influenza A and B vaccine trials among US military students demonstrated a protective efficacy of 69% and greatly encouraged more research.[101] The DoD continued to test various types of influenza vaccines, both inactivated and attenuated,[94,102] and these studies led to the present successful strategy of altering yearly the antigenic makeup of this vaccine. Numerous public health organizations conduct surveillance for influenza infections. The focus of such surveillance is the antigenic makeup of wild viruses. Today, the military relies on a whole-cell, inactivated type of vaccine, which combines the antigenic makeup of type A and B viruses considered to be most threatening for the year ahead. This vaccine is given annually to all US military personnel.

Adenovirus

Soon after the discovery of adenovirus in 1953,[103,104] it was learned that this pathogen was an important cause of acute respiratory disease among military personnel, especially recruits.[105]

Description of the Pathogen

Adenovirus has been classified into 51 serotypes. These serotypes may have antigenically recognizable subtypes. Serotypes 4 and 7 account for most military adenovirus respiratory epidemics. Serotypes 3, 12, 14, and 21 also cause acute respiratory disease among military populations but to a lesser extent.

Epidemiology

Adenoviruses are transmitted through respiratory droplets and person-to-person contact. Adenoviruses are thought to have a worldwide distribution, and incidence rates among military trainees often have been high, especially during winter months.[107–109]

Before vaccines were developed, adenovirus infections caused 10% of US Army recruits to be hospitalized and, during winter months, explained 90% of all hospital admissions of recruits.[106] Hillman also estimated that during the winter months, adenoviruses accounted for 77% of all recruit respiratory disease.[107] Most often, adenovirus infections occurred during the first 3 weeks of recruit training,[108] and only the newest military personnel were affected.[109] However, among US Marine Corps trainees, infection was often delayed until postrecruit training.[110,111] In general, military trainees were found to be at much higher risk of infection than were similar civilian populations.

Pathogenesis and Clinical Findings

Studying adenoviruses is confounded by asymptomatic carriage and asymptomatic infection.[112,113] It is not understood why some people suffer significant clinical disease when infected and others remain asymptomatic. Some evidence indicates that adenovirus infection, when associated with infection from other respiratory pathogens, results in more severe disease.[114] The virus is thought to invade respiratory tissues and, after a several-day incubation period, to cause clinical disease and sometimes viremia. Some adenoviruses may cause prolonged infection, such as chronic pharyngitis. Evidence also suggests that latent adenovirus infection may reactivate and cause clinical disease in the immunocompromised.

Adenovirus respiratory disease often causes fever, cough, pharyngitis, and rhinitis. The infection may progress to a lower respiratory tract infection, which is generally milder than that caused by *S pneumoniae*. Adenoviruses also cause gastrointestinal symptoms, epidemic keratoconjunctivitis, and epidemic pharyngoconjunctival fever, but respiratory disease is the most common presentation among military recruits.

Diagnostic Approaches

Today, adenoviruses are detected through culture and various antigen or nucleic acid detection techniques. Culture and identification of adenovirus are relatively easy; however, serotyping traditionally requires a reference laboratory to perform neutralization tests using specific horse or rabbit antisera. In patients with symptoms, the detection of adenovirus generally is accepted as evidence of infection. Epidemiologic studies often rely on serologic evidence of infection, which is gained through several methods, including complement fixation, neutralization tests, hemagglutination-inhibition antibody tests, and ELISA tests.[115,116]

Recommendations for Control

The DoD has developed a number of adenovirus vaccines.[117,118] Early inactivated vaccines against serotypes 3, 4, and 7 were effective, given separately or in combination, in greatly reducing military recruit respiratory morbidity.[117] The inactivated vaccines suffered from production difficulties, however, and some seed virus cultures were contaminated with other viruses.[119,120] Later, live vaccines were developed for serotypes 4, 7, and 21. These vaccines caused excellent seroconversion and had few side effects when given orally as enteric-coated tablets. The success of the serotypes 4 and 7 vaccines led to their adoption by the DoD as routine preventive therapy in the early 1970s, and they remain very effective, when available.[119] Because of the infrequency of military epidemics from serotype 21 virus, the serotype 21 vaccine was not developed further or used. In addition to vaccine intervention, DoD researchers also explored prophylactically administering serum immune globulin against acute respiratory tract infection. Results of these trials were mixed; some show a protective effect but not as protective as adenovirus vaccine.[121–123]

Due largely to economic reasons, the sole manufacturer of adenovirus vaccines ceased production in 1996. The last stores of adenovirus 4 and 7 vaccines were depleted in early 1999. Subsequently, large adenoviral respiratory disease epidemics occurred among numerous US military populations,[124–127] causing costly morbidity and loss of training time. Recent serological studies demonstrate that approximately 90% of trainees enter military service are susceptible to either type 4 or type 7 adenoviral infection.[128] Despite this current and likely future

morbidity and cost-benefit studies[129,130] that demonstrate large financial savings with vaccine use, at the time of this writing the Department of Defense had not yet secured a new adenovirus vaccine manufacturer.

Emerging Pathogens

With the myriad available antibiotic therapies and an assortment of effective vaccines, one might think that today's military preventive medicine personnel are well equipped to control most respiratory diseases. This might be true if pathogen-host relationships were not changing, but most certainly they are, and military populations continue to suffer from respiratory disease. In the 1980s, along with the more-virulent *S pyogenes* isolates came a newly recognized manifestation of infection, streptococcal toxic shock syndrome.[131] This syndrome and other forms of invasive *S pyogenes* infection with the same rapid tissue destruction and high mortality rates, such as necrotizing fasciitis, have caused considerable alarm among military populations. Risk factors for these rare invasive diseases have not been well identified, but available data suggest that persons with human immunodeficiency virus infection, diabetes, cancer, or varicella infection or who abuse alcohol may be at increased risk.[132]

The success of various antibiotics in controlling *S pneumoniae* and *S pyogenes* infections may soon be overshadowed by the pathogens' development of resistance to penicillin and erythromycin. Already some DoD clinicians have changed empirical therapies, and the increasing prevalence of antimicrobial resistance promises to be a continual military problem.

Some successful childhood vaccines have caused unexpected adult pathology by postponing natural infection until the adult years. Such is the case with *Bordetella pertussis*; studies[133] have shown that the childhood immunity induced by pertussis vaccine wanes in adulthood, and the proportion of US adults susceptible to infection has increased with time. A recent study[134] has shown that up to 26% of university students who report 6 or more days of cough may have evidence of acute pertussis. A similar study[135] of coughing Marine Corps trainees in 1989 demonstrated that 17% were infected. Since the yield of oral culture among *B pertussis* adults is poor and no good, rapid diagnostic techniques are available, recognizing such infections will be a problem for tomorrow's military clinician (Figure 38-4).

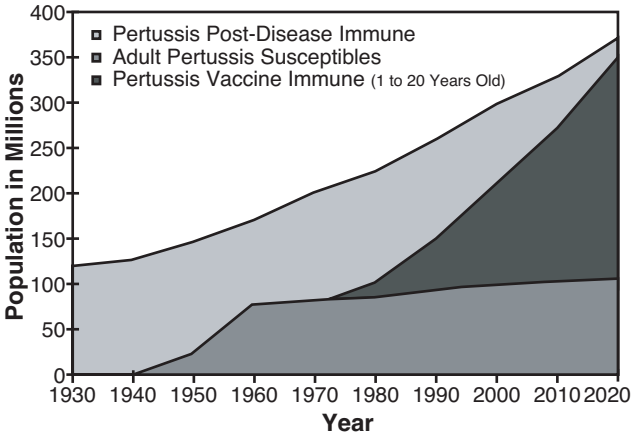

Fig. 38-4. Increasing numbers of US adults susceptible to pertussis, in millions of persons by year.
Adapted by Phil Larkins with permission of the *Pediatric Infectious Disease Journal* from: Bass JW, Stephenson SR. The return of pertussis. *Pediatr Infect Dis J*. 1987;6:141–144.

Summary

Respiratory disease remains a major cause of morbidity for today's military populations. Despite a number of preventive measures military personnel still suffer morbidity for *S pyogenes*, *S pneumoniae*, *M pneumoniae*, *C pneumoniae*, influenza, and adenovirus infections. Respiratory outbreaks often occur in an explosive fashion, and if the etiologic agent or agents are not easily recognized, the military preventive medicine officer may face a dilemma: wait for definitive diagnosis while the epidemic continues to build, or venture an empiric intervention that may later be judged inappropriate or expensive, and may have its own morbidity. Having an understanding of the most common pathogens, as describe din this chapter, and an understanding of their epidemiology (Table 38-2) prepares the preventive medicine officer to make good public health recommendations.

[Gregory C. Gray, MD, MPH]

MENINGOCOCCAL DISEASE

Introduction and Military Relevance

Meningococcal disease is currently an infrequent yet important problem for the military medical officer. Few, if any, infections can kill as quickly or panic the population involved so thoroughly. Despite significant gains in knowledge, the disease remains an enigma. It is caused by an exceedingly

TABLE 38-2

CHARACTERISTICS OF INFECTIOUS AGENTS TO CONSIDER DURING MILITARY EPIDEMICS

Incubation Period (d)	Organism	Epidemiologic and Clinical Clues
1-3	Influenza viruses	Very acute onset; headache, fever, malaise; onset may be followed by bacterial pneumonia; affects both veteran and new military personnel
1-3	*Streptococcus pyogenes*	Acute onset; sore and inflamed throat, fever; often associated with epidemics
1-3	*Streptococcus pneumoniae*	Frequently preceded by viral infections; acute onset; high fever, rigors; often causes lobar pneumonia; often produces a characteristic sputum
4-12	Adenovirus	Acute onset; affects new military personnel; mild disease but can cause pneumonia; affects new military personnel
6-20	*Bordetella pertussis*	Gradual onset; adults generally have cough for 7 or more days; cough is severe and with paroxysms
6-32	*Mycoplasma pneumoniae*	Gradual onset; cough, malaise, chills but no rigor, mild pneumonia; 50% with positive cold agglutinins
10-30	*Chlamydia pneumoniae*	Acute or gradual onset; pharyngitis, cough, hoarseness, fever; sputum is sparse; illness is generally mild

common, commensal organism that rarely results in symptomatic illness. The reasons for this common organism causing rare endemic disease, sporadic localized outbreaks, and periodic massive epidemics are not entirely clear. Although primarily a disease of children, adults brought together into crowded living conditions (eg, prisoners, military recruits) are at greatly increased risk of disease.

The Napoleonic armies experienced the *meningite de congelation* described by Baron Larrey in 1807. Not until 1886, however, when Weischelbaum noted the diplococcus on microscopic examination of cerebrospinal fluid of a Viennese victim, was the diagnosis of meningococcal disease well defined. Reliable rates of meningococcal disease in the US Army extend back to about 1900. Increased annual incidence of disease was clearly documented in association with military campaigns, to include the occupation of Cuba in 1907 (50/100,000) and the mobilization along the Mexican border in 1913 (35/100,000). In 1917 in association with the mobilization for World War I, rates of meningococcal disease exceeded 150/100,000 per year in the Army. As with the Mexican border mobilization, the abrupt increase in incidence was a result of epidemics in training camps and not from increased disease in seasoned, deployed troops.[136]

The last major wave of meningococcal disease to occur in the United States, both military and civilian, occurred in 1945. Significant outbreaks continued to occur at US military bases in the 1960s and 1970s, more than one of which resulted in the temporary closure of a basic training camp.[136–138]

While the use of antibiotics in the 20th century has drastically improved the outcome of meningococcal disease, case-fatality rates of 5% or more are still seen under optimal conditions. Medical research, much of it by the US armed services, has produced vaccines and drug regimens for the successful prevention of meningococcal disease. Nevertheless, meningococcal disease should remain a significant concern as long as the military assembles young adults or deploys personnel to areas of the world with high rates of meningococcal disease.

Description of the Pathogen

The responsible bacterium, *Neisseria meningitidis*, is a member of the genus *Neisseria*, which includes the closely related *N gonorrhoeae* and other bacteria found on human mucosal surfaces. The human nasopharynx is the habitat of these Gram-negative cocci measuring 0.6 to 1.0 μm in diameter. They are often seen in pairs (diplococci) with adjacent sides slightly flattened. On solid media, *N meningitidis* grows in colorless, transparent, nonhemolytic colonies. *N meningitidis* requires a degree of special handling; the organisms do not tolerate low humidity or extremes of temperature and grow best on blood-enriched media. Optimal growth occurs at 35°C to 37°C in a humid, microaerophilic atmosphere containing 3% to 10% carbon dioxide. Specimens, there-

fore, should be plated on warm chocolate agar and incubated in a candle jar without delay. When plating specimens obtained from nonsterile sites (eg, the nasopharynx), the use of selective media for *Neisseria* species is recommended (eg, Thayer-Martin [Martin-Lewis] medium—a chocolate agar with antibiotics added to suppress the growth of yeast and bacteria other than *Neisseria*). With this careful handling, the organism can usually be recovered within 24 hours of incubation.[139–143]

Definitive identification of genus is accomplished by analysis of the bacterial enzymes present. *Neisseria* species are identified from most other flora by the presence of cytochrome oxidase. Then, as a general rule, *N meningitis* is identified by its ability to metabolize glucose and maltose with the production of acid and its inability to metabolize sucrose or lactose.[139] Further classification of *N meningitis* is accomplished by analysis of the bacterial surface.

Based on the antigenic properties of capsular polysaccharides, at least thirteen serologic groups of *N meningitidis* (ie, A, B, C, D, E, H, I, K, L, X, Y, W-135, Z) have been designated. Historically, the majority of disease is caused by serogroups A, B, and C. The meningococcus is also found without a polysaccharide coat. Termed nonencapsulated strains, these colonies appear smooth in culture, as opposed to those colonies that produce large amounts of polysaccharide, which appear mucoid. These nonencapsulated strains have not been implicated in systemic disease and are most commonly found in the nasopharynx of asymptomatics.[140] Using sophisticated laboratory techniques, *N meningitidis* may be further classified into serotypes and subtypes based on the antigenic properties of the proteins and glycolipids in the bacterial outer membrane. This nomenclature may cause confusion because serogroup A may be called "serotype" or "type" A. The identification of serogroup is essential when planning public health strategy. In addition to differing properties of each serogroup, vaccines are available for only serogroups A, C, Y, and W-135. The identification of serotype and subtype is of particular use in the investigation of epidemics. Neither serogroup nor serotype, however, is necessary for the diagnosis or clinical management of meningococcal disease.

Epidemiology

Transmission

Transmission of the meningococci is person to person by direct contact of respiratory secretions or by respiratory droplet. The determinants of the distribution of meningococcal disease are complex and only partially understood. Colonization and infection are common; clinical disease is comparatively rare. Recovery of *N meningitidis* from the nasopharynx of healthy "carriers" is common and documented whenever sought. Most patients with symptomatic invasive meningococcal disease ("cases") are not infected by other cases, in case-to-case spread, but rather from healthy carriers.[142,144p340–345] Carriage rates are dependent on age, varying from 1% or less in infants to 20% to 40% in young adults. Increased carriage rates are associated with outbreaks; rates approaching 100% have been documented in military training camps during outbreaks.[143,145] Despite this association, carriage rates of 25% or greater are often documented in the absence of clinical disease. Additionally, while upward of 50% of military recruits have been documented as asymptomatic carriers of a pathogenic strain, the majority of carriers generally do not harbor the strain of meningococcus responsible for the disease in their midst.[142]

While carriage is responsible for the majority of disease, it is also responsible for the development of natural immunity to the meningococcus. Asymptomatic carriage and mildly symptomatic infection result in the production of protective humoral antibodies within 2 weeks, which persist at high levels for months. Immunity in the neonatal period results from transplacental transfer of humoral antibodies. In early childhood, carriage of atypical, nonpathogenic strains begins a process of recurrent sensitization and antibody production that continues throughout life.[146] These humoral antibodies are protective not only against the particular strain but also against other, but not all, strains of meningococci. Individuals who become ill generally lack effective humoral antibody against the specific pathogenic strain and become ill within the 2-week window between infection and antibody production. This explains the well-documented fact that meningococcal disease is a disease of new recruits and not seasoned service members, even when those seasoned personnel are deployed to areas of higher rates of disease. Interestingly, cases often have demonstrable, effective humoral antibody against most meningococci before infection, but it is simply not effective against the specific strain to which they succumb. To further muddy the waters, several researchers believe that induction of IgA antibody from other infections may be important in epidemic disease. This "two-bug" model postulates that induction of high levels of circulating IgA may block the action of the normally protective

humoral antibodies to the capsular polysaccharide, so that disease results from invasive strains to which the individual is "immune."[145–147]

The epidemiology of *N meningitidis* has been described as serogroup specific. The US epidemics of the first half of the 20th century were due primarily to serogroup A, as is still true in developing countries, particularly in Africa.[142] Now serogroups B and C are responsible for 90% of meningococcal disease in the United States. Serogroup C has been associated with most outbreaks in older children and young adults in developed countries, while serogroup B is responsible for the majority of endemic disease, particularly that seen in infants. In the military, meningococcal disease is a disease of training camp: it is caused by serotypes A, B, or C very early in training but after that is caused mostly by serotype B.[136,148]

Geographic Distribution

The geographic distribution of meningococcal disease, as with almost all infectious diseases, has changed significantly over the past 200 years.[149] While the Napoleonic armies were experiencing the *meningite de congelation*, essentially simultaneous epidemics were documented in Geneva, Canada, New York, Ohio, and Virginia. The 19th century then experienced a succession of epidemic waves, also retrospectively attributed by most medical historians to the meningococcus, crashing over Europe and North America. The first half of the 20th century was also marked by the propagation of several waves, generally at 5- to 10-year intervals, over the same areas. These later waves extended to include sub-Saharan Africa, now widely known as the "meningitis belt." In the second half of the 20th century, an abrupt shift in the pattern of disease occurred. Sub-Saharan Africa continued to have large epidemics, most notably in 1942 to 1951 and 1960 to 1962 and in conjunction with the hajj (the annual Islamic pilgrimage to Mecca). Meningococcal disease in the US and Europe, on the other hand, dwindled to rare endemic disease and small, sporadic outbreaks.

Incidence

For the past several decades, the annual incidence of meningococcal disease in the United States civilian population has remained in the range of 1-2/100,000, with the highest incidence of 17/100,000 found in the first year of life. Rates decline swiftly to less than 1/100,000 in the US adult civilian population.[140] The success of meningococcal vaccine use in military recruits has been striking[150] (Figure 38-5).

Case-fatality rates from invasive meningococcal disease have varied depending on the nature of the infection, the quality of the medical care, and the underlying health of those afflicted. Before any modern treatments, the mortality rate was 75% to

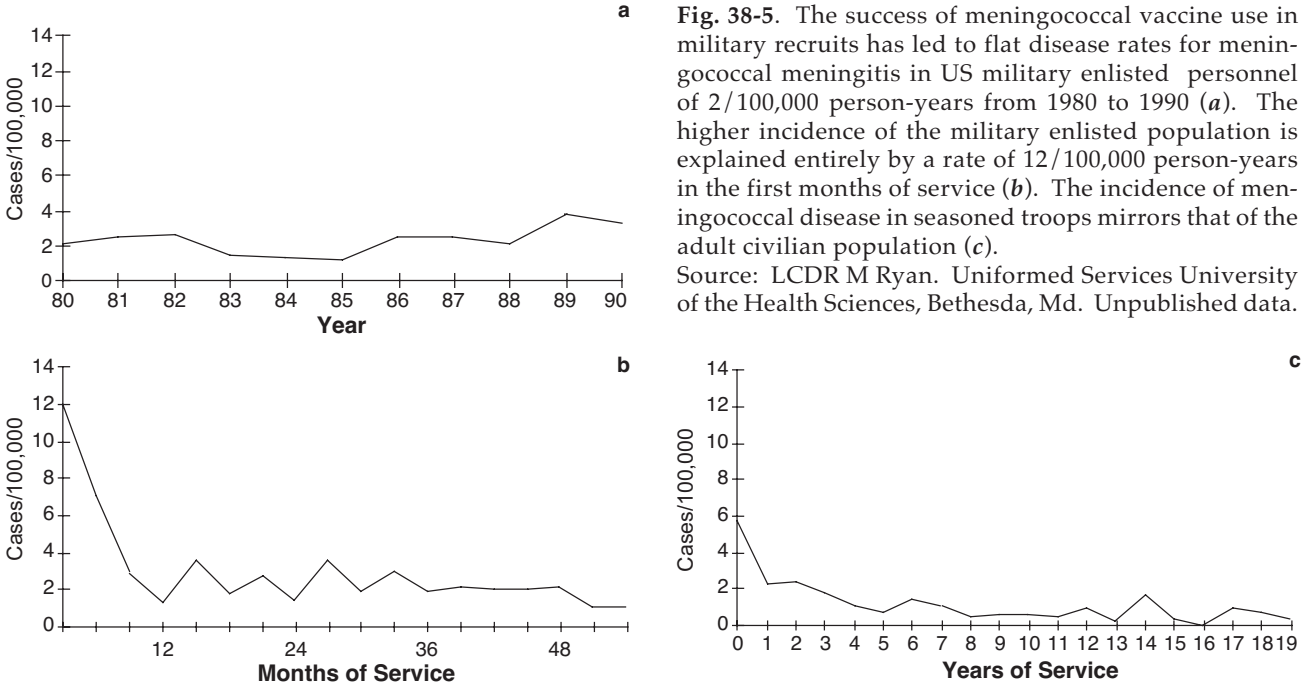

Fig. 38-5. The success of meningococcal vaccine use in military recruits has led to flat disease rates for meningococcal meningitis in US military enlisted personnel of 2/100,000 person-years from 1980 to 1990 (***a***). The higher incidence of the military enlisted population is explained entirely by a rate of 12/100,000 person-years in the first months of service (***b***). The incidence of meningococcal disease in seasoned troops mirrors that of the adult civilian population (***c***).
Source: LCDR M Ryan. Uniformed Services University of the Health Sciences, Bethesda, Md. Unpublished data.

95% or greater. In undeveloped countries and in untreated cases, similar case-fatality rates are still encountered. In the United States in the 1990s, the case fatality rate for meningococcal disease is between 10% and 15%.[140–142] Higher rates are seen in cases of meningococcemia without meningitis and at the extremes of age. As with many other infectious diseases, crowded living conditions, poor hygiene, stress, and poor nutrition are associated both with meningococcal disease and higher case-fatality rates. In addition to the groups noted above, certain other populations are more susceptible to invasive disease. Especially at risk are those with surgical or functional asplenia and those with deficiencies in the complement pathways. Cases with complement deficiencies are at increased risk for re-infection; many authors recommend testing all cases for such conditions. Also at increased risk are those with underlying chronic illnesses that decrease general immunocompetence, including but not limited to human immunodeficiency virus infection, malignancy, alcoholism, diabetes mellitus, systemic lupus, and renal or hepatic disease.[140–144] In a recent, population-based study, two thirds of all adult cases had decreased immunocompetence due to one or more of these conditions.[151]

Pathogenesis and Clinical Findings

The pathogenesis of *N meningitidis* continues to be elucidated. The organism has pilli that adhere and gain entry into the nonciliated cells found in the nasopharynx. Once inside, the organisms are able to transmigrate to the submucosal tissues and vasculature. If the organism gains access to the bloodstream, the polysaccharide capsule thwarts the normal defense mechanism of phagocytosis. In the absence of humoral antibody allowing for the opsonization and destruction of the invading meningococcus, the impressive cascade of destruction begins. The rapid doubling time of the meningococcus coupled with a process termed blebbing, where portions of the bacterium's membrane pinch off into small sacks of endotoxin, account for the organism's ability to kill in hours. The large amounts of endotoxin interact with macrophages and other defense cells to produce cytokines, vasoactive lipids, free radicals, and tissue necrosis factor. All of these substances disrupt the vascular endothelium, accounting for the rash, petechia, and purpura associated with full-blown meningococcal disease. Recent research has implicated the extremely high levels of tissue necrosis factor in the destruction of larger vessels and organs, to include Waterhouse-Friderichson syndrome, a syndrome of multi-organ failure, shock, and galloping disseminated intravascular coagulopathy (DIC).[140,142,143]

The result of meningococcal infection ranges from the trivial to the catastrophic. The majority of meningococcal infections are asymptomatic or subclinical. Significant meningococcal infection may be preceded by an unremarkable upper respiratory infection (URI) prodrome of cough, headache, and sore throat. Spontaneous resolution of mild meningococcal URIs (including those with *N meningitidis*–positive blood cultures) has been documented in distinctly fortunate individuals. With or without the prodrome, those not so fortunate may experience a violent onset of disease consisting of fevers spiking to 40°C or higher, chills, malaise, weakness, myalgias, and arthralgias. Acute systemic disease generally presents as meningitis alone, meningitis with septicemia, or septicemia alone. Very rarely (less than 5% of the time), meningococcal disease may present in a different fashion, such as an isolated sinusitis, septic arthritis, or chronic meningococcemia. In the earliest stages of the infection, the patient may appear to have an unremarkable URI (ie, headache, malaise, and slight fever—a presentation all too common to any primary care physician). In a matter of hours, however, the patient appears distinctly septic; mild hypotension to profound shock may appear early or even occur at presentation.[140–144] Unlike the mild prodrome, this striking presentation once seen is not likely to be forgotten. This extraordinarily rapid progression of disease is the reason that all new soldiers with URI symptoms and fever are hospitalized for observation by the US Army.[136]

The classic petechial rash of meningococcal disease occurs in about three fourths of those with bacteremia. The petechial rash may be present only sparingly on the conjunctiva, soft palate, axilla, groin, wrists, or ankles. Petechia may also be in areas constricted by clothing. Confusing the issue, petechia may be absent with meningococcal disease or may be present with other illnesses for different reasons (eg, on the face after violent coughing or vomiting). Additionally, the rash may begin as a fine maculopapular (morbilliform) rash and then progress to petechiae. The degree of petechial rash corresponds roughly to the degree of thrombocytopenia and severity of disease. Accordingly, petechiae that coalesce into large purpuric lesions are associated with fulminant disease. Other features indicative of a poor prognosis include shock at pre-

sentation, rapid progression of petechia to purpura, fever greater than 40°C, leukopenia, and thrombocytopenia or other evidence of DIC. Especially ominous are extensive purpura, hemorrhagic bullae, or peripheral gangrene.[140,142,143]

Diagnostic Approaches

The definitive diagnosis of meningococcal disease is made with the recovery of the meningococcus from a normally sterile site, such as blood or cerebrospinal fluid (CSF). Blood cultures are positive in about 30% of those with meningitis and 70% or more of those with clinical meningococcemia.[140] Gram's stain of the CSF of those with meningitis will demonstrate purulent CSF and the Gram-negative diplococcus. Counterimmunoelectrophoresis or latex agglutination of meningococcal antigen in the CSF, serum, or urine is routinely used, although recent authors have questioned its clinical utility.[152] Gram's stain of skin lesion aspirates and the buffy coat of blood will occasionally reveal organisms but is not recommended for routine diagnosis. Other laboratory findings may be seen that are consistent with significant bacterial infection but are not specific for meningococcal disease, such as a peripheral blood leukocytosis with increase of earlier myelocytic forms (a "left shift"). The differential diagnosis of systemic meningococcal disease is not long. Systemic infection with *Haemophilus influenza* type b or streptococcus may have similar presentations, to include presentation (rarely) with a petechial skin rash. Rocky Mountain spotted fever, other rickettsial diseases, and viral diseases with morbilliform or hemorrhagic exanthems may also present similarly to meningococcal disease.[140,142,143]

Recommendations for Therapy and Control

The successful treatment of meningococcal disease does NOT wait on a definitive diagnosis.[140,142,143,153] When the diagnosis of meningococcal disease is suspected, whether from meningeal signs, evidence of septicemia, or a febrile URI with rash in a new recruit, antibiotic therapy must follow within minutes. The presumptive diagnosis of meningococcal disease is a medical emergency. The meningococcus is sensitive to a variety of antibiotics, including penicillin, third-generation cephalosporins, choramphenicol, and quinolones. Penicillin remains the drug of choice for the treatment of meningococcal disease, despite reports of relative resistance around the world (Table 38-3). In small children, clinicians must anticipate the possibility of infection with *Haemophilus influenza* type b resistant to penicillin by their initial choice of antibiotics. The successful treatment of meningococcal disease in garrison or in the field rests on the prompt initiation of antibiotics. Sophisticated life-support techniques clearly favor recovery but do

TABLE 38-3

ANTIBIOTIC TREATMENT OF MENINGOCOCCAL DISEASE IN ADULTS

Antibiotic	Dosage
Penicillin G	300,000 U/kg-d IV in divided doses q 4 h (maximum dose $24x10^6$ U/d)
	or
Ampicillin	150-200 mg/kg-d IV in divided doses q 6 h (maximum dose 12 g/d)
	or
Chloramphenicol*	100 mg/kg-d IV in divided doses q 6 h (maximum dose 4 g/d)
	or
Ceftriaxone†	100 mg/kg-d IV in divided doses q 12 h (maximum dose 4 g/d)
	or
Cefotaxime†	200 mg/kg-d IV in divided doses q 4 h (maximum dose 12 g/d)

* For those severely allergic to penicillin
† For those mildly allergic to penicillin; also effective against *Haemophilus influenza* type b
kg-d: kilograms per day; IV: intravenously; q: every
Sources: Apicella MA. Meningococcal infections. In: Bennett JC, Plum F, eds. *Cecil Textbook of Medicine*. 20th ed. Philadelphia, Penn: W. B. Saunders; 1996: 1618–1622; Apicella MA. *Neisseria meningitidis*. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 4th ed. New York: Churchill Livingstone; 1995: 1896–1909; Griffiss JM. Meningococcal infections. In: Isselbacher KJ, Martin JB, Braunwald E, Fauci AS, Wilson JD, Kasper DL, eds. *Harrison's Principles of Internal Medicine*. 13th ed. New York: McGraw-Hill, Inc.; 1994: 641–644.

not justify transfer of a patient with suspected meningococcal disease to a higher level of care without first administering antibiotics. Similarly, antibiotics must not be withheld in the field in an attempt to get positive blood cultures at the next level of care. Antibiotic therapy should be continued in confirmed cases for at least 7 days or for 4 to 5 days after the patient is afebrile.

The patient should be placed in respiratory isolation for the first 24 hours of treatment, with special care given to disposal of respiratory secretions. Aside from isolation and the early initiation of appropriate antibiotics, treatment of systemic meningococcal disease is supportive and will be determined by the level of sophistication of the treatment facility. Fluid resuscitation, fluid and electrolyte balance, oxygenation, and maintenance of visceral perfusion are frequent concerns. The treatment of DIC, when diagnosed, remains controversial; heparin, whole blood, cryoprecipitate, or any combination of these three have been employed with varying degrees of success. Lastly, the patient discharged after successful treatment should receive rifampin chemoprophylaxis, as intravenous antibiotics may not eliminate nasopharyngeal carriage.[140,142,143]

After the end of World War II, the US military instituted the mass use of prophylactic sulfonamides to eliminate nasopharyngeal carriage in all basic trainees. This program was quite successful in military and civilian settings for almost 2 decades until this widespread use of antibiotics lead to sulfonamide-resistant meningococci. Large outbreaks at US Army and Navy training camps in the early 1960s forced not only the temporary closure of bases but also intensive research into vaccine development.[136–138] Using the polysaccharide coats as antigens, the Walter Reed Army Institute of Research produced effective vaccines against serogroup C in 1969. In 1971, routine immunization against serogroup C was begun; other serogroups soon followed (A/C in 1978 and A/C/Y/W-135 in 1982). After the initiation of these immunizations, rates of meningococcal disease in the military fell drastically, approaching those of the civilian population (1-2/100,000)[136] (see Figure 38-5). In contrast to the success with other serogroups, an effective vaccine against *N meningitidis* serogroup B has not yet been approved for use. Interestingly, the serogroup B polysaccharide is identical in structure to a polysaccharide found in human nervous tissue and therefore is not immunogenic. Current research in this area has included using protein components of the organism's outer membrane as antigens and attempting to find similar capsular polysaccharide antigens that might confer protection against serogroup B.[140,142,154,155]

The meningococcal vaccine is a success when given to recruits on entry to military service. What remains unclear is when, if ever, the vaccine should be repeated. As noted above, meningococcal disease has historically been a disease of training camps and not a problem for seasoned personnel even in areas of increased endemic disease. It is difficult, however, for a military medical officer to withhold a safe, proven vaccine from personnel deploying to an area with a documented epidemic of meningococcal disease. The most significant question—the duration of protection from the meningococcal vaccine—has not been answered. Several studies have demonstrated poor immunogenicity and rapid decline of detectable antibodies in children less than 4 years of age. A cross-sectional study among US Air Force personnel suggested detection of vaccine-induced antibody above prevaccination levels 10 years after immunization,[143,156] but measurement of antibody is a surrogate measurement for immunity and not infallible. Due to this and issues discussed above (eg, cases having demonstrable antibody against meningococcus before infection, the natural immunizing effect of carriage unrelated to vaccination), the actual duration of protection from meningococcal vaccine is likely to remain unknown for some time. The US military has generally erred on the side of being conservative by re-immunizing at 3- to 5-year intervals in the event of deployment to areas with documented epidemic disease. This strategy is not universal, however, as is demonstrated by the Navy's decision to forgo immunization of Marines deploying to the Persian Gulf War.[157] As with other polysaccharide vaccines, there is no immunologic memory leading to a booster effect with subsequent immunizations. Clear indications for immunization include military recruits on entry to training, patients with functional or surgical asplenia, and those with deficiencies of the complement pathways.

After the remarkable success of prophylactic sulfonamides ended, attention quickly turned to finding other effective prophylactic regimens. Rifampin was found to eliminate nasopharyngeal carriage and quickly became the drug of choice for chemoprophylaxis (Table 38-4). Rifampin use is not without its problems, however, and patients must be told to expect reddish-orange discoloration of urine, tears, feces, and sputum. Although harmless, the discoloration of tears will permanently stain soft contact lenses. More importantly, rifampin may interfere with the action of oral contraceptives. Sexu-

TABLE 38-4

PROPHYLACTIC CHEMOTHERAPY OF *NEISSERIA MENINGITIDIS* CONTACTS

Antibiotic	Dose
Rifampin	Adults: 600 mg po bid for 2 d
	Children > 1 mo: 10 mg/kg-d; divided doses po bid for 2 d
	Children < 1 mo: 5 mg/kg-d; divided doses po bid for 2 d
	OR
Ciprofloxacin	Adults: 500 mg po (single dose)
	OR
Ceftriaxone	Adults: 250 mg IM (single dose)
	Children < 15 y: 125 mg IM (single dose)
	OR
Sulfadiazine*	Adults: 1 g po q 12 h for 2 d
	Children > 2 mos: 150 mg/kg-d (not to exceed adult dose) in divided doses q 12 h for 2 d

* For use against documented sulfa-susceptible strains only; no longer manufactured in the United States

bid: two times a day, po: by mouth, kg-d: kilograms per day, q: every, IM: intramuscularly

Sources: Apicella MA. Meningococcal infections. In: Bennett JC, Plum F, eds. *Cecil Textbook of Medicine*. 20th ed. Philadelphia, Penn: W. B. Saunders; 1996: 1618–1622; Apicella MA. *Neisseria meningitidis*. In: Mandell GL, Bennett JE, Dolin R, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 4th ed. New York: Churchill Livingstone; 1995: 1896–1909; Griffiss JM. Meningococcal infections. In: Isselbacher KJ, Martin JB, Braunwald E, Fauci AS, Wilson JD, Kasper DL, eds. *Harrison's Principles of Internal Medicine*. 13th ed. New York: McGraw-Hill, Inc.; 1994: 641–644.

ally active patients must be advised to take appropriate precautions. Unlike the sulfonamides, which may still be used in mass prophylactic campaigns against susceptible organisms, rifampin has been associated with the rapid appearance of resistant organisms and is not recommended for mass chemoprophylaxis. Ciprofloxacin and ceftriaxone may also be used for chemoprophylaxis; they share the advantage of requiring only a single dose.[140–142]

Meningococcal infection can kill a previously healthy young adult within hours of the first symptom and, in an outbreak, do this several times in the community within a few days. These qualities combine to produce a disease that truly can terrify the public. The preventive medicine officer must be informed immediately of the admission of a suspected case of meningococcal disease. Close contacts of the case, defined as household contacts and those with direct, face-to-face contact with the case, suffer an increased risk of disease several hundred times that of the general population and should receive chemoprophylaxis. An exception to this somewhat restrictive recommendation concerns children in daycare and institutionalized persons, to include military recruits. Persons in these particular high-risk groups should receive prophylaxsis for even minimal contact, (eg, being present in the same daycare facility or sleeping in the same open-bay barracks).[144] Many authors recommend simultaneous immunization if the outbreak is due to a vaccine-preventable serogroup.[140,142,143] Because of the poor immunogenicity in young children, serogroup C vaccine is not recommended for those under the age of 2 years. Factors associated with increased disease, (eg, overcrowding, poor nutrition) should be remedied if possible. Investigation of the outbreak is limited to identifying contacts for chemoprophylaxis, alleviating factors associated with disease, and encouraging vigilance for the first sign of possible meningococcal disease. Screening the population using throat or nasopharyngeal cultures has not proven effective in controlling outbreaks.[144]

The public health emphasis in controlling meningococcal outbreaks should be placed on active surveillance, heightened awareness, prompt diagnosis and treatment of those ill, and effective communication to the public. The public health official must carefully convey an accurate assessment of risk to groups with varying degrees of medical sophistication. The goal is to motivate these groups sufficiently to ensure appropriate identification of contacts and heightened awareness of the early symptoms of disease without starting a panic. This being said, it is extraordinarily difficult to contain the fear in a community struck by several cases of meningococcal disease. An experience in Canada underscored again the sensitive nature of the issues in meningococcal outbreaks. In response to an outbreak in Ontario in 1991, a mass voluntary immunization campaign resulted in over 400,000 immunizations at a cost of at least US $7,000,000. Over 145,000 young adults were immunized in Ottawa alone less than a month after the first case. Debate continued for years in the medical literature as to whether the media coverage of the outbreak and the immunization campaign it engendered were appropriate.[158]

[Brian Feighner, MD, MPH]

TUBERCULOSIS

Introduction and Military Relevance

Understanding and controlling the risks posed by tuberculosis to the health of US military forces remain as relevant today as they were to preventive medicine specialists during World War I and World War II. Recruits continue to enter military service with preexisting tuberculosis infections. Military deployments and long-term assignments to regions of the world with high rates of tuberculosis infection and disease in the host population place US military personnel at increased risk for acquiring a tuberculosis infection, potentially with a multidrug-resistant organism. Militarily unique environments, such as ships and barracks, put large numbers of people together in close living and working arrangements for extended periods of time—ideal conditions for person-to-person transmission of tuberculosis. War and operations other than war, especially those requiring support for refugees, displaced persons, and prisoners of war, increase the risk for exposure to tuberculosis while requiring knowledge of tuberculosis treatment and control measures unique to those populations.

As early as 1854, tuberculosis (or phythisis pulmonalis) was recognized as a particular problem of shipboard life in the Navy.[159] During the US Civil War, the Army experienced 13,499 tuberculosis hospitalizations and 5,286 tuberculosis deaths among white soldiers, but control and treatment measures received no specific attention.[160] The Navy and Marine Corps had annual tuberculosis admission rates of 6 to 12 per 1,000 members in the 1880s.[159] By the early 1900s, the military services began to stress physical examinations as the main control measure to identify men with tuberculosis and to exclude them from military service. More than 50,000 men were excluded from Army service during World War I, yet more than 2,000 soldiers died from tuberculosis and 19 per 1,000 were hospitalized annually with tuberculosis.[161] Tuberculosis was the Army's leading cause of discharge for disability. During the war, the naval services' hospital admission rate was approximately 5 cases per 1,000 per year.[159]

Tuberculosis among military entrants remained a problem at the start of World War II. To improve tuberculosis screening of entrants, the military services had installed radiographic equipment to perform chest roentgen examinations or photofluorograms at many recruit centers in the months before the war. By the end of 1942, chest radiographs became a required part of the entrance physical examination, resulting in 1% of Army recruits being rejected for tuberculosis. During the war, the annual incidence of tuberculosis was 1.0 to 1.75 per 1,000 in the Army and 1.0 to 3.25 per 1,000 in the Navy and Marine Corps, with the higher rates occurring at the beginning and end of the war.[159,161] The higher rates at the war's end were primarily due to universal chest radiographs upon discharge, which identified many new cases of minimally active tuberculosis. While soldiers with foreign service had slightly higher rates of tuberculosis at separation processing, most new infections were probably due to exposure to fellow soldiers, not to civilians, with tuberculosis. Among US service members who had been prisoners of war, rates of active tuberculosis were 37 per 1,000 prisoners of the Japanese and 6 per 1,000 prisoners of the Germans. At the war's end, tuberculosis among displaced persons and civilians liberated from concentration camps in Germany, Italy, and Japan presented a significant challenge to military medicine[161] (see Chapter 3 ,The Historic Role of Military Preventive Medicine and Public Health in US Armies of Occupation and Military Government). Several Army hospitals in Germany were designated for the treatment of tuberculosis patients, while tuberculosis control programs were part of the efforts to rebuild public health infrastructures.

By 1950, routine chest radiographs of active duty members and tuberculin tests for all recruits were common practice in all services. Annual tuberculosis admission rates dropped below 1 per 1,000 sailors and Marines.[159] During the Korean War, however, 2.6% of Army casualties evacuated to the United States for care required treatment for tuberculosis. The rate of active tuberculosis among US service members who had been prisoners of the North Koreans was 1.5%.[162]

In Vietnam, US personnel had varying degrees of contact with a civilian population with a high rate of infection and disease. Almost 50% of 17- to 18-year-old Vietnamese and nearly all Vietnamese adults had tuberculin test evidence of infection; one study showed 32% of adults had radiological evidence of active infection. US military personnel experienced rates of tuberculin test conversion of 3% to 5% after 1-year assignments in Vietnam, while personnel remaining in the United States had a 1% per year conversion rate.[160]

Since World War II, there has been a downward trend in the proportion of military entrants with

preexisting tuberculosis infection. A study of 1.2 million US Navy recruits from 1958 to 1969 demonstrated that 5.2% were tuberculin test reactors.[163] Among all Air Force recruits in 1964 and 1965, 4.2% were reactors using a multiple puncture test.[164] By 1990, 2.5% of 2,416 Navy recruits were tuberculin reactors with a 10-mm induration; 19.2% of foreign-born recruits and 1.6% of recruits born in the United States were reactors with 10-mm or greater induration.[165]

In the past decade, tuberculosis has maintained a low but ever-present profile in the US military. In the 1980s, an estimated 1% of sailors and Marines converted on their tuberculin tests each year.[166] Sailors participating in deployments in 1986 and 1987 involving numerous port visits in South America were diagnosed with active tuberculosis at a rate of one case per 1,000 person-years and had rates of tuberculin test reactions three times greater than the rate among sailors on other Atlantic Fleet ships.[167] Tuberculosis exposure was a concern for military personnel of all services involved in the care of refugees and displaced persons in the Caribbean region, Africa, and Southeast Asia. During 1995, approximately 40 cases of tuberculosis were reported in active duty US military personnel (Army data: Army Medical Surveillance Activity, Washington, DC; Navy data: Naval Environmental Health Center, Norfolk, Virginia; Air Force data: Armstrong Laboratories, Brooks Air Force Base, Texas).

Tuberculosis has presented a special challenge in the closed environments on ships. The most notable outbreak occurred on the destroyer USS Richard E. Byrd in 1966.[168,169] A sailor with symptomatic cavitary tuberculosis was on the ship for 6 months until he was diagnosed. There were seven secondary cases of pulmonary tuberculosis; 47% of the enlisted crew converted on their tuberculin test reactions. In 1987, a similar scenario on an amphibious ship resulted in 216 tuberculin test converters, 25% of the total crew.[170] In these shipboard outbreaks, the highest rates of tuberculin test conversion (more than 80%) were in those sailors who berthed in the same compartments as the source case.[169,170] A 1998 outbreak on an amphibious ship produced 17 cases of pulmonary or pleural tuberculosis, 171 (18.3%) tuberculin test convertors among the ship's crew, and 525 (25.2%) convertors among embared Marines.[171] Frequently, the risk extends to the entire crew because of the closed shipboard environment and the extended exposure associated with duty at sea, which equals or exceeds that experienced by most household contacts of tuberculosis cases ashore. Exposure on shore to tuberculosis is much less intensive, but an outbreak has been documented at an isolated Army installation.[172]

Description of the Pathogen

In humans, chronic tuberculosis infection of the lungs and other organs is caused by *Mycobacterium tuberculosis* and less commonly by *M bovis*, which causes similar infections in cattle. *M tuberculosis* is a slow-growing, nonmotile bacillus, whose waxy cell wall resists decolorization by acid alcohol during staining, resulting in its "acid fast" characteristic. The waxy coat allows *M tuberculosis* to resist drying and germicides. Mycobacteria are susceptible to moist heat and ultraviolet light from both sunlight and artificial sources.

Epidemiology

Transmission

Exposure to airborne *M tuberculosis* from a person with pulmonary or laryngeal tuberculosis is the primary mode of transmission of tuberculosis. Droplet nuclei (1-5 μm diameter), produced when the infected person coughs, sings, or sneezes, dry and can remain airborne for several hours or longer. When inhaled, droplet nuclei can be carried directly to the alveoli of the lungs, where the primary infection is established. The incubation period from infection to either development of a reactive tuberculin test or evidence of a primary pulmonary lesion is 4 to 12 weeks. Unpasteurized milk can serve as the vehicle for transmission of *M bovis* from infected cows to humans.

Tuberculosis is not a highly communicable infection, but the factors affecting its spread from one person to another vary and can create localized outbreaks. Generally, only patients with pulmonary or laryngeal tuberculosis will spread infection. Communicability increases if the source case is coughing, sneezing, or singing. The presence of acid fast bacilli in sputum and cavitary disease increase communicability. Other factors include the length of time the patient has been symptomatic (especially coughing) before diagnosis, the closeness and duration of contact, and the ventilation and other environmental features of the contact space. In the United States, approximately one fifth of close contacts of a source case with active pulmonary tuberculosis will acquire a new tuberculosis infection from the exposure. Adequate treatment rapidly reduces the infectiousness of tuberculosis patients.

Geographic Distribution

Worldwide, tuberculosis causes 3 million deaths annually and is the leading cause of death among

adults from a single infectious agent.[173] In 1990, there were an estimated 7.5 million cases of tuberculosis worldwide.[174] Two billion people—one third of the world's population—are infected with *Mycobacterium tuberculosis*.[173]

Incidence

Tuberculosis incidence in the United States declined to 7.4 cases per 100,000 population in 1997, the lowest rate since national surveillance began in the 1930s, but this still represents almost 20,000 new tuberculosis cases. An increasing proportion of cases (39%) was among foreign-born persons. Resistance of *M tuberculosis* isolates to isoniazid or rifampin (two first-line drugs in the treatment of tuberculosis) increased; 7.6% were resistant to at least isoniazid and 1.3% were resistant to at least isoniazid and rifampin.[175]

Pathogenesis and Clinical Findings

After inhalation, *M tuberculosis* bacilli are carried to the alveoli where they are ingested by alveolar macrophages and eventually transported to hilar lymph nodes. Most primary infections are asymptomatic, although some patients present with a primary tuberculosis pneumonia or pleurisy with effusion a few weeks after their initial infection. Once tuberculosis infection is established, the lifetime risk of developing active disease is about 5% to 10%, with the greatest risk (1% to 4%) occurring in the first year after acquiring infection. Preventive therapy significantly reduces but does not eliminate the risk of developing active disease. For more than 90% of persons infected with *M tuberculosis*, the only evidence of tuberculosis will be a reactive tuberculin test and occasionally radiographic evidence of a primary pulmonary infection, such as parenchymal scarring or calcified lymph nodes.

Reactivation tuberculosis, most commonly confined to the lungs, occurs months to years after the primary infection in up to 10% of persons with tuberculosis infections. The risk of reactivation increases in persons with immunocompromising conditions, such as human immunodeficiency virus (HIV) infection, and in those taking immunosuppressive medications. The most common presentation is one of chronic systemic and pulmonary symptoms and findings. Infiltrates and single or multiple cavities, most commonly in the upper lobes, are present on chest radiographs (Figure 38-6). Extrapulmonary presentations of tuberculosis include tuberculosis adenitis, genitourinary infection, skeletal tuberculosis, and meningitis. Miliary tuberculosis involving multiple organs presents as a febrile wasting disease of unknown origin. Pulmonary and extrapulmonary tuberculosis are acquired immunodeficiency syndrome–defining diagnoses in HIV-infected persons.

Diagnostic Approaches

Awareness

The best tool for diagnosing tuberculosis is a high index of suspicion. Failure to suspect tuberculosis even after multiple visits to military sick call has contributed to delays in diagnosis and higher rates of new tuberculosis infections among contacts in military outbreaks.[169,170] Pulmonary tuberculosis should be suspected in per-

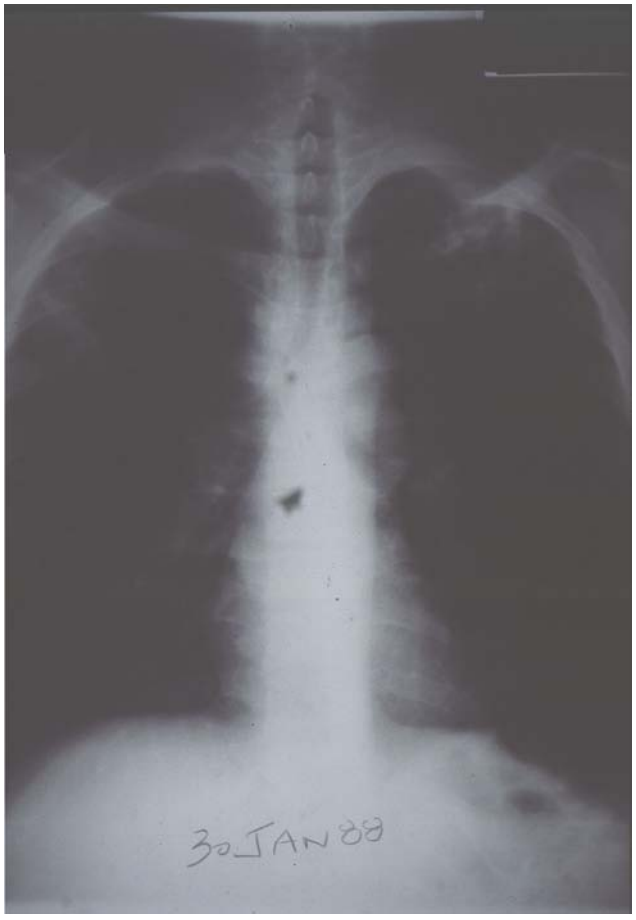

Fig. 38-6. This chest radiograph demonstrates cavitary disease characteristic of pulmonary tuberculosis. Radiograph: Courtesy of the Walter Reed Army Medical Center, Washington, DC.

sons with a productive, prolonged cough (of more than 3 weeks' duration) or in persons with fever, chills, night sweats, easy fatigability, loss of appetite, weight loss, or hemoptysis. Diagnostic suspicion should increase for persons with a history of exposure to tuberculosis or of a positive tuberculin test, persons born in foreign countries with a high incidence of tuberculosis, or persons in other high-risk groups for tuberculosis. The evaluation should include a thorough history, physical examination, chest radiograph, tuberculin test, and HIV test. A positive finding on either the tuberculin test or chest radiograph is not diagnostic of tuberculosis, while no reaction to a tuberculin test or a normal chest radiograph does not exclude a diagnosis of tuberculosis.

Culture

Demonstration of mycobacteria in sputum or another specimen is necessary to diagnose tuberculosis; a confirmed diagnosis is only possible with a positive culture for *M tuberculosis.* Smears of sputum and other specimens should be stained and examined for acid-fast bacilli. Culture examination and confirmation of *M tuberculosis* may take 3 to 6 weeks. Initial isolates on all patients should be tested for drug susceptibility.

Radiometric methods and genetic probes provide more rapid confirmation of specific mycobacteria growing in culture. To provide earlier confirmation of tuberculosis disease, enzyme-linked immuno-sorbent assays, radioimmunoassays, and chemical detection methods are being developed to identify mycobacterial antigens and other cellular products in cerebrospinal fluid, sera, and other clinical specimens.[176,177]

Tuberculin Test

A tuberculin test is the only method available to identify persons infected with *M tuberculosis* in the absence of active disease. The Mantoux method involves an intradermal injection of 0.1 mL (5 tuberculin units) of purified protein derivative tuberculin into the surface of the forearm. The injection should create a discrete wheal of the skin 6 to 10 mm in diameter. A tuberculin test is read on the second or third day after administration by measuring the diameter of induration (not erythema) transversely to the axis of the forearm and recording the measurement in millimeters. Tuberculin tests should not be administered using a jet injector.[178] While the multiple-puncture device for administering tuberculin may be useful in screening large, low-risk populations (eg, children in low-risk communities), routine screening of such populations and use of multiple-puncture devices are discouraged.[179,180] The Mantoux method is the best method for testing military service members, health care workers, and others who will have serial screenings and for evaluating patients and contacts for evidence of tuberculosis infection. Repeat testing of uninfected persons does not sensitize them to tuberculin.[179]

Interpretation of a person's tuberculin test reaction requires combining the size of the induration with the person's risk-group information.[179,181] The most common "positive" tuberculin test reactions in a military population are:

- a tuberculin test reaction of 5 mm or larger in a person who had close contact with a patient with infectious tuberculosis,
- a tuberculin test conversion (evidence of a new infection) of a 10 mm or larger increase from the baseline tuberculin test within a 2- or 3-year period,
- a tuberculin test reaction of 10 mm or larger in foreign-born persons from countries with high prevalence rates of tuberculosis (eg, countries in Asia, Africa, Eastern Europe, and Latin America) or members of high-risk minorities, and
- a tuberculin test reaction of 15 mm or larger in any person (Table 38-5).

Those infected with *M tuberculosis* may have no reaction to a tuberculin test if they have been infected within the previous 4 to 12 weeks or if their cell-mediated immunity is suppressed.

A positive tuberculin test reaction in a person vaccinated with Bacillus of Calmette and Guérin (BCG) vaccine usually indicates infection with *M tuberculosis*. Many countries with a high prevalence of tuberculosis vaccinate infants with BCG vaccine.[179,181] While BCG vaccine is effective in preventing tuberculosis disease such as meningitis in children, its effectiveness in preventing infection and disease in adults is debatable.[181] BCG vaccine status generally should be ignored in evaluating persons for tuberculosis or in interpreting tuberculin test reactions.[179]

False-positive and false-negative tuberculin reactions can occur from improper administration or reading of the test (eg, reading erythema rather than induration, leading to a false positive; injecting too little tuberculin or injecting it subcutaneously, leading to a false negative). The most common cause of

TABLE 38-5

INDICATIONS FOR PREVENTIVE THERAPY FOR TUBERCULOSIS INFECTION

Risk Factor		Tuberculin Reaction Size (mm) Threshold
Highest Risk	Young child (< 5 y of age) who has had a recent contact with a tuberculosis-infected person*	0
	Immunosuppressed person with recent contact with a tuberculosis-infected person*	0
	Recent close contact with known tuberculosis-infected person	5
	HIV infection (known or suspected)†	5
	Old tuberculosis on chest radiograph	5
Increased Risk	Intravenous drug users	10
	Patients with predisposing medical condition‡	10
	Recent immigrants (within the last 5 y) from high-prevalence countries	10
	Medically underserved, low-income populations	10
	Residents of chronic care and correctional facilities	10
	Tuberculin test conversion within last 2 years	10
	Children younger than 4 y of age	10
	Infants, children, and adolescents exposed to adults in the highest risk categories	10
No Risk Factor		15

* Treat presumptively until repeat test
† If anergic, treat if probability of tuberculosis infection is high
‡ Diabetes mellitus, conditions requiring prolonged, high-dose corticosteroid therapy and other immunosuppressive therapy, chronic renal failure, some hematologic disorders, certain malignancies, weight loss of 10% or more of ideal body weight, silicosis, gastrectomy, jejunoileal bypass, and chronic malabsorption syndromes

Adapted from: Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR*. 2000;49(RR-6):1–54.

a physiologic false-positive reaction is a cross-reaction with the antigens of nontuberculous mycobacteria or BCG vaccine. Physiologic false-negative reactions can occur because of anergy (eg, in the immune impaired HIV-infected person) or the "booster phenomenon."[182]

The booster phenomenon may occur in anyone who receives a tuberculin test many years after acquiring their initial infection with *M tuberculosis* or another mycobacteria or after receiving BCG vaccine. Although the reaction to the initial tuberculin test is interpreted as negative, the tuberculin antigen stimulates recall of delayed hypersensitivity to mycobacteria. A subsequent tuberculin test produces an induration of increased size (a boosted response) that may be interpreted falsely as evidence of a new infection. Use of a two-step Mantoux test is one solution to the booster phenomenon, especially in persons who will be tested periodically as part of a tuberculosis surveillance program.[182] A first tuberculin test is administered. If it is negative, a second tuberculin test is administered 1 week later. If the second test is positive, it represents a "boosted" reaction; if negative, the person is considered uninfected. The result of the second test becomes the baseline for comparison during subsequent testing. At present, the military services are not using two-step testing for recruits. Military populations with a higher risk of acquiring tuberculosis infection, such as health care workers or inmates and staff of military prisons, may benefit from two-step testing when beginning a serial screening program.

Recommendations for Therapy and Control

Drug-resistant and multidrug-resistant tuberculosis is an emerging problem in the United States and worldwide.[173–175] Tuberculosis in a military patient, especially one who is deployed, presents a challenge. Because of the characteristics of military service, potential drug-resistance patterns for the patient's isolates may not be inferred from the resistance patterns in the local population. Every attempt must be made to obtain adequate samples for culture and drug susceptibility testing before treatment is begun. Because tuberculosis is a chronic infection, it is reasonable to defer treatment (especially with an inadequate drug regimen) until the patient can be transferred to a medical treatment facility with the capabilities to collect specimens for culture and drug susceptibility testing and with the antimycobacterial agents required for an optimal drug regimen.

Therapy

For the initial, empiric treatment of tuberculosis, the preferred regimen in 1998 is four drugs: isoniazid, rifampin, pyrazinamide, and either streptomycin or ethambutol. For the first 2 months or until drug sensitivities are known, a four-drug regimen almost always guarantees that the organism will face at least two agents to which it is susceptible. This approach reduces the opportunity for the organism to develop any or any further drug resistance. Treatment continues for a minimum of 6 months with a minimum of two drugs, usually isoniazid and rifampin, if the organism is proven to be susceptible to all agents. If a patient's organism displays or develops drug resistance, the results of initial and follow-up cultures and sensitivities must determine the optimal drug regimen for each patient. A patient should always be receiving at least two drugs to which the organism is susceptible.[181,183] If the organism is resistant to isoniazid or rifampin or the treatment regimen does not contain either drug, treatment should continue for 18 to 24 months. Directly observed therapy, daily initially and eventually two to three times per week, for 6-month treatment courses is strongly recommended by the World Health Organization and the Centers for Disease Control and Prevention (CDC). Directly observed therapy improves compliance, increases the completion rate for full treatment courses, and slows the development of drug-resistant organisms.[173,181,183]

Patients should be seen at least monthly for an evaluation of their response to treatment, compliance with their drug regimen, and symptoms of adverse effects. The common adverse effects of the frequently used antituberculosis agents include:

- isoniazid—hepatotoxicity and pyridoxine-associated peripheral neuropathy,
- rifampin—gastrointestinal upset and accelerated clearance of other drugs through hepatitic microsomal enzyme induction,
- pyrazinamide—hepatotoxicity and hyperuricemia,
- ethambutol—retrobulbar neuritis, and
- streptomycin—ototoxicity.[181]

At a minimum, patients require these baseline tests: liver enzymes, bilirubin, creatinine, and complete blood and platelet count. Patients taking ethambutol require baseline tests for visual acuity and red-green color perception. If baseline results are normal, routine monitoring is not required.[181] Subsequent evaluations and monitoring are guided by symptoms, clinical assessments, and any coexistent risk factors.

A patient with suspected pulmonary or laryngeal tuberculosis should be placed in tuberculosis isolation in a private room with appropriate ventilation and other engineering controls, such as negative pressure in the room and adjoining hallways, ventilation providing at least six air changes per hour, and air exhausted directly to the outside or recirculated only after HEPA (high-efficiency particulate air) filtration. The patient should remain in the isolation room with the door closed and should cover his or her mouth and nose with a tissue when coughing or sneezing. Health care providers and visitors should wear respiratory protection when entering the isolation room. In field settings and operational environments, isolation rooms and procedures should be established as much as possible. Increasing natural ventilation and exposing patient spaces to natural ultraviolet light (sunlight) can help dilute airborne droplet nuclei and reduce the infectiousness of *M tuberculosis* in the air.[184] If a tuberculosis patient must leave the isolation room, the patient should wear a surgical mask covering the nose and mouth; attendants and other staff do not need to wear masks. Patient movements should be scheduled to minimize contact with other patients, staff, and visitors.

After a treatment regimen is begun, most patients who are infected with a drug-susceptible organisms will become noninfectious within days to a few weeks. Indications of reduced infectiousness include decreased cough, fewer acid-fast bacilli on sputum smears, and improvement in systemic signs and symptoms. The risk of transmission is low if the patient has had three negative smears of sputum collected on three separate days. Patients who remain infectious may return home and resume normal activities if their degree of infectiousness is low, ongoing contacts (eg, in the household or workplace) have already been exposed and are being monitored, and the environment is not conducive to transmission (eg, outdoors rather than indoors).[184]

If a patient with symptomatic pulmonary or laryngeal tuberculosis must be moved to another medical treatment facility, the patient should wear a surgical mask. Ground transportation is preferred; transmission of tuberculosis from a highly infectious passenger to other passengers and flight crew has been documented during a long airplane flight.[185] If air transportation is necessary, use of a rotary-wing aircraft with open doors provides excellent cabin ventilation. Transportation in fix-winged, pressurized aircraft should be avoided if

possible until adequate antimycobacterial treatment has been instituted. When a symptomatic tuberculosis patient must travel by air, aircraft routing should minimize the flight time and the patient should be seated to limit contact with other passengers and crew and, if possible, be downstream in the cabin ventilation flow.

Control

Screening for tuberculosis infection in US military populations is done for several purposes. Recruits receive tuberculin tests when they arrive at recruit training for two purposes: (1) to identify the recruits with preexisting tuberculosis infection and then provide appropriate preventive therapy and (2) to establish for all recruits a baseline test result for comparison with tuberculin tests later during military service. Recruits with reactive tuberculin tests receive chest radiographs and clinical evaluations, which periodically lead to a diagnosis of active tuberculosis. Subsequent tuberculosis screening varies among and within the services. Because of the substantial risk of tuberculosis transmission in the shipboard environment, the Navy and Marine Corps require annual tuberculin testing for personnel on ships and for those assigned to deployable units. For all services, screening before and after deployments and overseas assignments is a common practice. The medical plan for an operation usually dictates the tuberculosis screening requirements based on the endemic disease threat and the nature of the military operations. A tuberculin test within 12 months of deployment is adequate for establishing the predeployment status. A tuberculin test administered 45 to 90 days after the deployment allows service members who acquired a new tuberculosis infection during the deployment to receive preventive therapy at the earliest possible opportunity. Results of postdeployment screening provide an assessment of the military-specific risk of tuberculosis exposure associated with the deployment. All of the services require annual tuberculosis screening of health care personnel. For other health care beneficiaries, the services follow CDC recommendations for screening for tuberculosis infection in population groups that experience disease and infection rates in excess of the general population.[177,179] Foreign-born spouses and other family members from most countries in Africa, Asia, and Latin America are a high-risk group; they should be screened for tuberculosis and tuberculosis infection when they enter the military health care system or immigrate to the United States.[179] For the foreign-born person, the risk of developing active disease is highest in the first few years after arrival in the United States. In countries where tuberculosis is highly endemic, screening host-nation employees for evidence of active tuberculosis disease through tuberculin tests and chest radiograph and referring them for treatment may reduce the rate of transmission to US forces and their families.

Preventive therapy provides substantial protection against developing clinically active disease in a person infected with *M tuberculosis*—65% for a 6-month regimen with isoniazid and 70% to 90% (depending on compliance) for a 12-month regimen. The recommendations for preventive therapy and its duration vary with the person's tuberculosis risk factors, age, and size of tuberculin test reaction[179] (see Table 38-5). The two most common indications for preventive therapy of a military member are (1) close contact with a newly diagnosed infectious tuberculosis case and a tuberculin test reaction of 5 mm or larger induration and (2) recent tuberculin test converters. US Navy and Marine Corps recruits with tuberculin test reactions of 10 mm or larger receive preventive therapy (if not previously received) regardless of risk factors and age to minimize the risk of developing tuberculosis on ships.

The primary preventive treatment regimen is isoniazid daily in a dose of 300 mg (10-15 mg/kg daily for children, to a maximum dose of 300 mg/d) for 9 months. A 6-month regimen of isoniazid (at least 180 doses administered within 9 months) is also effective.[179] Children should receive 9 months of preventive therapy. The greatest barrier to effective preventive therapy is compliance,[184] which is a particular challenge in young, otherwise healthy military personnel. Directly observed therapy with twice-weekly isoniazid (15 mg/kg up to 900 mg) is an effective option to improve compliance. Preventive therapy regimens with rifampin (10 mg/kg daily, up to 600 mg/d for 4 months) or rifampin-pyrazinamide (daily for 2 months) have been shown to be acceptable alternatives for contacts of patients with isoniazid-resistant, rifampin-susceptible organisms.[179]

Before starting isoniazid preventive therapy, a history, physical evaluation, chest radiograph, and HIV test are necessary to exclude persons with current active tuberculosis, previous adequately-treated tuberculosis, previous adequately treated tuberculosis infection, or contraindications.[179] The evaluation also identifies persons requiring special precautions or monitoring. Contraindications to isoniazid preventive therapy include previous isoniazid-associated hepatitis or other severe adverse reactions and acute or unstable liver disease from

any cause. Isoniazid-induced hepatotoxicity is the major adverse effect. Older studies had found that the occurrence of hepatitis increased with age: 0.3% for those 20 to 34 years of age and 1.2%, for those 35 to 49 years of age. More recent studies have demonstrated that isoniazid is well tolerated, with a lower risk for hepatic side effects. Currently, baseline liver function tests are recommended for HIV-infected persons, pregnant women and those in the immediate postpartum period, persons with a history of liver disease, daily users of alcohol, and those at risk for chronic liver disease. Although isoniazid does not appear to harm the fetus, pregnant women should generally begin preventive therapy after delivery. Concurrent therapy with pyridoxine is indicated for persons at risk of isoniazid-associated peripheral neuropathy, pregnant women, and persons with seizure disorders.[179] The interaction of isoniazid and phenytoin requires monitoring serum levels of phenytoin.

Patients on isoniazid preventive therapy should be evaluated monthly for compliance and for signs and symptoms of active tuberculosis, hepatotoxicity, or other adverse effects.[179] Failure to keep an appointment or fill a prescription indicates noncompliance and requires a follow-up contact.[184] Unexplained or persistent anorexia, nausea, vomiting, dark urine, icterus, rash, paresthesias of the hands and feet, persistent fatigue, weakness, fever, or abdominal pain (especially right upper quadrant tenderness) should prompt an evaluation, including liver function tests. Transient, mild abnormalities of liver function tests may occur in 10% to 20% of people taking isoniazid. For persons with abnormal baseline liver function tests or at risk for hepatic disease, such as daily users of alcohol, liver functions tests should be obtained monthly during preventive therapy. Isoniazid should be stopped if the aspartate aminotransferase (AST) level is three to five times the upper limit of normal or if the patient is symptomatic and has increased liver enzymes.[179]

Tuberculosis infection without evidence of active disease is not disqualifying for military service. Persons with evidence of a tuberculosis infection (a reactive tuberculin test) but without clinical or radiographic evidence of active disease are not infectious, regardless of whether they have started, completed, or never received preventive therapy. Military service members with reactive tuberculin tests without evidence of active disease are fully deployable. Upon transfer or separation, a military service member on isoniazid preventive therapy needs counseling on the importance of continuing therapy, an adequate supply of isoniazid, and explicit instructions on reporting to the military preventive medicine service or civilian public health department on arriving at the new location. The current military preventive medicine service should contact the receiving military or civilian public health office to "hand off" the military service member and minimize the opportunities for incomplete or inadequate preventive therapy.

Active tuberculosis disease is a notifiable or reportable disease in the public health reporting systems of each service, every state, and the US Public Health Service. At the unit or local level, the local military preventive medicine service should be notified as soon as tuberculosis is suspected. The preventive medicine service will initiate and conduct a contact investigation, coordinate with the civilian health department if required, and make the required notifications to the military and civilian public health surveillance systems.

A contact investigation is essential to identify others with undiagnosed tuberculosis who require treatment for their disease and who may be a source of ongoing transmission.[184] Contact investigations allow persons who have acquired a tuberculosis infection from their exposure to the source case to be identified early and given preventive therapy. Contact investigations proceed with concentric circles of tuberculin tests and clinical assessments of contacts. Close contacts, those sharing the same household or living spaces, are investigated first. Close contacts may also include work and social contacts of the case. If the level of infection (rate of tuberculin test converters) among the close contacts exceeds that expected in the general population, the investigation should expand to the next circle of contacts—those who share the same air as the case but not as frequently or as intensely as the close contacts. The investigation expands in concentric circles until the observed rate of tuberculosis infection is no greater than that expected in the general population. Most military outbreaks start with examination of the close contacts, those who share the same berthing space, barracks room, or work space. Frequently, if that assessment confirms that transmission has occurred, it is logistically easier to conduct a mass test of the remainder of the unit (eg, the entire ship's crew) than to try to discern varying levels of exposure in a population whose living, working and social arrangements may be extensively intertwined.[169,170,172] The contact investigation of a military member with tuberculosis commonly requires close coordination with the civilian public health department to ensure that nonmilitary contacts are evaluated. Special attention is required

when children may have been exposed to a person with active pulmonary tuberculosis. Newly infected children can progress rapidly to active disease. They should immediately start preventive therapy even if their initial tuberculin test is nonreactive and continue preventive therapy for a total of 9 months unless a repeat tuberculin test at 3 months is negative.[179]

The Occupational Safety and Health Administration has issued detailed enforcement procedures and standards for workplaces with employees who are occupationally exposed to tuberculosis.[186] These standards apply to health care facilities, correctional institutions, and other settings. The CDC has issued specific guidelines for preventing the transmission of tuberculosis in health care facilities.[187]

Tuberculosis Control among Displaced Persons

Among refugees and displaced persons, tuberculosis incidence has been found to be two to three times greater than the incidence in the general population.[188] The World Health Organization estimates that 50% of refugees are infected with tuberculosis.[173] Among refugees and displaced persons, the effects of intense crowding, undernutrition, and stress from other diseases are superimposed on a preexisting high prevalence of tuberculosis infection and disease. Famine increases the rate of mortality from tuberculosis. In 1983, tuberculosis was the third leading cause of death in Somali refugee camps and was responsible for 25% of adult deaths.[188] Coinfection with HIV and drug-resistant tuberculosis organisms increases the complexity of diagnosing, treating, and controlling tuberculosis disease among refugees and displaced persons.[173,189]

In refugee populations, identifying and treating patients with pulmonary tuberculosis is the most effective strategy for preventing morbidity, mortality, and further transmission of infection. Chest radiographs rather than tuberculin tests are frequently the more effective screening method.[188,189] Treatment programs should use locally recognized regimens that can be continued by national or nongovernmental organizations. The World Health Organization strongly recommends the use of directly observed therapy with multidrug, short-course regimens to improve compliance and to achieve higher cure rates in the mobile refugee patients.[173] Documentation of therapy, compliance, and response to treatment (eg, serial smears) remains important. Control of tuberculosis among refugees will have a significant long-term effect but often competes with the more acute problems of diarrheal disease, measles, and undernutrition. Tuberculin tests and use of preventive therapy are not recommended in refugees or displaced persons. HIV-infected persons with normal chest radiographs may benefit from preventive therapy with isoniazid.[189] If consistent with national policy, BCG vaccination of newborns is appropriate but does not contribute to tuberculosis control among youth and adults.

Tuberculosis may pose a significant problem for prisoners of war subjected to extreme crowding, stress from other diseases, and undernutrition, especially if their confinement has been prolonged. The clinical evaluation of repatriated or liberated prisoners of war or detainees should include tuberculin testing and chest radiographs.

[David H. Trump, MD, MPH]

SEXUALLY TRANSMITTED DISEASES AND HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Introduction and Military Relevance

The history of sexually transmitted diseases (STDs) and military forces is a long one. Edward IV of England invaded France in 1475 to reclaim lost provinces. In a successful attempt to buy off the enemy, Louis XI of France treated the English with royal hospitality. Louis XI provided whores, who took their own special revenge on the invaders. "Many a man was lost that fell to the lust of women, who were burnt by them; and their members rotted away and they died,"[190(p223)] claims one doleful English chronicler. Sexually transmitted diseases have been associated with the US military from its earliest campaigns. In 1778, Congress passed a resolution that military personnel afflicted with "the venereal disease" were to be fined, $10.00 for officers and $4.00 for enlisted personnel.[191]

There is no evidence to suggest US military personnel in the United States are more sexually active or have a higher STD rate than their age-matched civilian contemporaries. However, when deployed or stationed overseas, rates can increase dramatically. STD rates are closely associated with the degree of military activity, as was illustrated in the European theater in World War II.[192] In England before the Normandy invasion, US military STD rates were 35-40/1,000, falling to 5/1000 after D-day among troops in France. As US forces pushed into Europe, rates rose to 50/1000 but remained at 25/1,000 among combat troops. By September 1945, 4 months after Germany surrendered, the STD rate

had risen to 190/1,000.

The Vietnam War probably provided the highest incidence of military sexual activity and STD in US forces. Sexual abstinence was statistically abnormal for unmarried personnel.[193,194] In a 1973 study on a Navy aircraft carrier, the annual rate of gonorrhea was 582/1,000 men and of nongonococcal urethritis was 459/1,000 men.[195] Although these figures reflect repeat infections in some individuals, it is sobering to consider that statistically, every crewmember had at least one case of urethritis.

Traditionally, liberty is a high-risk time for military personnel to acquire STDs. For example, during a 6-day port call in the Philippines during the Vietnam War, the average US sailor had 1.2 partners and had intercourse three times (2.5 exposures per partner). After controlling for number of exposures and partners, 8.2% of whites and 19.1% of blacks acquired gonorrhea.[196] A repeat study several years later had similar findings.[197]

Considerable anecdotal evidence indicates STD rates in the military in recent years have been far lower, less than 1% in such recent operations as Desert Shield/Desert Storm (the Persian Gulf War), Restore Hope (Somalia), Restore Democracy and Uphold Democracy (Haiti), and Sea Signal (Guantanamo Bay). In training exercises in the early 1990s, such as Cobra Gold (Thailand), rates were also reported as being down, with anecdotal reports of extensive use (or at least acquisition) of condoms. Although it is difficult to quantify this decrease, the overall conclusion that STD rates are down among military personnel overseas seems justified. Three plausible causal factors have been postulated but have no specific data to support them: (1) In some operations, such as Desert Shield/Desert Storm, interaction with the local population was severely restricted and alcohol consumption was forbidden. These restrictions were successful in reducing not just STDs but also accidents, fights, and injuries. (2) Concerted efforts to emphasize the risks of sexual activity, especially acquired immunodeficiency syndrome (AIDS), and to emphasize the use of condoms for those who insist on being sexually active seem to be working. In particular, operational medical officers report their impressions that fear of AIDS has reduced sexual activity and increased the use of condoms in areas the military population associates with AIDS, such as Africa, Haiti, and Thailand. (3) There may be a new generation of military personnel, particularly in the senior enlisted leadership positions, with a changing attitude toward sex overseas. Sexual activity, particularly with prostitutes, may no longer be as acceptable on liberty as it was during the Vietnam War.[193,194]

General Epidemiologic Issues

A discussion of the general principles of STD epidemiology will be followed by specific discussions of the STDs of military relevance. General references applicable to sexually transmitted diseases are listed in Exhibit 38-1.

Transmission

STD epidemiology is complex, and our understanding of it is rapidly changing. It is often subpopulation-specific, with age, race, and socioeconomic status being the most important determinants,[198–200]

EXHIBIT 38-1

STANDARD REFERENCES FOR SEXUALLY TRANSMITTED DISEASES

- Holmes KK, Mardh PA, Sparling PF, et al, eds. *Sexually Transmitted Diseases*. 3rd ed. New York: McGraw-Hill; 1999.
- Chin J, ed. *Control of Communicable Diseases Manual*. 17 ed. Washington, DC: American Public Health Association; 2000.
- Centers for Disease Control and Prevention. *Sexually Transmitted Diseases Clinical Practice Guidelines*. Atlanta: CDC; 1991.
- Centers for Disease Control and Prevention. Recommendations for the prevention and management of *Chlamydia trachomatis* infections, 1993. *MMWR*. 1993;42(RR-12):1–39.
- Centers for Disease Control and Prevention. 1998 guidelines for treatment of sexually transmitted diseases. *MMWR*. 1993;47(RR-1):1–128.

so pooling of STD data may obscure important differences.

In general, the epidemiology of STD differs in major respects from other communicable diseases:[201] (*a*) the populations at risk are fractions of the total community (eg, young, sexually active adults; homosexual men), (*b*) doubling the population density does not double the rate at which new infections occur, (*c*) long-term, asymptomatic carriers play an important role in perpetuating the disease, (*d*) most STDs induce no practical immunity, (*e*) the course of the infection varies greatly among individuals, and (f) STD transmission rates are characterized by considerable heterogeneity within and between different populations. These differences make STD control a uniquely challenging part of infectious disease control.

Aral and Holmes[200] point out important differences in current STD epidemiology compared to that of the classic venereal diseases: (*a*) Among educated middle- and upper-class individuals in industrialized countries, classic STDs have declined rapidly, while these same diseases have remained stable or increased among largely marginalized subpopulations, such as urban dwellers, the poor, and minorities. (*b*) Prostitution, including anonymous sex-for-drugs exchanges, has reemerged as an STD multiplier in industrialized countries. (*c*) STDs can be divided into curable bacterial STDs and incurable viral STDs, a distinction with important implications. Bacterial STD control depends on health-seeking behaviors and early diagnosis and treatment. Viral STD control depends on primary prevention through general STD education and individual counseling. (*d*) Cases of viral STDs are rapidly increasing, and reservoirs of asymptomatic viral STD cases are much larger than the number of symptomatic cases. (*e*) In developing countries, the lack of resources to identify gonorrhea and chlamydia in women make these diseases epidemiologically similar to incurable viral STDs. (*f*) And for the first time since the preantibiotic era, behavioral change is the most important STD prevention and control strategy.

Overseas deployment or liberty calls are the most important factors related to military STDs. Overseas deployments provide the opportunity for the largely single, male, young adult force to participate in inexpensive, readily available sexual activity in an atmosphere of numerous rationalizations for such activity. Service members involved in an exhausting exercise or deployment with a busy operational tempo feel they deserve a break, a chance to let off steam. Overseas sex is part of military culture and tradition, including rites of passage such as sexually initiating "virgins," the concept of the "geographic bachelor," and the unspoken understanding that what happens on deployment will not be talked about back home. For individuals not planning a military career, overseas deployments may be perceived as an opportunity to see the world and do something exotic before settling into conventional civilian life. And for some individuals, taking advantage of the opportunity simply to have sex as often as possible is an integral part of their personal culture. Fallacious as these rationalizations may be, they may be perceived as an integral part of military overseas culture and need to be considered in attempts to reduce STD rates. The traditional "VD lecture" is not likely to influence behavior originating in these rationalizations.

In its battle to reduce STD rates, the military has tried to determine personality risk factors for acquiring STDs. World War II–era studies[202–207] identified military personnel at risk for STDs as less intelligent or educated (non–high school graduate), abusers of alcohol, often in legal trouble (military or civilian), dissatisfied with military service, and immature, socially maladjusted individuals with inadequate personalities. Studies during the Vietnam War in Australian soldiers[193,208] failed to find any dominant personality type associated with STD acquisition or much difference between those with STDs and control subjects, but alcohol use remained an association, as did younger age, less education, presence of military legal charges, and unmarried status. Studies of US Navy and Marine Corps personnel in the years immediately following the Vietnam War reached similar conclusions.[195,197,209–212]

A Navy epidemiologist named Melton tied the increased rate of STDs in young military personnel to the risk-taking behavior associated with youth and manifested by problems such as traffic accidents, smoking, drug use, and especially peer pressure and alcohol use.[213] Risk markers were being black, being young (younger than 20 years old), being unmarried, having less than a high school education, being in pay grades E1 through E4, having served less than 1 year in the Navy, and being on their first cruise.[214,215] Levine and colleagues[216] identified the same risk markers, as well as performance marks 3.4 or lower (out of 4.0), a General Classification Score of 55 or lower, and a history of disciplinary actions. Some caution is required in interpreting these studies, since they were carried out in a era when Navy morale was widely considered to be less than optimal.

As one reviewer summarized, "The stereotypical picture of the military patient with an STD is that of a young, low-ranking, poorly educated,

single male, who tends to abuse alcohol and to get into legal problems and who has usually had more than one episode of an STD."[214p92] To the extent that this stereotype is valid, there is little that is unique to the military in it; the picture is similar to those seen in many urban STD clinics. Hart,[208,217] however, veers away from the stereotype, attributing the high STD rates in his Vietnam studies to frequent intercourse with a highly infected prostitute population and "the environmental stresses of a war situation [which] produced behavior patterns which many participants would not otherwise experience."[208p546] Noting that 44% of married draftees, 56% of those over age 30, and 30% of those with more than a high school education had sex with prostitutes, he concluded that "behavior which would make one an outcast at home is considered quite normal here."[194p460] Vietnam may have been unusual in the degree of sexual activity exhibited by military personnel there, but the concept that war stress may induce increased sexual activity dates from at least World War II.[202,205,206]

In the civilian world, Rothenberg introduced the concept of STD core populations—predominantly marginalized urban, dense, low socioeconomic, ethnic, minority populations—whose behavior perpetuates disease transmission among members of the core, which in turn serves as an STD reservoir for others.[218–221] These reservoirs of STD sustain high transmission rates because of high rates of changing sex partners coupled with a high rate of endemic infection. They may also be the major source of antimicrobial resistance. Sex with members of these groups by nonmembers is an important risk factor in itself and serves to export STDs out of the reservoir. US military personnel are frequently exposed to such groups when they hire commercial sex workers (CSW) during deployments. This concept of core transmitters has been refined to suggest that local social structure may act as a barrier or facilitator to disease transmission and that this variable needs to be considered in evaluating transmission.[222] Further, STD epidemics are dynamic, moving through predictable phases.[223] With time, epidemics become localized in subpopulations characterized by progressively higher rates of sex partner change and less contact with the health care system.

Individual Risk Factors and Risk Markers. It is important to distinguish between *risk factors*, which relate to the probability of becoming infected and may be modifiable, and *risk markers*, which indicate presence of risk but no causal relationship.[200,224–241] Risk factors preeminently include sexual behaviors (eg, age at first intercourse, number of partners, rate of acquiring new partners, having casual partners, sex preference, sex practices) and health care behaviors (eg, nonuse of condoms and other barriers, late consultation for diagnosis and treatment, nonreferral of partners, noncompliance with therapy, douching). Risk markers include marital status, race, urban residence, and lower socioeconomic status. Some variables can function as either risk factors or risk markers (eg, age, gender, smoking, alcohol use, drug abuse, other STDs, lack of circumcision, contraceptive method). Numerous studies have been done with higher-risk populations, such as STD clinic patients. The most important factors have repeatedly been found to be younger age at first intercourse, increased number of partners, casual choice of partners, and partners who themselves are at high risk for STD. Adolescents in particular attempt to minimize the effect of having multiple partners by practicing serial monogamy (ie, having sex with only partner at a time but frequently changing partners).

Commercial Sex Workers. CSWs (prostitutes, hookers, "hooks") are most common in settings of poverty, social disintegration, and a double standard of sexual behavior; they play a major role in the increase of STDs in developing countries.[242,243] A reporter summed up the relationship between CSWs and the US military using an example from the Philippines: "The base and the town share a seamy symbiosis. Servicemen have money and a need to relax. Olongapenos have flesh and a need to eat."[244(pD-8)] In countries such as Japan, the cost of CSWs is sufficiently high that few US military personnel can afford them, making such countries low risk for STDs. In most developing countries, however, commercial sex is both readily available and inexpensive. US military personnel in one country typically paid less than $20 for a night with a CSW (plus tip), and shorter encounters could be had for much less. In one African city, some CSWs charged only 50 cents. In 1995, CSWs in Thailand were charging $4.00.[245] Low prices greatly enhance the spread of STDs by removing cost as a disincentive, by requiring CSWs to have multiple partners to obtain enough money, and by allowing military personnel to have multiple partners.

In countries where US military personnel frequently visit, other factors enhance and promote their access to CSWs. Locations of CSWs are usually convenient to military personnel (an important consideration if liberty is short) and typically provide familiar amenities such as beer (often relatively inexpensive), music (often live, of good quality, and current), and fellow Americans (often friends). In short, the locations where CSWs are found may be familiar, relaxing, comfortable, inexpensive, and

accessible.

Unlike the stereotype of prostitutes as hard individuals, CSWs often appear to be nice, friendly, and "clean" or uninfected. However, they are usually aggressive in going after customers, motivated by the fact that this may be the only source of income for themselves and their family, which may include a husband. The CSW may have expenses in addition to food and shelter, such as clothing and grooming or money to be paid to the bar where she works. Other job opportunities are limited or nonexistent, especially for those with minimal schooling. Manaloto and colleagues[246] studied 18 Philippine prostitutes who were positive for the human immunodeficiency virus (HIV). The women were poorly educated and came from low-income agricultural families. Returning to a low-income menial job was not attractive to them and working as a waitress or barmaid presented constant temptation to make extra money by having sex with customers.

Long practice makes CSWs persistent, aggressive, and very effective at contacting military personnel and enticing them into using their services. Liaisons are set up in numerous ways. The CSW may take the initiative in approaching a serviceman. If the serviceman voices concern about STDs, the CSW (in some countries) may honestly be able to say that she has been checked for disease at the local social hygiene clinic. Such clinics play an important role in reducing the prevalence of STDs among CSWs, particularly treatable STDs, but there is a strong economic motive to appear uninfected on examination. The CSWs achieve this by douching or taking oral antibiotics (often in subtherapeutic doses),[247] which are widely available without a prescription in developing countries.

Geographic Distribution

STDs are found worldwide. There is no evidence that the virulence or infectivity of STDs varies geographically.[248] An exception may be the HIV E clade, prevalent in Southeast Asia, which appears to be more infectious than other strains.[249] Differences in prevalence and incidence reflect such factors as the presence of STD control programs, availability of diagnostic and treatment services, population demographics, sexual behaviors, and the size of core-transmitter groups. For example, gonorrhea is more common in developing countries, while chlamydial infections are more common in the United States. This reflects the presence of effective gonorrhea control programs in the United States and their lack in developing countries.[200] In selected US cities with vigorous chlamydia control programs (eg, Seattle), the number of chlamydial infections has declined.

Incidence

The World Health Organization estimates there are 250 million STD cases annually, including 120 million cases of trichomonas infection, 50 million of chlamydia infection, 30 million of genital warts, 25 million of gonorrhea, 20 million of genital herpes, 3.5 million of syphilis, 2.5 million of hepatitis B virus infection, 2 million of chancroid, and 11 million of HIV infection.[250] Such figures provide an overall perspective, but there is great variability among different countries and populations. For example, in the United States an estimated 4 million to 5 million persons are infected with chlamydia each year,[251] compared to approximately 600,000 reported gonorrhea cases.[252] In most developing countries, gonorrhea rates exceed chlamydia rates.

Except for HIV, the incidence and prevalence of STD in the military cannot be determined with satisfactory reliability. Most reporting systems are fragmented and passive, and they suffer from significant underreporting despite being officially required. Statistics from particular operations or exercises may be available, but they cannot be generalized. Military STD rates cannot be directly compared to civilian statistics because the military population is largely young, sexually active, single, and male. While the highest military STD rates occur among the lower-ranking enlisted personnel, in parallel with the civilian community's experience, there is little information about STD incidence rates among officers, warrant officers, and senior noncommissioned officers. Because these individuals are older and better educated—the most junior officer is at least 22 years old and a college graduate and the most junior enlisted person is typically an 18-year-old high school graduate—their rates would be expected to be lower. Additionally, a record of an STD is not career-enhancing; older individuals are more likely to be career oriented and so more motivated and better able to avoid sexual exposure or to keep their records clean. They may collude with medical personnel to treat an STD without entering it in their health record or to use a euphemism such as "urinary tract infection." Being better paid than lower-ranking service members, they may be able to obtain medical treatment outside the military system.

A study[253] conducted from 1989 to 1991 looked at 1,744 male US Navy and Marine Corps personnel on two 6-month cruises to South America and Africa. Overall, 10% of the subjects acquired an STD

but only 10% of those were officers. Sexual activity on liberty was independently associated with younger age (17 to 24 years), nonwhite race, and single status. Prostitute contact was reported by 42% of the subjects, with 29% having one partner, 35% having two to three partners, and 35% having four or more partners. Enlisted personnel were more likely to have had prostitute contact than officers (43% vs. 26%). Although the overall reported rate of consistent condom use was high (but not 100%), it is not surprising that 10% of the subjects acquired an STD given the high rate of risky behavior. This study is consistent with studies showing young, nonwhite, single, military personnel have the highest risk of acquiring HIV infection and other STDs.[215,216,253–260]

Diagnostic Approaches

Several tests provide immediate information, which allows a rapid presumptive diagnosis and a prompt treatment decision. This is important because the rapidity with which military personnel can be returned to duty directly and strongly influences their willingness to come for treatment and their unit's willingness to let them go and rapid diagnosis and treatment help reduce STDs by rendering patients noninfectious. Another advantage is that these are simple tests that can be carried out under field conditions. Urethral and cervical Gram stains allow for the diagnosis of gonorrhea, nongonococcal urethritis (NGU), and mucopurulent cervicitis (MPC). The presence of Gram-negative intracellular diplococci is highly specific for gonorrhea, although the sensitivity in cervicitis is low (approximately 50% to 60%). MPC can also be presumptively diagnosed by the swab test or the cervical friability test. The leukocyte esterase test (LET) is a dipstick test that detects pyuria. It has the advantage, in males, of being noninvasive—a urethral probe is not required. It has a sensitivity of 46% to 100% and a specificity of 83% to 93% as a screen for chlamydia and gonococcal urethritis in sexually active teenage males.[261] EIA (enzyme-linked immunoassay) tests and monoclonal antibody tests for chlamydia are useful but may have somewhat limited sensitivity, especially in asymptomatic individuals and in males. A negative test result does not necessarily rule out chlamydia infection in exposed individuals. Chlamydia tests may yield false-positive results in men and women, an important concern in rape and other settings. CDC guidelines[262] discuss these issues in detail.

Bacterial culture and sensitivity tests can confirm *Neisseria gonorrhoeae* infection and determine bacterial sensitivity. The latter information can be useful for individual patients in whom antibiotic treatment fails; it can also provide population-based profiles of antibiotic susceptibility in different locations. Preventive medicine personnel should periodically arrange to collect 50 to 100 gonococcal isolates in areas where US forces deploy frequently or continuously and have them tested for sensitivity to a battery of antibiotics. Busy clinics that see large numbers of infected US personnel are ideal, but samples from CSWs seen in the local social hygiene clinic are also acceptable.

Polymerase chain reaction (PCR), ligase chain reaction (LCR), and a variety of other chlamydia tests based on DNA probe technology may make many current diagnostic techniques obsolete. They have the advantage of being rapid, specific, and capable of making a diagnosis from specimens that contain minimal amounts of pathogens. Although they are rapidly moving into commercial development, most are still research tools. Technological advancements, especially if they emphasize automation and user simplicity, could make these techniques the tools of choice for STD diagnosis. Drawbacks include the fact that these techniques are extremely sensitive to contamination, which can produce false-positive results especially in field settings, and that they are expensive for routine STD diagnosis.

Serological STD tests are used to diagnose syphilis, HIV infection, and hepatitis B virus infection. Sera can easily be obtained in a field setting and are relatively tolerant of storage conditions, although refrigeration is required. Most of these tests are not useful for immediate patient management because they cannot produce prompt results. Despite the delay in obtaining the results, they are important for population-based assessments and eventually for individual patient management. The RPR test for syphilis can provide immediate results; however, it has false-positive results. It may be appropriate to treat for presumptive syphilis on the basis of an RPR result, but, when possible, it is better to wait for a confirmatory test.

Self-treatment, particularly topical antibiotics used for genital ulcers, may interfere with the diagnosis of STDs. One study of 3,025 public STD clinic patients in the United States showed that 22% of patients self-treated, with 55% of those using a topical medication.[263] Since antibiotics can be bought without a prescription in many foreign countries, the potential for this practice interfering with STD diagnoses in military personnel is even greater, especially if the individuals belong to a unit that deals with STD among its members punitively.

Recommendations for Therapy and Control

The core roles of military preventive medicine regarding STDs are listed in Exhibit 38-2. In the absence of widespread effective methods and programs to decrease STD acquisition and transmission, the major control measure is prompt treatment that renders individuals noninfectious. Three approaches to finding infected persons are available: diagnosis and treatment of symptomatic individuals, screening of high-risk individuals, and contact tracing and partner notification.

Diagnosing and Treating Symptomatic Individuals

Diagnosis and treatment of symptomatic individuals is enhanced by a syndromic approach, that is, patient management decisions are made on the basis of symptoms and limited laboratory support, enabling rapid treatment. Advantages to this approach are many. Treatment to render individuals noninfectious occurs earlier than it would if clinicians waited for definitive laboratory results. Individuals who never return for test results have nevertheless been treated and so cannot spread their infection. (More than one third of patients in one STD clinic continued to be sexually active after becoming symptomatic or being informed they had been exposed to gonorrhea.[264]) Patients also spend less time in the clinic; this encourages individuals to come to the clinic, especially those who are not severely symptomatic.

Ensuring that individuals are seen and evaluated promptly and in a private and nonjudgmental fashion is crucial. Unless highly symptomatic, individuals are often reluctant to spend several hours being evaluated, and a service member's command will want to know the reason for any extended absence. A critical recommendation by the Centers for Disease Control and Prevention is that patients with uncomplicated STDs should be seen, diagnosed, and treated within 90 minutes.[265] The patient can be brought back later for follow-up or evaluation of an abnormal laboratory test.

In most military medical settings, service members concerned they may have an STD are seen by corpsmen, physician's assistants, or nurse practitioners, who successfully manage the bulk of STD cases without the involvement of a physician. Although this is an appropriate use of medical resources, it is necessary for the physician responsible for the STD clinic to ensure these health care providers are well trained, follow appropriate algorithms and guidelines, and know to call a physician for complicated cases. Complicated cases do occur, and aberrant treatment regimens and unnecessary steps do creep in and compromise the success of the clinic. STD clinics should use the CDC guidelines[265] for patient management and treatment, unless there are specific local reasons not to do so.

Screening

Screening may use epidemiologically identified risk factors, laboratory tests, or a combination of them. Screening can be effective in comprehensive, well-integrated, highly controlled health care systems. The usefulness of this approach is limited by the fact that several currently available diagnostic tests, particularly for chlamydia, are less sensitive

EXHIBIT 38-2

ROLE OF PREVENTIVE MEDICINE IN CONTROLLING SEXUALLY TRANSMITTED DISEASES

- Prevent, reduce, or ameliorate risky behavior that may result in acquiring an STD
- Interrupt transmission of STDs by ensuring that prompt diagnosis and treatment are available
- Counsel individuals who have acquired an STD how to prevent further transmission and to notify sexual partners so they may be treated
- Carry out, or arrange to be carried out, contact tracing of the sex partners of STD patients, when possible
- Collect, analyze, and disseminate epidemiologic information regarding the incidence and prevalence of STDs, including risk factors
- Collect, analyze, and disseminate antibiotic sensitivity data for bacterial STDs

STD: sexually transmitted disease

in asymptomatic individuals and that motivation to be screened may be low if the patient is asymptomatic. Adolescent males in particular are difficult to capture with screening methods.

An STD is a marker identifying an individual who has engaged in sexually risky behavior and who may have multiple STDs from current or previous liaisons. As such, the individual with an STD should also be tested for syphilis, HIV, and HBV. The individual may have acquired one of these in the past or in conjunction with the current STD. Follow-up testing for syphilis, HIV, or HBV depends on the risk for having acquired one of these diseases and, in the case of syphilis, whether the person was treated with antibiotics that would abort incubating syphilis.

Although it has never been official policy, for many years some ships' medical departments have offered members a self-screening opportunity, a "conscience check," on the way home from a deployment. Individuals who have been sexually active but are asymptomatic can be tested for syphilis and gonorrhea in an attempt to ensure they do not infect their wives or girlfriends. The yield and efficacy of this practice have never been evaluated. With the current knowledge of a broader range of STDs, the role of this practice is even more uncertain. The conscience check carries the danger of providing false reassurance if individuals do not appreciate the lower sensitivity of some tests and the inability to test in the field for some diseases. This false reassurance may evolve into a false belief that risky sexual behavior is acceptable because the medical department can catch and treat any problems before the individual returns home.

Contact Tracing and Partner Notification

It is increasingly difficult for public health and preventive medicine authorities to maintain the old model of tracking down, evaluating, and treating sex partners, generally referred to as contact tracing. This model, based on the experience with syphilis in the 1930s and 1940s, was applied to gonorrhea; it is not clear if it was effective. In recent years, numerous epidemiologic and public health changes have limited its effectiveness. These include a burgeoning population, including increasing numbers of STD cases; decreasing personnel and fiscal support for public health in general and STD work in particular; and changes in sexual activity that often make contact tracing impossible, eg, anonymous exchanges of sex for drugs or money, sex between strangers, and increased sexual activity in general. In many areas, contact tracing of sex partners may be limited to high-risk individuals, often locally defined (eg, women of child-bearing age who have been exposed to HIV).

Contact tracing may be possible when the contacts are largely within the military system, particularly within the same unit. Foreign countries that cater to sex-seeking tourists may have local social hygiene facilities and may regulate CSWs and so may allow contact tracing. But it is not clear whether impoverished countries where sex is a major industry have ever been able to follow the US-developed model for contact tracing or have interest in doing so. Preventive medicine personnel deploying overseas need to determine if such arrangements exist in popular liberty or recreation areas and make arrangements to share with the local health authorities the identities of sex partners provided by infected US military personnel. The Department of Defense uses the standard Public Health Service form CDC 73.2936S (8/91) for sexual contact reporting, as well as any required local civilian reporting form.

Contact tracing may be stymied by the inability or unwillingness of the patient to identify sex partners, as well as by other limitations. When the patient knows and can contact his or her partners, the patient must be urged to do so, a process known as *partner notification*. The health care provider should instruct the patient to tell the partner the STD diagnosis, make clear that the partner must be assumed to be infected even if the partner has no symptoms, and instruct the partner to see a health care provider for treatment.

The next crucial step after contact tracing and partner notification is epidemiological treatment (epitreatment) of sex partners, along with prompt treatment of the patient, to reduce STD transmission. All sex partners are presumed to be infected and must be promptly treated for the same diagnosis as the patient. Cultures and other tests can be obtained as appropriate, but epitreatment must be carried out when the partner is first seen, even if the partner denies symptoms or the possibility of infection, because an infected partner may go on to infect other persons. All sex contacts of patients diagnosed as having a treatable STD must receive epitreatment, using a regimen appropriate for the diagnosis. CDC guidelines[266] recommend sex partners of patients with gonorrhea, chlamydia, or nongonococcal urethritis be notified and referred for evaluation and epitreatment if they have had sex within 60 days before the onset of their symptoms or diagnosis. If the patient's last sexual contact was more than 60 days previously, the most recent sex

partner should be notified and treated. Although epitreatment is emphasized, a thorough evaluation is also needed. In a Baltimore, Maryland, STD clinic, 23% of women attending as STD contacts had multiple STDs, compared to 10% of noncontacts.[267]

It is important for individuals diagnosed with nontreatable STD to be notified also. Some treatment options may be possible, for example, HBV vaccine may be offered to an uninfected partner. Notification also allows partners to determine their own situation (eg, to be tested for HIV) and then, after appropriate counseling, take steps to prevent their transmitting the infection to others. For herpes simplex virus, it is particularly important for women to know they have been placed at risk. If they become pregnant, it allows them to notify their obstetrician, who can then take steps to protect the baby from a devastating neonatal herpes infection.

Medical personnel counseling or managing STD cases should avoid identifying an individual as the source of the infection simply because that individual seems obvious or is suspected by the patient. This can be particularly sensitive and emotional when an STD occurs in an ostensibly monogamous relationship. The first priority is to identify and treat all contacts promptly. Determining who infected whom is a secondary consideration, preferably carried out with the help of an experienced sexual contact tracer and good knowledge of the epidemiology of the STD being traced. Failure to be careful in identifying the epidemiologic course of the infection or in avoiding premature conclusions may create difficulties and barriers to managing these cases and may result in legal problems for the medical staff if they inaccurately identify the source of the infection. Often it is more accurate and more appropriate simply to say that it cannot be determined who infected whom.

Prevention

When US military personnel are stationed or deployed overseas for a prolonged period, US preventive medicine personnel should try to establish an effective working relationship with local public health authorities to reduce the prevalence of STD in the core groups of transmitters, such as CSWs. The US Navy in the Philippines worked closely with the Social Hygiene Department of Olongapo City, next to the Subic Bay Naval Base, and provided technical and consultative assistance, antibiotics, and laboratory support. Gonorrhea among registered CSWs, who were examined and treated at the Social Hygiene Department clinic every other week, had an incidence rate of 4%.[197] In contrast, unregistered CSWs, who were beyond the control of the department, had a gonorrhea rate of 40%. US Air Force personnel at nearby Clark Air Base similarly worked closely with the Social Hygiene Clinic in Angeles City. CSWs, particularly unregistered prostitutes, commonly used prophylactic antibiotics, which are available without prescription, in an attempt to protect themselves.[247] This practice offers no protection against STDs but does interfere with STD screening programs. The ability to intervene in a core group of CSWs may be limited to those STDs that can be readily diagnosed and treated by antibiotics or are vaccine preventable. However, attempts to eradicate infection by mass antibiotic treatment of all CSWs produce, at best, minor, transient reductions in STD rates.[268]

While treatment and screening are the most important step in controlling STDs, education is very important also. The challenge is to make the education more effective than the infamous "VD lectures" of the past by taking into account various behavioral factors.

Behavioral Considerations. There are no current, definitive, comprehensive data on US sexual behavior,[269] which greatly handicaps designing prevention programs. This is a critical deficiency because more than any other communicable disease, STDs are intimately and highly influenced by social behavioral factors. Data on sexual behavior come from mainly two sources whose relevance to a military population may be limited: inner city STD clinics and college campuses. A third source, prostitutes, may have relevance for the risks faced by deployed military personnel.[228]

Alcohol. Alcohol consumption promotes STD acquisition by reducing inhibitions and interfering with discrimination.[270] The relationship among alcohol, sex, and STDs was recognized far back in military experience. In World War I, under the influence of the social hygiene movement, military bases forbade the sale of any alcoholic beverages in a zone around the base extending for several miles. World War II–era studies identified alcohol use as a risk factor for STDs,[202–207] as did studies in the Vietnam War era,[193–195] a 1996 study of Thai military recruits,[245] and studies of STDs in civilians.[225,226] Attempts to reduce STDs must include education on the critical role alcohol plays in acquiring STDs and training and techniques to avoid or limit alcohol consumption.

Adolescent Risk-Taking Behavior. The majority of reported military STD cases occur among junior enlisted personnel, many of whom are still in their

teens. Studies of adolescent risk-taking behavior, although only partially overlapping military personnel at the older (late teen) end of these studies, probably have considerable relevance. Adolescents tend to have unplanned, sporadic sex, and sexual activity is strongly influenced by affiliation with peers who already are sexually active.[271] The largest proportion of military personnel at risk for STDs are members of a group—adolescents and young adults—that inherently tends to take risks in all aspects of life because they perceive themselves as invulnerable. Their profession itself is risky (eg, weapons firing, parachuting, Special Forces activities) and being comfortable with risky activities may—appropriately or not—generalize to other areas of their life. Prevention efforts must take this into account.

Behavior Change and Education. Since the onset of the HIV epidemic, it has become obvious that the "one size fits all" approach to STD education and prevention is neither appropriate nor effective. Programs must be tailored to gender, race/ethnicity, culture, sexual orientation, and probably level of education and socioeconomic status, among other factors. For example, a study of 914 heterosexual individuals seen in South Carolina STD clinics (with a 41% gonorrhea prevalence) looked at recruitment of sex partners.[272] It concluded that risk reduction counseling for men should target reducing promiscuity by reducing their number of sex partners and of casual sex partners. Women, mostly monogamous and therefore facing different problems, needed counseling about care in partner selection and use of condoms with their steady sex partners.

Boyer summarizes the key qualities of a good STD intervention program for adolescents: "Programs that are likely to be most effective are those that target cognitive and behavioral skills to increase adolescents' sense of self-efficacy and enhance their ability to communicate, problem-solve, and make appropriate decisions about engaging in sexual intercourse."[273p610] Programs must go beyond simply presenting knowledge about STDs. They must impart knowledge and skills to resist peer pressure, to negotiate condom use, and to project future consequences of their behavior. Alternatives to sexual intercourse and how to decide if and when to have sex should be included. Programs that emphasize skills are more effective and need to include multi-method and multi-media approaches. Didactic information about STDs must be current and accurate. It should also emphasize that some STDs have asymptomatic periods but still may be transmissible and that some STDs are life-long and incurable. Adolescent intentions to have sex are strongly related to beliefs and motivations about sex, as opposed to knowledge about STDs.[273,274]

Physicians and other health care providers can affect the health behavior of their patients.[275–278] Patients expect health counseling from their health care deliverers and interpret the absence of such counseling as indicating the issue is not important or they are not at risk. Physicians need to emphasize harm reduction rather than absolute elimination of all risk, since the latter is usually not realistic. Particularly in the area of HIV risk reduction, insistence on a "zero defects" approach may lead to "unrealistically high standards for evaluating programs (perhaps more exacting than for clinical research), and may overlook or undermine their effectiveness."[277p1145] Arguing that condoms should not be used because they are not 100% effective is particularly pernicious.

One study[279] showed evidence that teenage sexual behavior, as measured by condom usage, average frequency of sexual intercourse, age at first intercourse, and chlamydial infection, can change. Applying the techniques proven effective in an urban STD clinic on a group of teenagers,[279] an initial study suggested this approach may be effective with Marine Corps personnel.[280] Intervention and control groups were at high risk for STDs. They were young and predominantly single, had had an average of 18 lifetime sex partners and two partners in the past 3 months, and only 9% and 14% always used condoms (49% and 42% never used condoms). About 30% had paid for sex, and about 25% had had a prior STD. The intervention, based on the Information, Motivation, and Behavioral Skills (IMB) behavior model, consisted of four 2-hour initial sessions, plus a 2-hour follow-up session, and included didactic slides, interactive group exercises, deployment-specific videos, and homework assignments. Sessions focused on STD and HIV transmission, treatment, and outcomes; perceptions of risk and self-efficacy; peer influence; the impact of alcohol and drugs; and liberty-specific risk factors. Risky behavior was significantly reduced in the intervention group: alcohol consumption (84% vs. 91%), mean number of beers per day (7 vs. 9), and number of sexual partners (none: 61% vs. 44%; more than two: 11% vs. 17%).

Education and the "VD Lecture." Traditional didactic education about STDs seems to have little effect in reducing STD incidence. Jones and colleagues[207] found no correlation between knowledge of common STDs and risk for acquiring an STD in a study of 1,885 men on an aircraft carrier. Other stud-

ies[197,281] have suggested traditional educational efforts may reduce the incidence of STDs in military personnel. Hook,[282] after reviewing the available literature, concluded it is not clear such efforts actually result in behavioral changes that decrease STD acquisition. The traditional "VD lecture" is based on the assumption that military personnel do not know how STDs are acquired and that knowledge of the nature of STDs is an effective deterrent (eg, scare tactics showing vivid pictures of genital lesions). Neither assumption seems justified, with the possible exception of fear of AIDS. The problem likely lies in an individual conviction that although STDs are a risk, someone else will be the person who acquires one.

Some didactic information may be helpful in changing behavior, notably the distinction between curable and incurable STDs; the fact that many individuals are asymptomatically infected for prolonged periods but are capable of infecting others, including spouses; and that there are no simple, reliable ways to tell when a potential sex partner is infected. All STD education programs must stress abstinence as the only sure way to avoid acquiring an STD (Plan A); however, for those who will not be abstinent, there must be a Plan B. Its foundation is the consistent, proper use of condoms. All STD educational efforts need to identify sexually risky behaviors, which should be avoided (Exhibit 38-3).

STD educational programs may indirectly reduce STD rates by sensitizing individuals to the signs and symptoms of infection, which might otherwise be overlooked or ignored. To the extent that they result in earlier diagnosis and treatment, such efforts contribute to STD control. Behavioral perceptions may provide an opportunity for behavioral change. For example, World War II studies found 12% to 36% of whites and 50% of blacks believed intercourse is necessary to maintain good health.[204,207] Only 55% of those without an STD believed masturbation was injurious to health, compared to 75% of those with an STD.[204]

Condoms. Not having condoms available results not in a lack of sexual activity but rather in sexual activity without condoms. For sexually active individuals, condoms must be available and their use promoted. As a World War I prevention poster targeting soldiers going on furlough expressed it, "NO is the best tactic; the next, PROPHYLACTIC!" Condoms should be readily available in essentially unlimited quantities, and individuals should be encouraged to take as many as they want. Condom promotion should emphasize the use of a new condom for each sex act. Boxes of condoms should be available in numerous locations (eg, the medical clinic, bathrooms, locker rooms and gyms, galleys and mess halls, and lounges) selected to provide ready access with a degree of privacy, particularly from senior personnel. Not having condoms readily available and in large quantities markedly undermines efforts to promote safer sex practices. This lack implies condom usage is not really important (otherwise condoms would be available) and that the medical unit is not really interested in supporting the practices it urges people to follow.

Limiting the number of condoms that may be taken at one time, having individuals sign for the condoms they receive, and making individuals ask for condoms are all effective ways to discourage condom use. Any action that can be interpreted as monitoring condom usage, especially on an individual basis, should be avoided. A Navy physician once stationed himself at the gangplank of a ship tied up in a liberty port. Everyone going ashore was asked if he planned to have sex and offered a condom if the answer was affirmative. Much to the physician's surprise, few individuals admitted to this or accepted a condom. A dual authority figure—a physician and an officer—was publicly quizzing individuals about an activity not held in the highest regard by senior officers and in which they had

EXHIBIT 38-3

RISKY BEHAVIOR THAT PROMOTES ACQUIRING A SEXUALLY TRANSMITTED DISEASE

- Sex with prostitutes, including exchanging sex for drugs or other items
- Casual sex with strangers or casual acquaintances (eg, pick-ups, one-night stands)
- Sex with multiple partners, even if it is with only one partner at a time (serial monogamy)
- Sex between men
- Sex with an individual who uses intravenous drugs
- Sex with a partner who has multiple sex partners or who has other sex partners who use intravenous drugs
- Sex with partners who may have a sexually transmitted disease
- Sex without a condom

EXHIBIT 38-4

PROPER USE OF CONDOMS

- Use only latex condoms, not natural membrane condoms (natural membrane condoms may transmit a virus)
- Store condoms in a cool, dry place out of direct sunlight
- Do not use condoms in damaged packages or those that show obvious signs of age (eg, brittleness, stickiness, or discoloration)
- Handle condoms with care to prevent tears or punctures
- Put on the condom before any genital contact to prevent exposure to fluids that may contain infectious agents; hold the tip of the condom and unroll it onto the erect penis, leaving space at the tip to collect semen without trapping air in the tip
- Use adequate lubrication; do not use petroleum- or oil-based lubricants (eg, petroleum jelly, cooking oils, shortening, lotions) because they weaken the latex
- Replace a broken condom immediately
- Take care after ejaculation that the condom does not slip off the penis before withdrawal; hold the base of the condom while withdrawing; withdraw the penis while it is still erect
- Use a fresh condom each time; never reuse a condom

Adapted from: Centers for Disease Control and Prevention. Condoms for prevention of sexually transmitted diseases. *MMWR*. 1988;37:133–137.

been advised not to participate.

Medical and preventive medicine personnel need to teach condom users how to use them properly and effectively (Exhibit 38-4). Condom effectiveness has been studied by measuring two outcomes, pregnancy and STD acquisition. Pregnancy typically occurs 10% to 15% of the time over the course of a year but may be as infrequent as 2% for couples using condoms correctly and consistently. Two recent reviews[283,284] indicate condoms are effective in preventing numerous STDs, including HIV, as have other studies.[279,285–287]

The Thai government developed an active program to decrease HIV transmission among its CSWs, which included buying and distributing condoms, disciplining commercial sex establishments that did not consistently use condoms, and bluntly promoting condoms as a way to reduce HIV infection through advertising campaigns.[288] This was influenced in part by a high rate of HIV seroconversion among military recruits, largely associated with heterosexual intercourse with CSWs.[254,285] From 1989 to 1993, use of condoms by CSWs increased from 14% to 94%, and the rates of the five major STDs decreased 79%. Related studies suggest the problem of continued STD transmission may be due in part to inconsistent condom use, failure to use condoms with girlfriends (as opposed to CSWs), and alcohol use.[245,288] A subsequent study found that HIV seroprevalence among Thai Army cohorts fell from the range of 10.4% to 12.5% (between 1991 and 1993) to 6.7% (in 1995), the proportion of men having sex with a CSW fell from 81.4% to 63.8%, and use of condoms increased from 61.0% to 92.5%.[289]

The range of effectiveness suggests condom failures are due to factors other than problems with the condoms themselves. Condom breakage rates in a variety of populations have been reported as 0.5% to 7%, with the higher figures associated with anal sex.[283] Breakage is usually due to the use of inadequate lubrication (particularly with minimal foreplay), petroleum-based lubricants (which degrade the latex), rough handling (particularly fingernail tears), or failure to leave adequate space at the tip of the condom. All these sources of "failure" are correctable by proper education in condom use and handling.

US personnel deployed overseas should not buy foreign condoms because they leak twice as much as US-made condoms.[290] The military supply system purchases the same standard condoms available to civilians.[291] Storage and transportation within the supply system may be a problem, however, so condoms should be checked for signs of deterioration from age or storage at temperature extremes.

Probably more important than mechanical fac-

tors in undercutting condom effectiveness is reluctance or inability to use them. For heterosexual men, use of drugs or alcohol is a major factor in failing to use condoms, followed by their partner not endorsing condom use.[270,292] Men were also less likely to use condoms if they reported being in love with their partners or had difficulty discussing condom usage with their partners. Women were less likely to use condoms if they were black, felt condoms decreased sexual pleasure, reported being in love with their partner, or had partners unwilling to use condoms.[270] Factors associated with condom usage included acceptance of condom advertising, perceptions of partner and peer acceptance of condoms, and effect on sexual pleasure.[293] Both the mechanical aspects of condom use and negotiating condom use with a partner can be taught to STD clinic patients, with a significant reduction of STD infections.[294] Ordering service members to use condoms is not effective, even when they are faced with possible punitive action. One half of 1,103 HIV-positive soldiers did not always use condoms, despite having been ordered to do so.[295]

Condom use by women may be particularly problematic.[296] A national survey found that overall only 41% of sexually active, never-married women aged 15 to 49 years used condoms and only 32% used them consistently.[297] Women at greater risk for STD and HIV (eg, those with larger numbers of lifetime partners) were even less likely to use condoms.[240] The perception that they might acquire AIDS did not influence condom use.[297] Negotiation of condom usage is particularly important for women, since women tend to have less control over the events of a sexual encounter, including the male partner's use of a condom. The traditional alternative suggestions that women should abstain or alter the number and selection of their partners may be less realistic for women than for men.[298,299] The so-called "female condom," approved by the Food and Drug Administration in 1993, offers a way for women to obtain greater control, but because of its price (and perhaps for other reasons which are not clear), it has not been widely accepted. Although a variety of other, female-controlled methods provide protection against some STDs,[299] Cates and colleagues[300] suggest the data are "inconclusive" regarding the absolute level of protection of spermicides against HIV and STD and recommend that both women and men who practice high-risk sex continue to use (male) condoms as their first line of defense.

It is sometimes argued that condoms should not be provided because they provide a false sense of confidence since they do not provide perfect protection. This argument misses the point. A number of individuals are going to engage in risky sexual behavior, despite all efforts to dissuade them. For these individuals, even some protection is an advantage. Individuals can be taught to use condoms properly and consistently. As Roper and Curran, (then, respectively, the Director and the Director for STD Prevention at the CDC) expressed it, "Our prevention message should be clear on this point: When used correctly and consistently, condoms are highly effective; when used otherwise, they are not."[301p502]

Alternative Recreational Outlets. Social activities and recreational facilities have always been considered vital to maintaining morale and directly or indirectly to keeping STD rates down.[202,203,205,207] Ratcliffe noted higher STD rates in units without recreational or social facilities,[207] suggesting the absence of such facilities may encourage sexual activity as an antidote to boredom and frustration. It is doubtful, though, that recreational activities can totally prevent STDs or reduce them below some baseline rate. The problem was succinctly expressed in the musical *South Pacific*: "We got volleyball and Ping-Pong and a lot of dandy games; what ain't we got, we ain't got dames!" [Used with permission of the estate of Oscar Hammerstein.]

Quarantine. Particularly in the past, STD cases were sometimes "quarantined," (denied liberty until they were demonstrated to be no longer infectious) to prevent them from infecting other people. Aside from its overall impracticality, quarantine has a more pernicious effect. Faced with a possible loss of liberty, symptomatic individuals who fear they may have an STD or the worried well who have simply exposed themselves will elect not to come to sick call until the last possible day. In the meantime, they remain sexually active and infect additional people. Individuals with curable STDs should be instructed not to have sex for an appropriate period, but they are rendered noninfectious within hours using current antibiotic regimens. Quarantine should never be used. It drives symptomatic cases underground and ultimately is self-defeating.

Patients presenting with a possible STD should have at a minimum a thorough examination of the genito-rectal area, including the inguinal lymph nodes. Women should have a pelvic examination, including visualization of the cervix. This requires the patient to undress from the waist to the knees. Other areas should be evaluated depending on the patient's history and suspected disease. For example, syphilis may produce a skin rash or cranial nerve

or meningeal symptoms; gonorrhea may produce a rash, joint symptoms, or pharyngitis. Evaluation of all genital ulcers should include consideration of syphilis, herpes, chancroid, and lymphogranuloma venereum. Patients should be serologically tested for syphilis, HBV, and HIV. The incubation period for HBV and HIV seropositivity is sufficiently long that a patient is unlikely to be seropositive from the current exposure. However, any STD is a marker indicating that a patient has been engaging in risky sexual behavior, and therefore the patient may be seropositive from a prior sexual exposure. Follow-up serologic testing for HBV and HIV infection should be strongly considered.

Specific Sexually Transmitted Diseases

Gonorrhea (Urethritis and Cervicitis)

Description of the Pathogen. Gonorrhea is caused by the bacterium *Neisseria gonorrhoeae*. Antibiotic resistance is a continual concern. Antibiotics of the penicillin, amoxicillin, and tetracycline types are no longer effective for most practical purposes. Spectinomycin resistance has been a problem in Asia, and quinoline resistance is a potentially emerging problem.

Epidemiology. Gonorrhea is almost always transmitted by sexual contact. Fomites are not usually considered to play a role in gonorrhea transmission. However, in an experiment at the Navy Environmental and Preventive Medicine Unit No. 2 in Norfolk, Virgina, an inflatable sex doll was inoculated in its "vagina" with a quantity of gonococci comparable to that delivered during a single sex act. The doll was maintained at room temperature under ambient conditions. Viable organisms, in sufficient numbers to infect a new partner, could be recovered for up to 24 hours. Sex toys should not be shared.

N gonorrhoeae is distributed worldwide. The rapidity of air travel from overseas deployments or exercises in high-risk areas is a particular concern to the military. Citing unpublished data, Berg reported on 28 cases of penicillinase-producing *N gonorrhoeae* (PPNG) acquired by US sailors and Marines in Southeast Asia.[214] Most (71%) had been exposed 1 to 3 days before departure; actual travel time was about 24 hours. Fifty-one percent became symptomatic the first day back in San Diego and were initially treated an average of 4.6 days after arrival. Eighteen percent had been sexually active before receiving effective treatment, an average of 12.3 days after arrival. Military deployments to Southeast Asia were possibly responsible for acquisition of the HIV E clade by eight Western hemisphere military personnel, including three US Navy personnel.[302,303]

Endemic gonorrhea has been largely eradicated in Europe, but incidence rates remain high among poor and minority populations in the United States,[304] with these groups closely resembling the populations of developing countries. The US gonorrhea rate, 240/100,000 cases annually (for approximately 600,000 cases a year[251]), can be compared to a rate of 14/100,000 in Sweden,[305] but equating the United States and Europe may not be valid.[198,199,306] In the United States, gonorrhea tends to cluster in lower-economic, inner-city populations, where the rate among African-Americans is 30 times higher than among whites.[307] Studies of male military personnel have found 2% to 10% have asymptomatic gonorrhea.[213,308–310]

Pathogenesis and Clinical Findings. The incubation period in men is 3 to 7 days, and occasionally it is as long as 18 days; 10% to 20% of those infected are asymptomatic. The incubation period in women is 7 to 60 days; 50% to 80% of infected women are asymptomatic. Coinfections are highly common; 5% to 30% of men and 25% to 50% of women with gonorrhea have chlamydia, and 40% of sex partners of men with gonorrhea have chlamydia. All gonorrhea cases are presumed to be coinfected with chlamydia and are cotreated with an antichlamydial antibiotic.

Acute urethritis is the most common manifestation of gonorrhea in men. Although the classic presentation is an abrupt onset of dysuria and copious purulent discharge ("running like a river and pissing razor blades"), gonorrhea may mimic nongonococcal urethritis (NGU) or may be asymptomatic. Distinguishing gonorrhea and NGU on the basis of patient history is unreliable.

Mild cervicitis and asymptomatic endocervical infection are common manifestations in women. Endometritis, salpingitis, and pelvic peritonitis, with the subsequent risk of infertility, may also occur. All forms of female gonococcal infection are commonly minimally symptomatic. Diagnosis based only on history and physical examination will miss many cases.

Diagnostic Approaches. In men, a Gram-stained urethral smear is diagnostic for gonorrhea if it demonstrates Gram-negative intracellular diplococci. It has a sensitivity of 90% to 95% in symptomatic men and 50% to 70% in asymptomatic men; its specificity is 95% to 100%. Specimens should be obtained by inserting a calcium alginate swab about 2 cm into the urethra and leaving it there for 10 to 30 seconds. It should be withdrawn with a twisting motion,

rolled (not smeared) over a glass slide, and then smeared onto a culture plate. The Gram stain can also diagnose NGU. STD laboratory personnel should be trained to report four possible Gram stain interpretations: (1) gonorrhea (presence of white blood cells and Gram-negative intracellular diplococci), (2) NGU (white blood cells without Gram-negative diplococci), (3) a nonspecific smear (cells and debris are present but in no diagnostic pattern), and (4) negative (a few epithelial cells or nothing). Ideally, the patient has not urinated for at least 4 hours before providing the urethral specimen because he may have temporarily washed out evidence of infection. If a patient with a history compatible with urethritis has a negative smear, diagnostic results may be obtained by having him return when he has not urinated for 2 to 4 hours. As a practical matter, though, taking patients as they come usually provides a diagnosis.

In women, a cervical Gram stain is 50% to 70% sensitive for diagnosing gonorrhea, with a specificity of 95% to 100%. Although a Gram stain may be useful, its relatively low sensitivity necessitates a culture. Anal cultures detect a few additional gonorrhea cases. They should be done if gonorrhea is suspected or the woman has been exposed to gonorrhea. (Women may become rectally infected from rectal intercourse or from rubbing infected secretions into the rectum.) When cervical specimens are taken for gonococcal culture, the speculum should be lubricated with only warm water to avoid the possibility of bacteriostatic agents in lubricants getting on the swab or cervix and producing a false-negative culture. Excess cervical mucus should be blotted away with a swab and then a different sterile cotton-tipped swab inserted into the cervical os. The swab should be moved from side to side for 10 to 30 seconds. It should be withdrawn, rolled on a glass slide, and then smeared on Thayer-Martin or other appropriate culture media (Exhibit 38-5).

Diagnosis and management of complicated gonococcal infections, such as disseminated gonococcal infection (arthritis-dermatitis syndrome), pelvic inflammatory disease, epididymo-orchitis, or gonococcal ophthalmia are beyond the scope of this chapter. They are prevented by the same means as uncomplicated gonococcal infections.

Recommendations for Therapy and Control. Pertinent, current CDC treatment recommendations are summarized in Exhibits 38-6 and 38-7.

Since 1994, there have been six reports of relative or high-level gonococcal resistance to ciprofloxacin, including treatment failures.[311–315] Most infections were probably acquired in Southeast Asia. A Japanese report[316] examined gonococcal isolates collected in 1992 and 1993 and compared them to those collected a decade earlier. The MIC50 (minimum concentration of antibiotic required to inhibit the growth of 50% of a collection of bacterial strains) had increased 4-fold and the MIC90 8-fold. In Baltimore, ciprofloxacin MICs in 1,846 gonococcal isolates did not increase from 1988 to late 1994,[317] which may be related to the limited use of quinolone antibiotics in that area. For now, quinolone antibiotics at recommended doses remain an acceptable treatment for gonorrhea,[318] but military personnel should be alert to the possible emergence of more widespread resistance among individuals infected in Southeast Asia.

Cotreatment of Chlamydia. Using azithromycin to treat coexisting chlamydia infections has the advantage over other antichlamydial antibiotics of much better compliance since it requires only a single dose, as opposed to 7 days of doxycycline treatment. Azithromycin powder can be dissolved to produce a suspension and administered to patients as directly observed therapy. Azithromycin has only been approved by the US Food and Drug Administration for use against proven chlamydia infections or for cotreatment of presumptive chlamydia when treating gonorrhea. Stamm and colleagues,[319] in a study of 452

EXHIBIT 38-5

CRITERIA FOR THE DIAGNOSIS OF GONOCOCCAL URETHRITIS

Suggestive Diagnosis—both:

- Evidence of mucopurulent exudate on examination

AND

- Sexual exposure to a partner known to be infected with *Neisseria gonorrhoeae*

Presumptive diagnosis—any **one** of these:

- Gram-negative diplococci on Gram stained urethral smear
- *N gonorrhoeae* cultured but not confirmed with sugar fermentation or other tests
- *N gonorrhoeae* detected by a nonculture laboratory test

Definitive diagnosis:

- *Neisseria gonorrhoeae* is both cultured and confirmed

Source: Centers for Disease Control and Prevention. *Sexually Transmitted Diseases Clinical Practice Guidelines*. Atlanta, Ga.: CDC; 1991.

EXHIBIT 38-6

TREATMENT OF URETHRITIS AND GONOCOCCAL OR CHLAMYDIA PROCTITIS IN MEN

Gonococcal Urethritis[*]

Cefixime 400 mg orally in a single dose

OR

Ceftriaxone 125 mg intramuscularly in a single dose

OR

Ciprofloxacin 500 mg orally in a single dose

OR

Ofloxacin 400 mg orally in a single dose

PLUS

Azithromycin 1 g orally in a single dose

OR

Doxycycline[†] 100 mg orally twice a day for 7 days

Nongonococcal Urethritis[‡] and Chlamydia Urethritis[§]

Azithromycin 1 g orally in a single dose

OR

Doxycycline[†] 100 mg orally twice a day for 7 days

Gonococcal or Chlamydia Proctitis

Regimens appropriate for gonococcal urethritis plus doxycycline 100 mg orally twice a day for 7 days.

Follow-Up and Abstention from Intercourse. Patients should be instructed to refrain from sexual intercourse until 7 days after the initiation of therapy and until all of their partners have been cured. Patients treated with a recommended regimen do not need to be seen in follow-up unless their symptoms recur. If symptoms recur, the patient should be reevaluated and retreated if there is evidence of infection. Patients who receive erythromycin may need to be reevaluated 3 weeks after completion of therapy.

Source: Centers for Disease Control and Prevention. 1998 guidelines for treatment of sexually transmitted diseases. *MMWR*. 1998;47(RR-1).

[*] Alternative single dose gonococcal regimens: Spectinomycin 2 gm IM, ceftizoxime 500 mg IM, cefotaxime 500 mg IM, cefotetan 1 gm IM, or cefoxitin 2 gm IM plus probenecid 1 gm orally. (Only cefoxitin requires probenecid.) Each of these regimens also requires antichlamydia treatment with azithromycin or doxycycline.

[†] Doxycycline can be taken with food, but Pepto Bismol, iron products, and antacids may bind with it and reduce its absorption.

[‡] Alternate nongonococcal urethritis regimens: erythromycin base 500 mg orally 4 times a day for 7 days, erythromycin ethylsuccinate 800 mg orally 4 times a day for 7 days, or ofloxacin 300 mg orally twice a day for 7 days. If only erythromycin is available but a patient cannot tolerate the erythromycin regimens just given, one of the following regimens may be used: erythromycin base 250 mg orally 4 times a day for 14 days or erythromycin ethylsuccinate 400 mg orally 4 times a day for 14 days.

[§] Alternative chlamydia urethritis regimens: erythromycin base 500 mg orally 4 times a day for 7 days, erythromycin ethylsuccinate 800 mg orally 4 times a day for 7 days, or ofloxacin 300 mg orally twice a day for 7 days.

men, demonstrated that a single dose of 1 gm of azythromycin was as effective as standard doxycycline treatment for NGU. An accompanying editorial,[320] a study of azythromycin for cervicitis,[321] and one for chlamydial infections in both sexes[322] argue that azithromycin, although more expensive than doxycycline, is cost effective because it prevents complicated infections and additional infections.

Treatment Failures. Preventive medicine units periodically receive reports of "ceftriaxone-resistant gonorrhea" or gonorrhea "resistant" to other antibiotics. These reports usually reflect an unacknowledged reinfection or a faulty diagnosis. Antibiotic resistance is determined in the microbiology laboratory, a resource not readily available to most field or operational units. Such reports are, in almost all cases, actually reports of treatment failure. There are a number of possible explanations. The symptoms may represent an untreated or improperly treated chlamydia coinfection. It may be a recurrence of a simultaneous chlamydia infection, despite the patient's having taken antichlamydia medicine. If it is gonorrhea, it is almost always a reinfection, but the patient may not admit this because of the patient's belief that he or she could not be infected a second time. Reasons for this belief include an erroneous assumption that the patient's sex partner was treated simultaneously (and therefore could not reinfect the patient) or that the patient had sex with a different partner who was

EXHIBIT 38-7

TREATMENT OF CERVICITIS AND GONOCOCCAL OR CHLAMYDIA PROCTITIS IN WOMEN

Gonococcal Cervicitis[*]

Cefixime 400 mg orally in a single dose

OR

Ceftriaxone 125 mg intramuscularly in a single dose

OR

Ciprofloxacin 500 mg orally in a single dose

OR

Ofloxacin 400 mg orally in a single dose

PLUS

Azithromycin 1 gm orally in a single dose

OR

Doxycycline[†] 100 mg orally twice a day for 7 days

Mucopurulent Cervicitis

Women with mucopurulent cervicitis should be tested for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* and treatment based on those test results. Empiric therapy for either or both of these entities should be considered if (*a*) the patient is suspected of being infected, (*b*) the prevalence of these infections is high in the patient population, and (*c*) the patient may be difficult to locate for treatment.

Chlamydia Cervicitis[‡]

Azithromycin 1 gm orally in a single dose

OR

Doxycycline[†] 100 mg orally twice a day for 7 days

Gonococcal or Chlamydia Proctitis

Regimens appropriate for gonococcal cervicitis plus doxycycline 100 mg orally twice a day for 7 days

Pregnancy. Doxycycline and erythromycin estolate are contraindicated during pregnancy. Ciprofloxacin and ofloxacin are contraindicated in pregnant and lactating women and persons less than 18 years old. Preliminary data indicate azythromycin may be safe in pregnancy, but data are insufficient to recommend its use in pregnancy. Pregnant women may be treated for chlamydia using erythomycin base, erythromycin ethylsuccinate, or amoxicillin 500 mg orally 3 times a day for 7 days. A repeat evaluation of pregnant women for chlamydia 3 weeks after completion of therapy is recommended.

Follow-up and Abstention from Intercourse. Patients should be instructed to refrain from sexual intercourse until 7 days after the initiation of therapy and until all of their partners have been cured. Patients treated with a recommended regimen do not need to be seen in follow-up unless their symptoms recur. If symptoms recur, the patient should be reevaluated and retreated if there is evidence of infection. Patients who receive erythromycin may need to be reevaluated 3 weeks after completion of therapy.

[*] Alternative single-dose gonococcal regimens: Spectinomycin 2 g IM, ceftizoxime 500 mg IM, cefotaxime 500 mg IM, cefotetan 1 g IM, or cefoxitin 2 g IM plus probenecid 1 g orally. (Only cefoxitin requires probenecid.) Each of these regimens also requires antichlamydia treatment with azithromycin or doxycycline.

[†] Doxycycline can be taken with food, but Pepto Bismol, iron products, and antacids may bind with it and reduce its absorption.

[‡] Alternative chlamydia cervicitis regimens: Erythromycin base 500 mg orally 4 times a day for 7 days, erythromycin ethylsuccinate 800 mg orally 4 times a day for 7 days, or ofloxacin 300 mg orally twice a day for 7 days.

IM intramuscularly

Source: Centers for Disease Control and Prevention. 1998 guidelines for treatment of sexually transmitted diseases. *MMWR*. 1998;47(RR-1).

thought to be uninfected (eg, a spouse). In a surprising number of these reports of antibiotic "resistance," a proper evaluation was not done at the time the patient reappeared. Instead, the medical provider simply accepted the patient's version of what happened and retreated the patient without obtaining any laboratory tests.

True treatment failures due to antibiotic resistance are highly important sentinel events and should be investigated thoroughly. The most impor-

tant action is to culture the infection and submit the gonococcal isolate for antibiotic sensitivity testing. Other steps in the investigation include reviewing the medical record and interviewing those involved to determine an accurate history of events, including which laboratory tests were done and the results. The patient should be thoroughly questioned about sexual exposures since the initial treatment, with an emphasis on identifying all sexual contacts and not simply those the patient thinks might have been the source of the infection. All contacts are presumed to be potential sources of infection and need to be evaluated accordingly.

Follow-up evaluation of uncomplicated gonococcal infections is generally not needed, because current treatment regimens based on ceftriaxone are highly effective and test-of-cure cultures are not needed. Instead, patients should be instructed to return if their symptoms persist or recur. Follow-up evaluation with test-of-cure cultures should be considered for alternative treatment regimens and particularly for patients in relationships in which all sex partnters may not be treated simultaneously, leading to possible reinfection (ping-pong infection). The patient and partners should be instructed not to have sex until 7 days after all medications have completed by everyone and the patient and partners are asymptomatic.

Gonococcal Pharyngitis

Epidemiology. Gonococcal pharyngitis can be acquired directly through oral sex.

Pathogenesis and Clinical Findings. Gonococcal pharyngitis is clinically indistinguishable from any other bacterial or viral pharyngitis. It is associated with disseminated gonococcal infection but often occurs as an isolated entity.

Diagnostic Approaches. Diagnosis is complicated by the common presence in the oropharynx of nonpathogenic *Neisseria* species, which can produce a false-positive Gram stain. Definitive diagnosis requires culture with the added step of sugar fermentation testing to identify specific *Neisseria* species. The throat swab specimen must be swabbed directly onto a Thayer-Martin culture plate. The standard culturette device used for streptococcal pharyngitis is poorly effective as a transport medium for gonococci.

Throat cultures for gonorrhea should be obtained from homosexual men with pharyngitis, individuals with pharyngitis and genital or rectal symptoms, individuals with pharyngitis and who have had recent sex contact with someone who has gonorrhea, and individuals engaging in risky sexual behavior whose symptoms have not responded to treatment for a "strep throat." Because eradication of *Neisseria* from the oropharynx can be difficult, two test-of-cure cultures are required, 4 days apart. Cultures must be scheduled after the patient has finished his or her antibiotic treatment for chlamydia. Although doxycycline or azithromycin may not eradicate *N gonorrhoeae*, they may have sufficient activity to cause a false-negative culture.

Recommendations for Therapy and Control. See Gonorrhea and Exhibit 38-8**.**

EXHIBIT 38-8

TREATMENT OF GONOCOCCAL PHARYNGITIS

Ceftriaxone 125 mg intramuscularly in a single dose

OR

Ciprofloxacin 500 mg orally in a single dose

OR

Ofloxacin 400 mg orally in a single dose

PLUS

Azithromycin 1 gm orally in a single dose

OR

Doxycycline* 100 mg orally twice a day for 7 days

Follow-up. Gonococcal pharyngitis is more difficult to treat than gonococcal infections of the urogenital and rectal areas. Few regimens reliably cure such infections more than 90% of the time. Patients should be instructed to return for reevaluation if their symptoms persist or recur. Chlamydia coinfection of the pharynx is unusual, but coinfection at genital sites sometimes occurs. Therefore treatment for both gonorrhea and chlamydia is recommended.

Pregnancy. Doxycycline is contraindicated in pregnancy; information is insufficient to recommend azythromycin in pregnancy. Ciprofloxacin and ofloxacin are contraindicated in pregnant and lactating women and persons less than 18 years old. See Exhibit 39-6 for alternate antichlamydia drugs that can used during pregnancy.

* Doxycycline can be taken with food, but Pepto Bismol, iron products, and antacids may bind with it and reduce its absorption.

Source: Centers for Disease Control and Prevention. 1998 guidelines for treatment of sexually transmitted diseases. *MMWR*. 1998;47(RR-1).

Chlamydia (Urethritis and Cervicitis)

Description of the Pathogen. The intracellular bacterium *Chlamydia trachomatis* causes the infection commonly referred to as "chlamydia."

Epidemiology. Chlamydia is transmitted by sexual intercourse and is found worldwide. In the United States, chlamydia infections do not appear to cluster geographically but reporting is not uniform.

In the United States, 35% to 50% of NGU cases are caused by *C trachomatis*.[144p257–261] Studies of male military personnel have found 7% to 11% have had asymptomatic chlamydia infections.[310,323] Gynecologic screening of female US Navy recruits found 10% had asymptomatic cervical chlamydial infections.[324]

Pathogenesis and Clinical Findings. In both sexes, chlamydia often occurs as a coinfection with gonorrhea, and the two conditions can mimic each other. In men, chlamydia most commonly appears as urethritis, but complications include epididymitis, infertility, and proctitis (in men practicing receptive anal intercourse). The incubation period is 7 to 10 days and asymptomatic infections are common. In women with symptomatic infections, manifestations include endocervicitis and other gonorrhea-like conditions. Complications include salpingitis, ectopic pregnancy, and proctitis. In women, the incubation period is 7 days onward (the maximum time period is not known), and more than 90% of women infected are asymptomatic.

Diagnostic Approaches. Nonculture chlamydia tests are commercially available. Most have overall sensitivities of 60% to 90%.[261] Sensitivity correlates with symptomatology and may be 100% in individuals with a profuse discharge. At the other extreme, many of these tests have not been evaluated in asymptomatic individuals, especially men; the tests' sensitivity in these individuals may be low. PCR and LCR chlamydia tests are highly sensitive and specific, especially when used in combination. They are not widely commercially available and are notorious for their sensitivity to contamination, which limits their use under field conditions. Commonly available chlamydia tests can produce false-positive results, and caution is advised when such results may have legal implications,[262] for example, in rape cases. In such cases, verification with a second test is recommended, preferably one which uses a different epitope. The CDC has developed guidelines for using and interpreting chlamydia test results,[73] which consider such factors as prevalence of chlamydia in the population of interest, patient gender, and whether a false-positive result would have adverse effects. Serologic tests for chlamydia are not considered reliable and are not recommended.

Recommendations for Therapy and Control. Uncomplicated chlamydial infections treated with doxycycline or azithromycin do not routinely require follow-up, unless symptoms persist or recur. Retesting after 3 weeks should be considered for patients who are treated with other medications. Individuals should also abstain from sex until 7 days after completing medications (see Exhibits 38-6 and 38-7).

Chlamydia screening in men is somewhat problematic. Healthy young men rarely seek medical attention and usually avoid testing that requires a painful urethral swab. Chlamydia infections are common in sexually active young men, but the symptoms, if present, may be minimal or ignored. At least 10% are asymptomatically infected. Data on the sensitivity and specificity of nonculture chlamydia tests are limited because manufacturers may not evaluate chlamydia diagnostic tests in young men, particularly asymptomatic ones. A LET only requires a urine specimen. A positive result indicates white blood cells are present, but these may be due to gonorrhea, chlamydia, or some other infection.

Sexually active young women are also at high risk for chlamydia infection and typically have no or minimal symptoms. MPC is easily diagnosed but is insensitive as an indicator of chlamydia infection. A diagnosis of MPC is useful because it allows treatment initiation, but the diagnosis of MPC does not justify avoiding other tests. A variety of nonculture chlamydia tests are very sensitive, but have both false-positive and false-negative results. Generally accepted criteria identifying women who should be screened for chlamydia infection include any of the following:[262] (*a*) Presence of mucopurulent cervicitis, (*b*) a sexually active woman younger than 20 years old, (*c*) a woman 20 to 24 years old who either uses barrier contraception inconsistently or has either had a new sex partner or more than one sex partner in the past 3 months, (*d*) a woman older than age 24 who uses barrier contraception inconsistently and has either had a new sex partner or more than one sex partner in the past 3 months, and (*e*) a pregnant woman in a high-prevalence area for chlamydia. All screening programs should be based on local STD epidemiology, whenever possible. When a false-positive result may have adverse social, psychological, or medicolegal results, positive results should be verified with a different test.

Nongonococcal Urethritis

NGU is a urethral infection caused by any of a number of pathogens other than *N gonorrhoeae*. It is commonly diagnosed on the basis of a urethral discharge and evidence of urethral inflammation (presence of white blood cells) without making a specific etiological diagnosis. The term predates the demonstration of chlamydia as the commonest cause of NGU and originally simply meant that no organism could be identified as the cause of the infection. For practical purposes, NGU is a male infection. Women may occasionally have symptoms of a bladder infection that is chlamydial in origin. This is referred to as the "acute dysuria syndrome" or the "dysuria pyuria syndrome."

Obsolete terms for NGU are postgonococcal urethritis and nonspecific urethritis (NSU). Use of the latter term should be discouraged because it implies NGU is not a sexually transmitted disease. NGU has been attributed to beer and other alcoholic beverages, spicy foods, caffeine, masturbation, too much or too little sex, allergies, "toxins," and "strain." None of these are etiologic agents, a fact that bears emphasis because such beliefs reinforce the idea that NGU is not a sexually transmitted disease. The old practice of proscribing these agents as part of the treatment of NGU should be avoided, because doing so may undermine the credibility of medical personnel.

Description of the Pathogens. By definition, NGU is not caused by *N gonrrhoeae*, a fact that manifests itself in the absence of Gram-negative diplococci on a urethral Gram stain. NGU is caused by the intracellular bacterium *C trachomatis* or the mycoplasma *Ureaplasma urealyticum*. Herpes simplex virus, the protozoan *Trichomonas vaginalis*, and possibly *Mycoplasma genitalium* are rare causes of NGU. These latter agents should be considered when the medication prescribed to treat NGU has no effect on symptoms.

Epidemiology. NGU is transmitted in the same way as gonorrhea, and its etiological agents are distributed worldwide. Gonococcal and nongonococcal urethritis have sufficient epidemiologic overlap that all cases of gonococcal urethritis are presumed to be coinfected with chlamydia (the commonest etiological agent of NGU), and treated as such. Further, urethritis diagnosed solely on the basis of a purulent or mucopurulent discharge, a positive LET, or the demonstration of 10 WBC or greater per high power field when examining first void urine, should be treated for both gonorrhea and chlamydia. *C trachomatis* causes about 25% to 55% of NGU, although the proportion decreases with age. *Ureaplasma urealyticum* causes up to 20% of NGU, perhaps more. *Trichomonas vaginalis* is an unusual cause of NGU in US studies, but is a more common cause in European studies. Herpes virus rarely causes NGU.

Pathogenesis and Clinical Findings. NGU is classically described as having milder symptoms than gonorrhea, with either no dysuria or dysuria described as itching or tingling. The urethral discharge is clear and mucoid, may be scanty, and may be present only on awakening in the morning. Distinguishing NGU from gonorrhea on the basic of clinical presentation is unreliable, however, since either disease can mimic the other. Asymptomatic infection is common.

Diagnostic Approaches. Although diagnostic tests are now available to identify *C trachomatis*, the most common cause of NGU, the concept of NGU is a highly utilitarian one in any setting where available lab tests may only be capable of demonstrating the presence of urethral inflammation (Exhibit 38-9). Diagnosing NGU allows the patient to be treated effectively and promptly, a key step in pre-

EXHIBIT 38-9

CRITERIA FOR THE DIAGNOSIS OF NONGONOCOCCAL URETHRITIS

Suggestive Diagnosis

- History of urethral discharge plus one of the following:
  - Sexual exposure to a person known to have an NGU-causing organism
  - Positive leukocyte esterase test
  - < 5 WBC per oil field on a Gram stained urethral smear*

Presumptive Diagnosis

- Abnormal urethral discharge

OR

- ≥ 5 WBC per oil field on a Gram stained urethral smear*

PLUS

- Exclusion of gonococci on Gram stain

*Mean of five oil fields
WBC: white blood cell
Source: Centers for Disease Control and Prevention. *Sexually Transmitted Diseases Clinical Practice Guidelines*. Atlanta: CDC; 1991.

venting the spread of infection. Recommended treatment regimens are highly active against the two agents that cause nearly all case of NGU.

Treatment. See Exhibit 38-6**.**

Mucopurulent Cervicitis

MPC in women may be a clinical analogue of NGU in some respects. Like NGU, it is a syndromic diagnosis based on demonstrating cervical discharge and inflammation rather than a specific etiologic agent. Its presence may allow the initiation of treatment. The etiological agents of MPC are not fully known. Both *N gonorrhoeae* and *C trachomatis* are associated with MPC, although neither organism can be demonstrated in most MPC cases. Moreover, cervical infections with these organisms may not demonstrate MPC. Most cases of MPC are asymptomatic, although cervical examination reveals a purulent or mucopurulent endocervical exudate. Some women have an abnormal vaginal discharge and vaginal bleeding (eg, after sexual intercourse).

Diagnosis. Exhibit 38-10.

Treatment. See Exhibit 38-7.

Proctitis

Description of the Pathogen. Acute sexually transmitted proctitis is most commonly caused by *N gonorrhoeae* and, especially in men who have sex with men, *C trachomatis*. *Treponema pallidum* and herpes simplex virus are also causes.

Epidemiology. These infections are most commonly acquired by receptive anal intercourse. In some cases, they may be acquired by other means (eg, digital intercourse, sex toys).

Pathogenesis and Clinical Findings. Most cases are asymptomatic or mildly and nonspecifically symptomatic (eg, rectal itching, mild discharge). Perhaps 10% of cases have anorectal pain, tenesmus, or grossly bloody discharge. Anoscopy reveals normal mucosa or nonspecific proctitis. Herpetic proctitis reveals ulcerative lesions or fissures. Syphilitic proctitis reveals chancres.

Diagnostic Approaches. Anoscopy may reveal pus, and a Gram stain may reveal white blood cells. (The Gram stain may also reveal Gram-negative diplococci in gonococcal proctitis, but this is only 30% sensitive.) Ulcerative lesions and fissures suggest herpes or syphilis. Other diagnostic tests should be obtained if available.

Treatment. If pus, white blood cells, or Gram-negative diplococci are seen, the patient should be treated as for gonococcal urethritis, plus doxycycline 100 mg orally twice a day for 7 days. Other or additional treatment should be guided by laboratory results.

EXHIBIT 38-10

CRITERIA FOR THE DIAGNOSIS OF MUCOPURULENT CERVICITIS*

Suggestive Diagnosis

- 10-30 WBC per oil field on a Gram stained cervical smear

PLUS

- Sexual exposure to a person known to have MPC-causing organisms

Presumptive diagnosis—any one of these

- Presence of yellow mucopurulent endocervical exudate†
- Swab-induced endocervical bleeding
- ≥ 30 WBC per oil field on a Gram stained cervical smear

WBC: white blood cell

* Whenever possible, women with MPC should be tested specifically for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* and a treatment decision made on the basis of those test results. If there is a high local prevalence of gonorrhea or chlamydia and the woman may be difficult to locate for treatment, empiric treatment should be considered. For further details see Centers for Disease Control and Prevention. 1998 Guidelines for treatment of sexually transmitted diseases. *MMWR*. 1998;47(RR-1):1–128.

† Swab test consists of inserting a cotton swab into the cervix to obtain a specimen of endocervical mucopus. The swab is withdrawn from the vagina and held up to a dark background and examined with a bright light. The presence of yellow or yellow-green mucopus indicates a positive test.

Source: Centers for Disease Control and Prevention. *Sexually Transmitted Diseases Clinical Practice Guidelines*. Atlanta: CDC; 1991.

Herpes

Description of the Pathogen. Genital herpes is caused by infection with the herpes simplex virus, usually type 2.

Epidemiology. HSV is transmitted by sexual contact. Because HSV can easily be inoculated on any mucous membrane or through any break in the skin, individuals with herpes labialis ("fever blisters," "cold sores") who engage in oral sex may infect

their partners.

Asymptomatic shedding of HSV also occurs, although this appears to be a transient event, and relatively few virions are shed. About 1% of infected women shed asymptomatically at any time, and one study found that half of women diagnosed by culture as asymptomatic shedders noticed genital lesions *after* being informed of this.[325] Up to 75% of primary HSV genital infections may be subclinical. These and related studies have led to the conclusion that the commonest form of HSV transmission is asymptomatic.

HSV is distributed worldwide. HSV2 antibody is found in 20% to 30% of US adults and in up to 60% of those in lower socioeconomic groups or those with multiple sex partners.[144]

Pathogenesis and Clinical Findings. In first-episode symptomatic herpes, after an incubation period of 7 to 14 days, the patient experiences sensations such as tingling, itching, pain, dysuria, or vaginal discharge, which may occur almost anywhere in the genital area. Up to 4 days later, the symptoms intensify, and then multiple small clear vesicles appear, commonly described as "water blisters." These may occur on the perineum, vulva, vagina, cervix, or penis. The initial episode may be a systemic illness, particularly in patients who have never been exposed to HSV, and the patient may complain of systemic viral illness symptoms, including herpetic pharyngitis. After 24 to 48 hours, the vesicles begin to turn cloudy and change into pustules. The pustules spontaneously rupture, leaving smooth, red ulcers that are 2 to 5 mm in diameter, shallow, flat, very painful, and nonindurated. The ulcers may coalesce, forming larger irregular ulcers. After a few days, the ulcers begin to dry and crust over. First-episode genital herpes may last as long as 2 to 4 weeks, with new ulcers recurrently developing. New lesions are infectious for 7 to 12 days. First-episode herpes is commonly accompanied by bilateral tender inguinal adenopathy, sometimes sufficiently painful that the patient walks with a stooped over, bow-legged gait. A small proportion of individuals have painless ulcers.

HSV remains viable in the dorsal ganglia for the rest of the individual's life. Periodically, particularly within the first several years after the initial infection, HSV becomes active again and genital lesions recur. A large variety of factors are said to precipitate recurrences (eg, sexual intercourse, stress, fever, menstruation, birth control pills, temperature change, sunlight), and these factors vary among individuals. Most occurrences, however, appear to have no identifiable precipitating factor. Recurrences are characterized by being much milder and briefer than the initial episode, sometimes lasting less than 24 hours. In about half the cases, recurrences are signaled by premonitory paresthesias in the genital area, leg, or foot, which begin hours to 2 days before onset. Recurrent lesions are usually infectious for only a few days.

Diagnostic Approaches. Genital herpes is usually diagnosed clinically, particularly when the characteristic vesicles are present. The ulcers are typically clean, shallow, nonindurated, and painful, but descriptions of genital ulcers are at best rules of thumb. Any genital ulcer should include in its differential diagnosis herpes, syphilis, chancroid, and (less likely) lymphogranuloma venereum. A history that the ulcer began as a vesicle or that it has recurred supports a diagnosis of herpes. Herpes viral culture is the gold standard for diagnosis, with 80% to 90% sensitivity and 100% specificity,[261] but it is not readily available. Tzanck preps are made by staining a smear of fluid from the base of the vesicle or ulcer and looking for multinucleated giant cells, the remnants of epithelial cells that have fused together. It is about 60% sensitive. Both culture and Tzanck prep are more likely to be positive the earlier and more characteristic the lesions. HSV serology is generally not reliable. Only a primary episode of herpes can be serologically confirmed, by a 4-fold titer increase in acute and convalescent sera.

Recommendations for Therapy and Control. The role of anti-HSV therapy is largely limited to symptomatic treatment of initial episodes (because these tend to be significantly symptomatic and prolonged) and to control of frequent recurrences (generally defined as more than six recurrences per year). Most recurrences are too mild and transient to benefit from treatment. Acyclovir reduces viral shedding and pain and speeds healing but does not eradicate HSV. There is no evidence acyclovir provides effective prophylaxis against either acquiring or transmitting HSV (Exhibit 38-11).

Herpes produces psychological reactions out of proportion to the minimal pathological changes. Patients may deny the diagnosis, become significantly depressed and angry for long periods, complain of decreased self image and self-worth (being "damaged goods"), and spend considerable time and effort searching for alternative treatments. The health care provider needs to be supportive and should consider referring the patient to a herpes support group.

Patient education is important and needs to emphasize that there should be no sex when lesions are present, that the types and efficacies of treat-

EXHIBIT 38-11

TREATMENT OF GENITAL HERPES

First Clinical Episode of Genital Herpes*

Acyclovir 400 mg orally 3 times a day for 7-10 days

OR

Acyclovir 200 mg orally 5 times a day for 7-10 days

OR

Famciclovir 250 mg orally 3 times a day for 7-10 days

OR

Valacyclovir 1 g orally twice a day for 7-10 days

Episodic Recurrent Infection†

Acyclovir 400 mg orally 3 times a day for 5 days

OR

Acyclovir 200 mg orally 5 times a day for 5 days

OR

Acyclovir 800 mg orally twice a day for 5 days

OR

Famciclovir 125 mg orally twice a day for 5 days

OR

Valacyclovir 500 mg orally twice a day for 5 days

Daily Suppressive Therapy‡

Acyclovir 400 mg orally twice a day

OR

Famciclovir 250 mg orally twice a day

OR

Valacyclovir 500 mg orally once a day

OR

Valacyclovir 1 g orally once a day

Pregnancy. The safety of systemic acyclovir or valacyclovir in pregnant women has not been established. A registry of women who have received acyclovir (or valacyclovir) in pregnancy has been established. Data thus far do not indicate an increased risk for major birth defects after acyclovir treatment. The first clinical episode of genital herpes during pregnancy may be treated with acyclovir. Life-threatening maternal infections (eg, disseminated infection, encephalitis, pneumonitis, hepatitis) should be treated with intravenous acyclovir. Routine administration of acyclovir to pregnant women who have a history of recurrent genital herpes is not recommended at this time. Prenatal exposures to valacyclovir and famciclovir are too limited to provide useful information on pregnancy outcomes.

* Treatment may be extended if healing is incomplete after 10 days of therapy.

† Patients treated for recurrent herpes should be provided with either medication or a prescription to have on hand at the time of a recurrence. Treatment of recurrent herpes is most effective if started when a prodrome develops or within 1 day of the onset of symptoms.

‡ Daily suppressive therapy with famciclovir or valacyclovir is not currently recommended for more than 1 year. Although patients have been on acyclovir suppressive therapy for as long as 6 years, annual reevaluation of the need for suppressive therapy should be conducted. Patients may adjust psychologically to the recurrences, and in many patients the frequency of recurrences decreases with time.

Source: Centers for Disease Control and Prevention. 1998 guidelines for treatment of sexually transmitted diseases. *MMWR*. 1998;47(RR-1).

ment are limited, and that infected women are at particular risk of infecting their babies. Genital herpes can infect a neonate during delivery with devastating consequences, so all pregnant women with genital herpes or who have had sex with someone who has genital herpes should be instructed to alert their obstetrician.

Individuals with active genital lesions should refrain from sex during any prodromal symptoms and until the lesions are gone. Condoms offer less protection against acquiring HSV than other STDs because lesions may be in locations not covered by the condom, but their use should be encouraged with new and uninfected partners. Because asymptomatic HSV shedding occurs between ulcerative episodes, partners may become infected even in the absence of overt lesions. Asymptomatic shedding occurs more often with HSV2 infection and within the first 12 months after infection.

Syphilis

Description of the Pathogen. Syphilis is caused by the spirochete *Treponema pallidum.*

Epidemiology. Syphilis is transmitted by direct contact with infectious lesions or fluids, usually during sexual intercourse. It can be transmitted from mother to fetus transplacentally or at delivery. It is found worldwide.

Pathogenesis and Clinical Findings. Syphilis has an incubation period of 10 to 90 days, averaging 21 days. Primary syphilis is a chancre, classically described as a clean, punched out, smooth, red, painless (unless secondarily infected) lesion, which is indurated sufficiently to feel like the cartilage in the tip of the nose. Atypical and multiple lesions are not uncommon. Chancres are typically found in the genital area and around the mouth and rectum but may appear anywhere on the body. The heal spontaneously in 3 to 6 weeks. Chancres are associated with unilateral or bilateral regional adenopathy, which is firm, discrete, moveable, and painless. The presence of any genital ulceration must put syphilis in the differential diagnosis.

Secondary syphilis is a cutaneous, systemic disease, most notable for a characteristic maculopapular rash. It occurs within 6 months of exposure, usually within 6 weeks, and often overlaps the resolving chancre in occurrence. The rash, which occurs in about one third of cases, is painless, nonpruritic, and often generalized. It may involve the mucous membranes (called a mucous patch), tends to follow cleavage lines, especially on the trunk, and has a predilection for the palms and soles. The lesions are discrete, sharply demarcated, and scaly; they are also darkfield positive, although it may require scraping the lesion to exposure serous material to demonstrate this. The eruption may last a few weeks or as long as a year. Up to 25% of untreated cas es may have a relapse of the rash, and 5% may have one to three additional relapses. Alopecia of the eyebrows and scalp occurs.

Secondary syphilis is an often protean disease, which may begin with a flu-like syndrome (eg, malaise, myalgia, headache, sore throat), with mild anemia, elevated white blood cell count and elevated sedimentation rate. There is a generalized adenopathy, with hard, rubbery, painless nodes. Splenomegaly is common, and hepatomegaly is sometimes seen. Latent syphilis is a serologic diagnosis and is divided into *early latent* (infected less than 1 year) and *late latent*.

Central nervous system disease can occur with any stage of syphilis. It may manifest itself as ophthalmologic symptoms (eg, uveitis, neuroretinitis, optic neuritis), auditory abnormalities, cranial nerve palsies, or meningeal signs and symptoms. Such patients should have a cerebral spinal fluid examination (white blood cell, protein, CSF-VDRL (Venereal Disease Research Laboratory) and be treated for neurosyphilis (Exhibit 38-12). The CSF examination should be repeated every 6 months. If the pleocytosis has not decreased after 6 months or the spinal fluid is not normal after 2 years, retreatment should be considered.

Diagnostic Approaches. Primary and secondary syphilis may be diagnosed by darkfield microscopy, using serous exudate from the chancre or condyloma lata lesions. Although sensitive and highly specific for diagnosing early syphilis, this technique is usually only available in large medical centers or dermatology clinics. Darkfield microscopy may be falsely negative if topical antibiotics have been applied to the lesion.

The majority of HIV-infected syphilitics can be diagnosed in the same manner as non-HIV infected cases. Syphilis in HIV-infected individuals may, however, take a florid and greatly accelerated course, further complicated by falsely negative serologic tests. Diagnosis in these cases may depend on Warthin-Starry staining of biopsied lesions.

Serodiagnosis of syphilis is based on two types of tests: the nontreponemal tests (ie, VDRL rapid plasma reagin [RPR]; RPR circle), which are used for screening and quantitative follow-up, and the tests for treponemal antibody. When the chancre first appears, 30% to 50% of cases are nonreactive. Patients should be retested in 1 week and at 1 and 3 months. It is important to realize that only about 60% to 90% of primary syphilis cases may be VDRL positive, with the percentage reaching 100% only when the disease has reached its secondary phase. VDRL seropositivity wanes in later stages, even without treatment.

The nontreponemal tests may be falsely negative due to the "prozone phenomenon," in which very high antibody titers overwhelm the test system. Patients highly suspected of having syphilis, particularly secondary syphilis, who have negative tests should have the test repeated with instructions to the laboratory to dilute the serum. Nontreponemal tests may also be falsely positive. The tests cross react with the organisms of yaws, endemic syphilis (bejel), and pinta. There is no way to distinguish among these entities serologically, so clinical judgment must be used. Biological false positives also occur and are divided into acute and chronic reactions. Acute biological false-positive reactions may be due to a variety of viral agents (eg, hepatitis, mononucleosis, viral pneumonia, chickenpox, measles), malaria, some immunizations, and, notably, pregnancy. Chronic false positives are due to

EXHIBIT 38-12

TREATMENT OF SYPHILIS

Primary and Secondary Syphilis and Early Latent Syphilis

Benzathine penicillin G 2.4 million units IM in a single dose

Late Latent Syphilis and Latent Syphilis of Unknown Duration

Benzathine penicillin G 7.2 million units total dose, administer as 3 doses of 2.4 million units intramuscularly at 1-week intervals

Neurosyphilis*

Aqueous crystalline penicillin G 18-24 million units a day, administered as 3-4 million units intravenously every 4 hours for 10-14 days

OR

Procaine penicillin 2.4 million units intramuscularly a day *plus* Probenecid 500 mg orally 4 times a day, both for 10 to 14 days

Penicillin Allergy. Penicillin-allergic patients with primary, secondary, or early latent syphilis should be treated with doxycyline 100 mg orally twice a day for 2 weeks or tetracycline 500 mg orally 4 times a day for 2 weeks. Patients with late latent or latent syphilis of unknown duration should be treated with doxycycline or tetracycline for 4 weeks. With any of these regimens, close follow-up is essential to ensure patient compliance. Patients with neurosyphilis who are allergic to penicillin should be desensitized to penicillin and treated with one of the penicillin regimens or treated in consultation with an expert.

Pregnancy. Doxycycline and tetracycline are contraindicated in pregnancy. Pregnant women who are allergic to penicillin should be desensitized and treated with penicillin.

Management of Sex Partners. Persons who were exposed within the 90 days preceding the diagnosis of primary, secondary, or early latent syphilis may be infected even if they are seronegative. Such patients should be treated for presumptive primary syphilis. Persons who were exposed more than 90 days before the diagnosis should be treated presumptively for primary syphilis if serologic tests are not available immediately and the opportunity for follow-up is uncertain. For purposes of partner notification and presumptive treatment of exposed persons, patients who have latent syphilis of unknown duration with high nontreponemal titers ($\geq$ 1:32) should be considered as having early syphilis. Long-term sex partners of patients who have late syphilis should be evaluated clinically and serologically for syphilis and treated on the basis of the evaluation findings. The time periods before treatment used for identifying at-risk sex partners are: (*a*) 3 months plus duration of symptoms for primary syphilis, (*b*) 6 months plus duration of symptoms for secondary syphilis, and (*c*) 1 year for early latent syphilis.

Follow-Up. Patients should be examined clinically and serologically at 6 and 12 months after treatment; more frequent follow-up may be prudent if long-term follow-up is uncertain. Patients who have signs or symptoms that persist or recur or who have a sustained 4-fold increase in a nontreponemal test titer probably failed treatment or were reinfected. These patients should be retreated after reevaluation for HIV infection. Unless reinfection is certain, a lumbar puncture should also be performed. Most experts recommend retreatment with 3 weekly injections of benzathine penicillin G 2.4 million units, unless the lumbar puncture demonstrates neurosyphilis is present. Management of patients with a coexisting HIV infection or in whom the nontreponemal titer fails to decline is beyond the scope of this chapter. Patients with latent syphilis should be evaluated with a quantitative nontreponemal serologic test at 6, 12, and 24 months.

Other Considerations. All patients with latent syphilis should be evaluated clinically for evidence of tertiary disease (eg, aortitis, neurosyphilis, gumma, iritis). Patients with syphilis and any of the following findings should have a prompt cerebrospinal fluid examination: (*a*) neurologic or ophthalmic signs or symptoms, (*b*) evidence of active tertiary syphilis, (*c*) treatment failure (titer increases 4-fold; an initially high titer [$\geq$ 1:32] fails to decline at least 4-fold; signs or symptoms attributable to syphilis develop in the patient), or (*d*) HIV infection with latent syphilis or syphilis of unknown duration.

*The procaine penicillin regimen should only be used if compliance can be assured. Some experts also give 2.4 million units IM of benzathine penicillin at the end of either of the neurosyphilis regimens.

Source: Centers for Disease Control and Prevention. 1998 guidelines for treatment of sexually transmitted diseases. *MMWR*. 1998;47(RR-1).

connective tissue diseases (a false-positive VDRL may be the earliest sign of systemic lupus erythematosus), immunoglobulin abnormalities, narcotic addiction, advanced age, malignancy, and leprosy. Biological false-positive titers are usually low. A positive test cannot be assumed to be a false positive simply because a patient has a condition that may cause a false-positive result. This is particularly true for pregnant women, because syphilis may have devastating consequences to the fetus. The serologic diagnosis should be promptly confirmed or ruled out with a confirmatory test. In cases where a confirmatory test is not readily available or the patient is unreliable, it may be necessary to treat the patient as if he or she has syphilis, in order to prevent possible disease progression and transmission to future sex partners.

The treponemal tests measure antibodies to treponema, using *Treponema pallidum* as an antigen. They are far more specific than the screening tests (although not sufficiently specific to distinguish syphilis from other treponemal infections such as yaws) but are also technically more difficult to perform and more costly. For these reasons, the treponemal tests are used to confirm positive results from the screening tests. The two tests used are the fluorescent treponemal antibody absorbed (FTA-ABS) and the microhemagglutination treponemal pallidum (MHA-TP) tests, which yield comparable results. The FTA-ABS is somewhat more sensitive than the VDRL and may be positive a few days earlier. In general, treponemal tests remain positive for life. If treatment is begun sufficiently early, however, the treponemal test will become nonreactive within 2 years in about 10% of cases.

Military field units customarily use only the rapid plasma reagin (RPR) test, often only the qualitative RPR. This can create diagnostic problems because confirmatory testing may not be readily available. This forces the health care provider to use clinical judgment in deciding whether to treat a possible case of syphilis, with accompanying implications for the accuracy of epidemiologic reporting of syphilis cases.

Recommendations for Therapy and Control. Penicillin treatment renders patients noninfectious within 24 to 48 hours. In the absence of treatment, the duration of infectiousness is variable and difficult to predict. Patients are infectious for at least a year after their initial infection and possibly for as long as 4 years. After that time, syphilis is only transmitted congenitally or by blood transfusion or blood contact. Because the VDRL test provides quantitative titers, it can be used to follow the results of treatment. Titers should be obtained at 3-month intervals for a year. During adequate treatment of primary and secondary syphilis, titers should fall 4-fold by 4 months and 8-fold by 8 months (see Exhibit 38-12).

Human Immunodeficiency Virus Infection and Acquired Immunodeficiency Syndrome

HIV has military implications that make it unique among STDs. US forces deploy to areas, such as Africa and Thailand, where HIV is highly prevalent, particularly among commercial sex workers. It is the only STD for which the US military mandates and routinely carries out screening, followed by an extensive program of support and medical treatment of those found to be infected. HIV-seropositive individuals are restricted from overseas service.

Description of the Pathogen. The human immunodeficiency virus, a retrovirus, has two types: type 1 and type 2. HIV 1 is found worldwide. HIV 2 is largely confined to western Africa.

Epidemiology. HIV infection is transmitted by sexual exposure or exposure to infected blood and is found worldwide. The combination of STDs and HIV infection has created what Wasserheit aptly termed "epidemiologic synergy,"[326] in which the interaction of these diseases promotes and enhances the spread of all of them. Diseases that cause genital ulcers increase the likelihood of acquiring HIV by providing entry portals.[327–329] Nonulcerative diseases produce inflammatory changes that may also offer opportunities for HIV acquisition.[328–331] Transmission of HIV in the opposite direction may also be enhanced because ulcers and inflammation may provide greater opportunities for virus shedding.

Studies of US Army personnel who seroconverted for HIV found these risk factors: increasing numbers of female sex partners, nonsteady partners, having sex on the first day of acquaintance, sex with prostitutes, and sex with partners who had multiple partners.[260,332] The risk perhaps was epitomized by the finding that those who had sex on first encounter with 3 or more partners had an odds ratio of 6.9 for HIV infection.

HIV infection rates are an exception among STDs in the US military in that mandatory testing, combined with a reliable laboratory test, has produced accurate incidence and prevalence information. Testing of applicants for military service between 1985 and 1989 revealed a seropositivity rate of 0.34 per 1,000 but with a marked geographic variation.[289,333] Rates were greater than 2 per 1,000 in urban areas of Maryland, New York, Texas, and the

District of Columbia. Initial testing of 1,752,191 active duty personnel who remained on active duty as of April 1988 revealed an overall HIV seroprevalence of 1.3 per 1,000. Blacks were 3.6 times and Hispanics 2.5 times as likely as non-Hispanic whites to be seropositive for HIV-1.[334] Prevalence was highest among those who were male, unmarried, and of enlisted rank. Incidence rates (per 1,000 person-years) have been less than 1. The Air Force incidence rate declined from 0.19 to 0.17 between 1987 and 1990.[254] Army rates fell from 0.77 (1985-1987) to stabilize at about 0.22 after 1988.[255,335] Navy and Marine Corps incidence rates for 1986 to 1988 were 0.69 and 0.28 respectively.[256] The Navy incidence fell from 0.55 in 1990 to 0.26 in 1995, while the Marine Corps rate fell from 0.28 to 0.11 during the same period.[336] Navy HIV infections were not associated with visits to foreign ports.[337] Rates among Army reserve personnel were comparable to those in active duty personnel.[338] The frequency of HIV testing for military personnel ranges from 1 to 3 years or more, depending on the individual service policy, the deployability of the unit, whether the unit is reserve or active duty, and other considerations such as the incidence rate. In general, rapidly deployable units are tested more frequently.

Pathogenesis and Clinical Findings. A discussion of AIDS and related management issues is beyond the scope of this book. The initial HIV infection may be asymptomatic, but an unknown proportion of individuals have an infectious mononucleosis–like illness a few weeks after the infection. This illness, particularly characterized by adenopathy, resolves quickly and is followed by seroconversion. Individuals seroconvert 6 to 12 weeks after infection, although some may require as long as 6 months. Infectivity begins about 2 weeks before seroconversion, creating a seronegative window of infectiousness. Individuals are infectious for life, although infectivity seems to be increased in the first few months of infection and in the terminal stages, when the viral burden is the greatest. Progression to deteriorating immune function, opportunistic infections, and frank AIDS requires 10 years on average but may occur as rapidly as in 1 year.

Diagnostic Approaches. Simple enzyme immunoassays (EIAs), suitable for field use, are available for diagnosing HIV. They have a relatively high rate of false-positive results and therefore require confirmation with the Western blot or another confirmatory test, which are not available in the field. Using EIAs in the field has limited practical use in the absence of a confirmatory test result. Unlike a positive RPR, which may indicate an infection that can be easily treated, there is no treatment for a putatively HIV-infected individual except counseling to avoid sexual exposure and to counteract the considerable trauma of being told he or she might have HIV infection.

Recommendations for Therapy and Control. HIV serotesting of applicants for military service began in fall 1985, with testing of active duty personnel commencing in January 1986. An organized program was implemented to obtain surveillance data on HIV infection among military personnel and in areas where they might deploy, to conduct behavioral research that might lead to reducing risky sexual behavior, and to develop HIV field tests, vaccines, and antiretroviral drugs.[339–341]

Notification of a service member that he or she is HIV positive takes place in various ways and locations, but certain common themes emerge. The matter is treated as confidential, with only the senior medical representative, the commanding officer, and a few other individuals being informed of the member's status (eg, the chaplain, the command's senior enlisted person). The reaction varies. A few members are not surprised, and some of these already know they are HIV positive from testing done outside the service. A few break down emotionally and begin crying. The majority act stunned, sometimes dramatically so. Denial is not unusual. A medical representative explains the implications of the HIV test results to the member and provides information as to what will happen next. It may be necessary to repeat this information at a later time, because the service member may not comprehend what is being said the first time. An individual may have many questions about the meaning of a positive HIV test and about AIDS. The basic information can be kept simple (Exhibit 38-13).

All services evaluate newly identified HIV-seropositive individuals at central locations. It is desirable to remove the servicemember as quickly as possible (eg, within 2 to 3 days) in case confidentiality is violated and to provide a supportive environment as quickly as possible. Suicide may be a concern. Seropositive individuals should be evaluated to determine whether suicide precautions are necessary, which may include escorting the individual to the evaluation center. Such precautions are rarely necessary, however, and are understandably resented by individuals who do not want the suicidal stigma added to the burden of being newly diagnosed as HIV-infected.

It is not necessary for field or shipboard medial units to query the HIV-infected individual as to how he or she may have been infected or by whom. This

EXHIBIT 38-13

WHAT TO TELL THE PATIENT ABOUT A POSITIVE HUMAN IMMUNODEFICIENCY VIRUS TEST

1. A positive test means you are infected with HIV, the virus that causes AIDS. You will be infected with this virus for the rest of your life.
2. You do not necessarily have AIDS now. If you had a negative test in the last few years, you probably will not develop AIDS for several years.
3. Current anti-HIV drugs are usually able to control the virus and delay the onset of AIDS for many years. They may be able to prevent you from ever getting AIDS.
4. Because you will have HIV in your body for the rest of your life, you can infect other people with this virus for the rest of your life. You can infect them by having sex with them, sharing needles with them when using drugs, donating blood, or breastfeeding your baby. What you can do about this will be explained in detail later. For now, you must not have sex with anyone or donate blood.
5. The test cannot tell us how you became infected.
6. The test cannot tell us when you became infected, except that it probably happened sometime between your last negative test and this test.

epidemiologic information will be obtained when the individual is evaluated to determine the extent and nature of his or her infection. The evaluation program will also assist the service member in notifying his or her sexual contacts. The evaluation programs vary but generally last 1 to 2 weeks and thoroughly evaluate the service member's health, determine the stage of HIV disease, and, if appropriate, begin anti-HIV medications. Psychological, sociological, and spiritual support is also provided for the individual and family. Detailed education and counseling is provided so the individual thoroughly understands HIV infection and AIDS, the probable course of the illness, and options regarding his or her career and other matters.

Genital Warts

Description of the Pathogen. Human papilloma virus (HPV) is the etiologic agent of genital warts (condyloma accuminata). There are over 30 strains of HPV, some of which are highly associated with cervical and other cancers.

Epidemiology. Genital warts, found worldwide, are transmitted by sexual contact. They are infectious, probably because trauma associated with sex releases virions, which are then rubbed into epithelial surfaces. By eliminating overt lesions, treatment probably reduces HPV infectiousness. However, because HPV virions are commonly present in normal skin, HPV-infected persons may infect others even in the absence of overt warts. Condoms may reduce the transmission of HPV but will not entirely prevent it. Because of the association with cervical cancer, women who have had genital warts or whose partners have had genital warts should have regular Pap smears.

Diagnostic Approaches. Diagnosis is by clinical appearance, but only a minority of infections present as overt lesions. Small lesions may require magnification to be seen.

Recommendations for Therapy and Control. Treatment removes visible, symptomatic warts but does not eradicate HPV or affect the development of cervical cancer. Removal may not decrease infectivity. Untreated, visible genital warts may resolve, remain unchanged, or increase in size and number. The numerous treatment regimens for genital warts may be divided into patient-applied (eg, podofilox 0.5% solution or gel, imiquimod 5% cream) or provider-administered (eg, cryotherapy, podophyllin resin 10%-25%, trichloracetic or bichloroacetic acid 80%-90%, surgical removal) treatments. The 1998 CDC treatment guidelines[266] should be consulted for the detailed instructions necessary to administer these treatments. The safety of podofilox, imiquimod, and podophyllin during pregnancy has not been established.

Lymphogranuloma Venereum

Description of the Pathogen. Lymphogranuloma venereum (LGV) is caused by the L1, L2, and L3 serotypes of *C trachomatis*.

Epidemiology. LGV is transmitted through direct contact with open lesions, usually during sexual intercourse. It is found worldwide and is endemic in Asia and Africa. It is more commonly diagnosed in men but that may be due to the large number of asymptomatic infections in women. In temperate climates, most cases are found in male homosexuals.[144]

Pathogenesis and Clinical Findings. The incubation period can be long and is divided into two phases. The initial period is 7 to 12 days and produces a transient papule, vesicle, or ulcer. This is

painless and in 60% to 90% of the cases is never noticed. The characteristic inguinal adenitis appears from 5 to 50 days later and in two thirds of the cases is unilateral. It is firm, hard, tender, and fixed to the skin. The "groove sign" or "shelf sign," a linear depression in the adenopathy due to Poupart's ligament running between the nodes, is a helpful diagnostic sign. Systemic manifestations include chills, fever, malaise, nausea, weight loss, headache, and arthralgias. If untreated, the adenitis enlarges, becomes fluctuant, and forms multiple tracts though the skin, which may drain for months. Adenitis is seen more commonly in men than in women, by a ratio of approximately five to one. Women usually have a cervical infection, which may persist for months. Persistent urethritis, proctocolitis, and chronic ulcerations may also occur.

Diagnostic Approaches. The diagnosis of LGV is usually clinical; the presence of purple erythematous skin discoloration over the adenopathy and the development of fluctuance are helpful diagnostic signs. Serological tests for LGV are not reliable and generally should not be used. The complement fixation can be considered positive if there is a 4-fold rise in titer or a single titer of 1:64 or greater. Adenopathy and adenitis are seen in both chancroid and LGV, but chancroid is distinguished by the coexistence of an ulcer. In LGV, the ulcer occurs before the adenopathy.

Recommendations for Therapy and Control. Untreated patients may remain infectious for months; all active lesions should be considered infectious (Exhibit 38-14).

Chancroid

Description of the Pathogen. Chancroid ("soft chancre," to distinguish it from the indurated chancre of syphilis) is a genital ulcerative disease caused by *Haemophilus ducreyi*, a short, fine, Gram-negative streptobacillus. It attacks only the skin, not the mucous membranes.

Epidemiology. Chancroid is spread by contact with discharges from open lesions, usually during sexual contact. It is most prevalent in tropical and subtropical areas. It is less common in temperate zones. In tropical and subtropical areas, the incidence of chancroid may be higher than syphilis and approach the incidence of gonorrhea.[144] Women are often asymptomatic carriers, and men are much more likely to be symptomatic. Chancroid often occurs in local epidemics.

Pathogenesis and Clinical Findings. Chancroid is notable for a remarkably short incubation period, 12 hours to 3 days; 5 days is the maximum. It begins as a small macule, which quickly progresses to a pustule and then to an ulcer. The ulcer is painful, tender, soft, and rapidly growing. It is irregular, ragged, and dirty and has undermined edges and a yellow-gray membrane. When skin surfaces are opposed (eg, under the foreskin), a "kissing ulcer" develops, but this is not unique to chancroid. Over 50% of patients develop inguinal adenopathy within a week. It is usually unilateral, fixed, matted, and tender. Untreated, the inguinal nodes often evolve into a bubo, which suppurates through the skin. Constitutional symptoms are mild or absent. Patients are infectious for as long as the original ulcer is present or lymph node sinus tracts are draining, which may be months.

Diagnostic Approaches. The diagnosis is usually clinical, and, as with all genital ulcers, syphilis and HSV infection must be included in the differential diagnosis. A Gram stain of a swab from the lesion may reveal the "school of fish" appearance (curved, parallel lines of bacteria adhering to mucous strands) said to be characteristic of chancroid. Usually, however, the smear simply reveals a wide variety

EXHIBIT 38-14

TREATMENT OF LYMPHOGRANULOMA VENEREUM

Recommended

Doxycycline 100 mg orally twice a day for 21 days

Alternate Regimen

Erythromycin base 500 mg orally 4 times a day for 21 days

Pregnancy. Pregnant women should be treated with erythromycin.

Follow-Up. Patients should be followed clinically until signs and symptoms have resolved.

Management of Sex Partners. Sex partners of patients who have LGV should be examined, tested for urethral or cervical chlamydia infection, and treated for LGV if they had sexual contact with the patient during the 30 days preceding the onset of symptoms in the patient.

Source: Centers for Disease Control and Prevention. 1998 guidelines for treatment of sexually transmitted diseases. *MMWR*. 1998;47(RR-1).

EXHIBIT 38-15

TREATMENT OF CHANCROID

Azithromycin 1 g orally in a single dose

OR

Ceftriaxone 250 mg intramuscularly in a single dose

OR

Ciprofloxacin 500 mg orally twice a day for 3 days

OR

Erythromycin base 500 mg orally 4 times a day for 7 days

Pregnancy. Ciprofloxacin is contraindicated for pregnant and lactating women and for persons less than 18 years old. Preliminary data indicate azythromycin may be safe in pregnancy, but data are insufficient to recommend its use in pregnancy.

Follow-up. Patients should be reexamined 3 to 7 days after initiation of therapy. If treatment is successful, ulcers improve symptomatically within 3 days and objectively within 7 days after therapy. Large ulcers may require more than 2 weeks to heal; in uncircumcised men ulcers under the foreskin are slower to heal. Clinical resolution of fluctuant lymphadenopathy is slower than that of ulcers and may require drainage even if the ulcers are resolving. Needle aspiration of buboes is a simpler procedure, but incision and drainage may be preferred over multiple needle aspirations.
If no clinical improvement is evident within 3 to 7 days, the clinician should consider: (*a*) Was the diagnosis of chancroid correct? (*b*) Is the patient coinfected with another sexually transmitted disease? (*c*) Is the patient coinfected with HIV? and (*d*) Is the ulcer due to a strain of *Haemophilus ducreyi* that is resistant to the antibiotic used for treatment?

Sex Partners. Sex partners who have had intercourse with the patient during the 10 days preceding the onset of the patient's symptoms should be treated with a regimen active against chancroid even if the partner has no symptoms.

Source: Centers for Disease Control and Prevention. 1998 guidelines for treatment of sexually transmitted diseases. *MMWR*. 1998;47(RR-1).

of organisms in no particular pattern and is considered nondiagnostic. The organism can be cultured, but this requires a well-equipped microbiology laboratory and a highly experienced microbiologist. Consultation with the microbiologist before collecting the specimen is advisable.

Recommendations for Therapy and Control. Treatment renders the patient noninfectious in 1 to 2 weeks (Exhibit 38-15).

[S. William Berg, MD, MPH]

VIRAL HEPATITIS

Introduction and Military Relevance

Jaundice has been identified since antiquity as a problem of armies in the field and in garrison. An epidemic in 1629 in military forces in Spa, Germany, during the Thirty Years' War underscores the longstanding threat of viral hepatitis to military operations. More than 72,000 cases occurred during the American Civil War.[342] From January 1943 through March 1945, there were more than 35,000 cases of infectious hepatitis among US personnel in the Mediterranean Theater of Operations, a loss equivalent to over 2 infantry divisions.[343] During the wars in Korea and Vietnam, viral hepatitis remained a significant problem for military physicians.[344]

During World War II, two types of hepatitis were clearly recognized: (1) infectious, characterized by a short incubation period and a benign outcome, and (2) serum, characterized by a longer incubation period with longer morbidity and occasional

chronic disease. These were subsequently renamed hepatitis A and hepatitis B. Ironically, recognition of hepatitis B was linked to reuse of unsterilized needles in arsenical therapy of syphilis[345] and the use during World War II of yellow fever vaccine that was stabilized with infectious human serum.[346–349] Figure 38-7 shows the incidence of jaundice cases during and immediately after World War II in the US Army.

Control of hepatitis A has been a major concern for US military forces in war and peace. Advances in sanitation, along with the discovery that immune globulin (IG) provided protection against hepatitis A[350,351] have, however, reduced the military threat of this disease in recent US military operations. The efficacy of IG was first demonstrated in an outbreak of epidemic hepatitis, which we now assume was hepatitis A, in a summer camp in 1944[350] and was confirmed in studies among US soldiers in World War II and more recently.[352–354] A large, controlled trial by the US Army during the Vietnam War determined that 5 mL of IG was as effective as 10 mL in preventing viral hepatitis.[355]

IG, though effective, is cumbersome to use. The prevalence of hepatitis A antibody has been decreasing in the general US population and hence also in the military population, putting these people at risk for hepatitis A both during and between deployments. The US Army has been very active in the development of a vaccine for hepatitis A. The first successful cell-culture-derived, formalin-inactivated hepatitis A vaccine was developed at the Walter Reed Army Institute of Research.[356] This prototype was shown to be safe and immunogenic for humans in 1986.

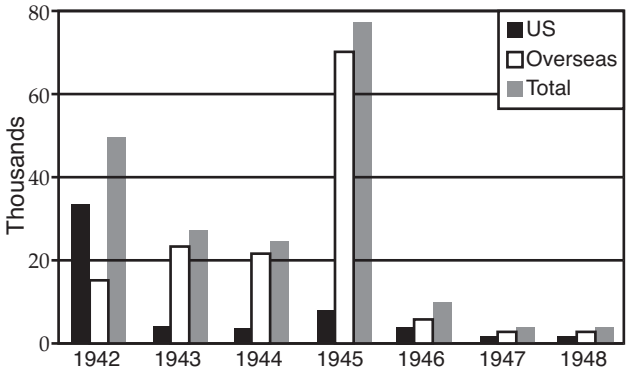

Fig. 38-7. The large number of cases of hepatitis in 1942 in the continental United Stated appears to be related to hepatitis B spread by specific lots of yellow fever vaccine containing infectious human sera, while the later rise in cases overseas primarily reflects hepatitis A contracted by US Army personnel in the European Theater of Operations.
Source: Havens WP Jr. The military importance of viral hepatitis. *U.S. Armed Forces Med J.* 1952;3:1013–1022.

Advances in trauma surgery, including increased use of blood transfusions, have led to an increasing awareness of the importance of hepatitis B and C to military medical personnel. The threat of transfusion-related hepatitis B and C for military personnel has been significantly reduced by the application of advances in basic virology, diagnostic testing, immunization, and screening of blood donors.[357] As in other segments of US society, the threat of sexually transmitted hepatitis will remain a problem for the foreseeable future.[348,358,359]

Description of the Pathogens

Table 38-6 outlines some of the characteristics of the hepatidities. Hepatitis A virus (HAV) is a member of the family *Picornaviridae* and is related to the enteroviruses and the rhinoviruses.[360] It is a nonenveloped, spherical virus 26 to 28 nm in diameter with single-stranded RNA of positive polarity. Unlike other picornaviruses, it is relatively resistant to heat, which accounts for its ease of transmission in partially cooked food.[361]

Hepatitis B virus (HBV) is an enveloped, double-stranded DNA virus of the *Hepadnaviridae* family; related viruses cause hepatitis in woodchucks and ducks.[362] The outer coat, hepatitis B surface antigen (HBsAg), is associated with intact virions (Dane particles) and other particles. The excess of antigen typically present in the blood during chronic infection is useful in diagnostic testing. It also supplies material for plasma-derived vaccines, which are no longer used in the US but are still used in other areas of the world.

Hepatitis C virus (HCV) is related to the flaviviruses, which cause dengue, yellow fever, Japanese encephalitis, but it is closer to the pestiviruses (flaviviruses of animals).[363] It is a spherical, lipid-enveloped particle ranging in size from 35 to 50 nm. The genome consists of a single-stranded RNA of positive polarity, 9.4 kilobases in size.

Hepatitis D virus (HDV) consists of a circular, single-stranded RNA molecule associated with delta antigen; this is surrounded by HBsAg. In the absence of hepatitis B infection, HDV cannot replicate. For this reason, HDV is considered a defective virus.[364]

Hepatitis E virus (HEV) is a small, round, nonenveloped virus, with properties similar to

TABLE 38-6

CHARACTERISTICS OF HEPATITIS VIRUSES

	Virus	Type	Distribution	Transmission	Special Characteristics
A	Picornavirus	RNA	Global	Enteric	Relatively heat resistant, vaccine preventable
B	Hepadnavirus	DNA	Global; highly endemic in Asia, Africa, Latin America	Parenteral, sexual, vertical	Chronic infection, carcinogenic, vaccine preventable
C	Flavivirus	RNA	Global	Parenteral, sexual, vertical	Chronic infection, cirrhosis, carcinogenic
D	—	RNA	Global; prevalence varies widely (highest reported prevalence: southern Italy, Africa, South America)	Parenteral	Defective virus (requires active HBV infection to replicate), unique delta antigen, vaccine preventable (HBV)
E	Calicivirus	RNA	Asia, Africa, Mexico	Enteric	Often via contaminated water, women in 3rd trimester of pregnancy especially susceptible to fulminant hepatitis
F	?	?	?	Enteric?, parenteral	Some cases may represent "silent" HBV infection by mutant HBV
G	Flavivirus	RNA	Global?	Parenteral	Post-transfusion hepatitis

those of the family *Caliciviridae*. Its genome is a single-stranded, positive-sense RNA of approximately 7.5 kilobases.[365] It infects swine, and this may play a role in the ecology of the virus.[366,367]

A candidate hepatitis F virus has been isolated from human stool and appears to be transmissible to primates.[368] Uchida and colleagues[369] believe that some cases of hepatitis F are caused by mutant hepatitis B variants with suppressed replication and HBV DNA expression.

Hepatitis G virus (HGV) is a small RNA virus, related to other flaviviruses and distantly to HCV. It is transfusion-transmissible and has a global distribution.[370] Currently there is substantial doubt regarding the role HGV plays in the pathogenesis of hepatitis. Studies[371,372] of community-acquired hepatitis and transfusion-acquired hepatitis cast doubt on the relation of HGV to disease.

Hepatitis F and G have been included here for completeness, but because they are not major causes of disease, they will not be discussed further.

Epidemiology

Hepatitis A and E (Fecal-Oral Transmission)

Hepatitis A and E are spread through fecal-oral contact. While transmission via blood contact has been described, it appears to be unusual.[373,374] Common-source foodborne and waterborne epidemics, including those caused by shellfish contaminated with human sewage, are well described. Poor hygiene and intimate contact (sexual or nonsexual) account for the spread of hepatitis A in daycare centers, among homosexuals, and in families. Spread occurs readily in households and daycare centers, although recent data suggest that, in the daycare setting, occupational exposure is uncommon under non-outbreak circumstances.[375] The risk of spread in a daycare center increases with the number of children enrolled who are younger than 2 to 3 years of age and who wear diapers. Most commonly, the adult daycare workers are symptomatic (icteric) with their disease whereas daycare attendees are frequently asymptomatic and have nonspecific disease manifestations; spread of hepatitis A frequently occurs in the daycare center before the index case is recognized. Because daycare in a military community is commonly provided by a central facility, an outbreak among young children may provoke rapid spread of hepatitis A to an active duty population.[376]

HAV is found worldwide (Table 38-7), but areas of high endemicity include Africa, Asia excepting Japan, the Mediterranean region, Eastern Europe, the Middle East, Central and South America, Mexico, and parts of the Caribbean region.

Several patterns of infection are described.[360] In developing countries with poor sanitation, infection is almost universal among children, so adults are immune; in such situations, nonimmune people

TABLE 38-7

HEPATITIS SEROPREVALENCE STUDIES IN SELECTED COUNTRIES

Country	Population Studied	HAV	HBV	HCV	Reference
Cambodia	Adults	100%	73%	6.5%	Thuring[a]
Singapore	Adults	27%	—	—	Yap[b]
Pakistan	Children	55.8%	2.97%	0.44%	Agboatwalla[c]
South Africa	White adults	50%	—	—	Sathar[d]
South Africa	Black adults	91%	—	—	Sathar[d]
Egypt	Adults	100%	66%	51%	Darwish[e]
Nicaragua	Adults	94.6%	6.5%	0%	Perez[f]
USA	Native Americans	76.2%	—	—	Shaw[g]

a. Thuring EG, Joller-Jemelka HI, Sareth H, Sokhan U, Reth C, Grob P. Prevalence of markers of hepatitis viruses A, B, C, and of HIV in healthy individuals and patients of a Cambodian province. *Southeast Asian J Trop Med Public Health*. 1993;24:239–249.
b. Yap I, Guan R. Hepatitis A sero-epidemiology in Singapore: A changing pattern. *Trans R Soc Trop Med Hyg*. 1993;87:22–23.
c. Agboatwalla M, Isomura S, Miyake K, Yamashita T, Morishita T, Akram DS. Hepatitis A, B, and C seroprevalence in Pakistan. *Indian J Pediatr*. 1994;61:545–549.
d. Sathar MA, Soni PN, Fernandes-Costa FJ, Wittenberg DF, Simjee AE. Racial differences in the seroprevalence of hepatitis A virus infection in Natal/KwaZulu, South Africa. *J Med Virol*. 1994;44:9–12.
e. Darwish MA, Faris R, Clemens JD, Rao MR, Edelman R. High seroprevalence of hepatitis A, B, C, and E viruses in residents in an Egyptian village in the Nile Delta: A pilot study. *Am J Trop Med Hyg*. 1996;54:554–558.
f. Perez OM, Morales W, Paniagua M, Strannegard O. Prevalence of antibodies to hepatitis A, B, C, and E viruses in a healthy population in Leon, Nicaragua. *Am J Trop Med Hyg*. 1996;55:17–21.
g. Shaw FE Jr, Shapiro CN, Welty TK, Dill W, Reddington J, Hadler SC. Hepatitis transmission among the Sioux Indians of South Dakota. *Am J Public Health*. 1990;80:1091–1094.

entering the community, such as military personnel, are at risk. In developed countries, fewer children are infected, and this leaves a larger pool of susceptible adults. In this setting, disease commonly occurs during breaks in either personal or communal sanitation. Epidemics may also occur in closed populations, with rapid spread and high prevalence. In addition to these age patterns, seasonal patterns have been described, with peaks in autumn or early winter in temperate climates.[377] Finally, several large groups are at higher risk for infection with HAV: workers in settings where high standards of sanitation are not met (eg, institutions for the mentally retarded, daycare centers), homosexual men, intravenous drug users, and travelers to areas with high incidence of HAV infection.

Contaminated drinking water appears to be the most prominent route of spread of hepatitis E.[378,379] Hepatitis E has a more geographically limited range than hepatitis A; originally described in India, it has been found throughout mainland Asia, Africa, and Latin America. Cases have also been reported from Italy and Spain. Of interest is the susceptibility of adults to HEV in countries with widespread childhood infection with HAV; since the mechanisms of spread are similar, it is unclear why this situation exists.[380]

Hepatitis B, C, and D (Body Fluid Transmission)

That hepatitis could be spread by intimate contact with blood or body fluids was noted in 1833, when an epidemic of jaundice occurred in Bremen among shipyard workers vaccinated against smallpox with human serum.[381] Discoveries by Blumberg in the 1960s led to the characterization of HBV as the predominant cause of bloodborne hepatitis.[382]

Hepatitis B is transmitted through blood or body fluids (eg, wound exudates, semen, cervical secretions, saliva). High levels of viremia correlate with infectivity of small inocula of blood.[383] Contracting hepatitis B through transfusion of blood or blood products, once a common mode of transmission, is now rare in the United States because of marked improvements in screening blood and blood products; the risk of HBV infection from a donor whose unit passes all screening tests is now estimated to be 1 in 63,000 (95% confidence interval, 31,000-147,000).[357] Other more common modes of transmis-

sion include sharing or reusing unsterile needles or syringes, percutaneous or mucous membrane exposure to blood or body fluids, and sexual activity. Hepatitis B infection among unvaccinated health care employees with the highest exposure to blood occurs at a rate of 1.05/100 person-years.[384] HBV is also spread efficiently by sexual contact; this is the most important source of hepatitis infection among the US military today.[358] HBV is readily transmitted vertically from mother to baby, although efforts to minimize this mode of transmission in the United States by vaccination of newborns have significantly reduced the numbers of infants infected. Hepatitis B virus can survive in the dried state for prolonged periods of time, and percutaneous contact with contaminated inanimate objects may transmit infection. Hepatitis B is not transmitted by the fecal-oral route and is found worldwide.

Unlike HAV, HBV produces chronic infections in a subset of patients. The burden of chronic disease is higher in areas where HBV infections are acquired earlier in life; a recent study[385] in China showed an overall HBV infection rate of 42.6%, with 10.3% testing positive for HBsAg. The highest risk of chronic infection occurs among infected neonates born to HBeAg-positive carrier mothers (80%-90%); of children infected before 6 years of age, chronic infection develops in about 30%. Healthy adults who become infected have a lower risk of chronic infection (< 5%); being male or having impaired immunity increases this risk.[386] Of interest, follow-up of the cohort infected by HBV-contaminated yellow fever vaccine during World War II showed a far smaller percentage of long-term carriage (0.26%).[347]

Hepatitis C

Hepatitis C is most commonly transmitted through direct contact with infected blood. In the United States, risk of transfusing blood infected with HCV has fallen to between 1 in 28,000 and 1 in 288,000 (mean: 1 in 103,000). HCV remains a significant problem among intravenous drug users. Sexual transmission of HCV appears to occur but at a much lower frequency than HBV. Sexual transmission appears likelier with longer duration of exposure to an infected partner[387] and coinfection with human immunodeficiency virus (HIV).[388] Vertical transmission also appears to occur uncommonly; the risk of transmission is proportional to the titer of HCV RNA in the mother.[389] Some health care workers are also at high risk for hepatitis C. Frequently, though, no source or risk factor can be identified. Seventy to ninety percent of parenterally transmitted non-A, non-B hepatitis is thought to be caused by the hepatitis C virus. Hepatitis C is distributed worldwide.

Pathogenesis and Clinical Findings

Viral hepatitis spans a wide clinical spectrum, from totally asymptomatic infection (detectable by specific serologic markers) to acute fulminant hepatitis with liver failure and death. In addition, certain agents (ie, HBV, HCV, HDV) produce chronic hepatitis, with a wide variation in outcomes (from asymptomatic to chronic hepatitis, cirrhosis, and hepatocellular carcinoma). The viruses will be considered separately.

Hepatitis A

The clinical presentation of hepatitis A ranges from asymptomatic infection to fulminant hepatitis. The majority of cases are either asymptomatic or mild; there is a higher risk for more significant symptomatology in adults.[390]

In adults, the clinical syndrome of acute hepatitis A presents 15 to 50 days after infection, with a mean of 30 days.[391,392] The abrupt onset of nausea, vomiting, fever (generally low grade), and vague abdominal discomfort marks the prodromal phase. Loss of taste for food and tobacco is common.[393] Within 2 to 7 days, jaundice and dark urine occur. Serum alanine and aspartate transaminase levels rise quickly during the prodromal period, peak around the onset of jaundice, and then fall rapidly (75% per week). Serum bilirubin peaks later and falls more slowly, but in 85% of cases the period of jaundice lasts less than 2 weeks. Complete clinical recovery by 6 months is the rule.[394] Fecal viral shedding begins late in the incubation phase but before the onset of symptoms. Typically, viral shedding ceases shortly after the onset of icterus and with onset of detectable IgM serum antibody.

Occasional patients will present with a clinical picture similar to acute bacteremia, with a high fever, myalgias, shaking chills, and prostration. Prolonged cholestasis may occur.[395] Such patients have prolonged hyperbilirubinemia and a prolonged clinical course of up to 12 weeks with pruritis, fever, diarrhea, and weight loss. Cholestasis will resolve spontaneously; corticosteroids may hasten its resolution but are likely to lead to a relapse. Relapsing hepatitis occurs in 3% to 20% of adult patients with hepatitis A.[396] Relapse typically occurs 4 to 5 weeks after the acute illness and is accompanied

by viral excretion in the stool.[397] The illness may last up to 40 weeks, although typically the duration is much shorter. IgM antibody to HAV persists throughout the relapse.

Fulminant hepatitis A is relatively rare, with an incidence of 1 to 8 per 1,000 clinical cases. It is more common in older adults and is characterized by rapidly deepening jaundice, hepatic encephalopathy, coma, and falling transaminase levels.[398] The fatality rate exceeds 50%.

Extrahepatic manifestations of HAV infection are rare and include evanescent rashes, transient arthralgias, arthritis, cutaneous vasculitis, and pancreatitis.

Hepatitis B

Acute hepatitis B infection in adults has a longer incubation period (40 to 180 days, average of 90 days) than hepatitis A.[399] The prodromal period may be longer also (up to 3 weeks). Hepatitis B is thought to be more severe than hepatitis A; however, this may be artifactual and based on the more common occurrence of acute hepatitis B in older individuals. During the prodrome of hepatitis B, immunologically related events such as urticaria and arthritis occur.[400]

Long-term consequences of HBV infection include chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Distinguishing between chronic HBsAg carriage and chronic hepatitis relies on demonstration of necroinflammatory changes on liver biopsy. Progression to cirrhosis is more common with active chronic hepatitis but may occur even in the presence of milder histologic abnormalities.[401] Progression to hepatocellular carcinoma was described early in the understanding of HBV infection.[402] The role of HBV in the etiology of hepatocellular carcinoma is now well established. The cohort of servicemen infected with HBV from the contaminated yellow fever vaccine administered in 1942 demonstrated a small excess rate of hepatocellular cancer when compared with controls.[346]

Hepatitis C

Acute HCV infection is more indolent than the other viral hepatitides. Approximately 25% of patients are icteric, and the mortality of acute HCV infection is low (< 1%).[403] HCV infection is a rare cause of fulminant hepatitis.[404] The propensity to develop chronic HCV infection is remarkable. Whereas 2% to 5% of adult patients with HBV develop chronic infection, greater than 50% of HCV infections become chronic. Chronic infection is more likely in males, in older patients, and with larger viral doses.[405] Chronic HCV infection is typically indolent, but despite little if any clinical symptomatology, it produces chronic hepatitis, fibrosis, and cirrhosis in many patients. Up to 25% of those infected develop cirrhosis.[406] Chronic HCV infection is also a major risk factor for developing hepatocellular carcinoma.[407]

As with HBV, HCV infection has been associated with a variety of extrahepatic manifestations. The links between HCV infection and essential mixed cryoglobulinemia,[408] membranoproliferative glomerulonephritis,[409] and porphyria cutanea tarda are strong, and it is suggested that patients with those diagnoses be screened for HCV.[410] Possible associations with other autoimmune diseases, such as Mooren corneal ulcers and autoimmune thyroiditis, also exist.

Hepatitis D

Because it cannot reproduce in the absence of active hepatitis B infection, the clinical manifestations of hepatitis D must be discussed in light of that viral infection. Acute hepatitis D infection occurs either as a coinfection with acute HBV infection or as a superinfection in a patient with chronic HBV infection;[411] the latter is more common. In cases of coinfection with HBV, the likelihood of chronic HDV infection is low (< 5%); when superinfection occurs, the risk of chronic HDV infection is 70% or more because of persistent HBsAg.[412]

Acute HDV hepatitis is clinically severe, with a mortality rate ranging from 2% to 20%.[413] The acute infection is likely to have a biphasic course and to be prolonged over months. Chronic HDV infection appears to result in a higher incidence of cirrhosis than either chronic HBV or HCV infection alone, with the majority of such patients dying of chronic liver disease. The progression to cirrhosis may be quite rapid, occurring as quickly as 2 years after infection.[414]

Hepatitis E

Clinically, HEV shares many characteristics of HAV, the other recognized enteric hepatitis virus. HEV infection has caused both epidemics and sporadic cases of acute hepatitis in developing countries.[415] Cholestasis is more pronounced than in typical HAV infection, with higher levels of serum bilirubin and alkaline phosphatase but lower levels of serum transaminases.[416] Prolonged jaundice may occur, but the disease is self-limited and does not lead to chronic hepatitis or to a carrier state. Recent studies[417] have documented that prolonged viremia and fecal shedding occur in 15% of HEV infections. This may

facilitate transmission.

In the developing world, outbreaks of HEV are most commonly caused by ingestion of fecally contaminated drinking water. In contrast to hepatitis A, young adults are more frequently affected, with higher attack rates for pregnant women. The case fatality rate may be particularly high (15% to 20%) for women in the third trimester of pregnancy.[418] Vertical transmission may be seen, with significant perinatal morbidity and mortality. It is unclear how frequently this occurs.[419]

Diagnostic Approaches

In the Field

The serologic diagnosis of hepatitis A, B, C, D, and E may be made in a regional medical center, a field hospital, a regional research facility, or a forward reference laboratory worldwide.[359,420–422] Most frequently, samples are collected in the field and transported to the regional facility for testing. Some shipboard laboratories may be able to set up commercial testing for hepatitis A, B, C, or D.

In Garrison

Viral hepatitis is suspected in the patient with typical symptoms whose liver function tests (especially serum levels of aspartate aminotransferase and alanine aminotransferase) are elevated, indicating parenchymal liver damage. The specific virus responsible for the hepatitis is distinguishable only by laboratory testing (Table 38-8), though certain epidemiologic settings and laboratory patterns may suggest a particular viral 2,000) are most characteristic of hepatitis A. Elevated alkaline phosphatase levels are not usually seen in hepatitis A and are indicative of a hepatitis-associated cholestasis. Nonspecific indicators in hepatitis A include an elevated level of total serum IgM, a mild lymphocytosis, and, occasionally,

TABLE 38-8

DIAGNOSIS OF VIRAL HEPATITIS AND THE APPROPRIATE INTERPRETATION OF IMMUNOLOGIC MARKERS

	Immunologic Marker	Interpretation				
		Ongoing/Recent Infection	Past/Resolution of Infection	Chronic Infection	Carrier State	Vaccinated
Hepatitis A	Hep A IgM	+	–	N/A	N/A	+
	Hep A IgM+IgG	+	+	N/A	N/A	+
Hepatitis B	HBsAg	+	–	+	+	–
	anti-HBc (IgG)	+	+	+	+	–
	anti-HBc (IgM)	+	–	–	–	–
	Hbe Ag	+	–	+	–	–
	anti-HBe	–	±	–	–	–
	anti-HBs	–	+	–	–	+
Hepatitis D	anti-delta IgM	+	–	–	–	N/A
	HD Ag	+	–	+	N/A	N/A
Hepatitis C	anti-HCV	±*	+	+	N/A	N/A
	HCV RNA PCR	±*	+	+	N/A	N/A
Hepatitis E	anti-HEV†	+	+	N/A	N/A	N/A

+ Marker present
– Marker absent
± Marker present or absent
* Requires 6 weeks to 9 months
† Not commercially available
PCR: polymerase chain reaction

atypical mononuclear cells on blood smear.

The specific diagnosis of hepatitis A is made based on the detection of antibody to the hepatitis A virus. The presence of hepatitis A IgM indicates ongoing or recent infection. The diagnosis of hepatitis A may be made based on a single positive specific IgM result because hepatitis A IgM is present at the time of the first rise in liver enzymes and the first clinical symptoms. Measurement of total antibody to hepatitis A (IgM plus IgG) is not useful in the diagnosis of acute disease unless a 4-fold rise in titer between acute and convalescent specimens is detected. A single positive total antibody to HAV simply indicates infection with the virus in the past.

The most commonly used specific assays for hepatitis A IgM are capture radioimmunoassays or enzyme immunoassays. These tests are highly sensitive and specific. IgM positivity may persist for 3 to 12 months following the onset of illness. False positives are rare but may be associated with administration of IG, recent transfusion, or maternal antibody transfer.

Highly specific and sensitive laboratory tests are commercially available for the multiple markers of hepatitis B infection. The pattern of positive hepatitis B markers provides not only a diagnosis of hepatitis B but often a rough estimate of the stage of the disease, the infectiousness of the patient, and the prognosis. Acute hepatitis B is characterized by positive markers for HBsAg, anti-HBc (IgG or IgM), and HBeAg. HBsAg is the most important marker for active infection since it is almost always present in acute infection. Blood or body fluids, with the exception of sweat, should be considered infectious when they are HBsAg positive. HBeAg can be detected in the serum of most patients in the early stage of infection; HBeAg disappears and anti-HBe appears during the resolution of infection. The presence of HBeAg during acute or persistent infection identifies those patients who are most infectious and in whom active viral replication is ongoing. The presence of anti-HBs either alone or with anti-HBc(IgG) is consistent with past hepatitis B infection. Alternatively, the presence of anti-HBs alone is consistent with hepatitis B vaccination. A persistently positive HBsAg accompanied by a positive anti-HBc(IgG) is found in healthy hepatitis B carriers. Patients with chronic hepatitis B display persistently positive HBsAg, anti-HBc(IgG), and HBeAg markers. (See addendum at the end of the chapter.)

The diagnosis of hepatitis D is only made in the presence of hepatitis B infection. Patients with delta antigen in the liver have antibody to delta antigen in their serum. Hepatitis D is diagnosed by a positive assay for anti-delta IgM and hepatitis D antigen, (HDAg). The presence of anti-HBc(IgM) accompanied by hepatitis D serologic markers identifies hepatitis B–hepatitis D coinfection. Coinfected chronic HBsAg carriers may be persistently positive for delta antigen.

The diagnosis of hepatitis C has been based on the detection of antibodies reactive with recom-binant proteins or synthetic peptides because hepatitis C cannot be grown in vivo to produce a sufficient quantity of viral antigen for laboratory use. HCV antibody enzyme linked immunosorbent assays (ELISAs) were developed for the screening of donated blood but have been widely used for diagnostic purposes. The first generation ELISAs were highly sensitive but poorly specific; false positives were common, particularly in populations with low prevalence of the disease. Second gener-ation ELISAs have shown improvement in both sensitivity and specificity and can make the diagnosis earlier in the infection. Nonetheless, even using second generation testing, only 70% of patients infected with hepatitis C show positive results within 6 weeks of infection.[423] Polymerase chain reaction for the detection of HCV has been developed and is being used increasingly in labor-atories, but its reliability is currently uncertain.[424]

No serologic test is commercially available now for the diagnosis of hepatitis E. The diagnosis is established by the appropriate clinical and epidemiologic characteristics, coupled with the exclusion of hepatitis A, B, C, and D, as well as other viral agents that produce a hepatitis as part of multi–organ-system involvement. Enzyme immunoassays based on recombinant hepatitis E viral proteins are being developed and appear to detect anti–hepatitis E proteins reliably.[425]

Recommendations for Therapy

Hepatitis A

The therapy and management of hepatitis A is supportive. Admission to the hospital is rarely needed; if good sanitation can be assured, patients may be managed at home or in barracks. Separate toilet facilities are needed if the patient has diarrhea or is incontinent of stool. Fulminant hepatic failure from hepatitis A is rare but may occasionally require liver transplant. No specific dietary or bed-rest restrictions have been shown to be of value. Generally, it is recommended that patients abstain from consuming alcohol.

Hepatitis B

No specific therapy has been shown to be of use in acute hepatitis B. As with hepatitis A, the duration of bed rest is dictated by the energy level of the patient. In young patients, early ambulation and mild exercise are not harmful. No dietary restrictions are of any benefit. Corticosteroids have been used in severe acute hepatitis, but controlled trials[426,427] of severe and fulminant hepatitis have shown either no benefit or a negative effect.

The therapy of chronic hepatitis B is more complex. The only agent known to have a lasting beneficial effect is interferon alpha, and hence recombinant interferon alpha is licensed in the United States for the therapy of chronic hepatitis B.[428] Interferon does suppress hepatitis B virus replication in all patients and has significant though clinically limited utility.[429] Therapy of 4 to 6 months' duration induces long-term remission in 25% to 40% of patients. Treatment is recommended for patients with persistently elevated serum levels of aminotransferases; detectable HBsAg, HBeAg, and HBV DNA in serum; chronic hepatitis as shown by liver biopsy; and compensated liver disease.[428] Suppression of hepatitis B markers may be either complete or partial and either permanent or temporary following treatment with interferon alpha. Interferon in high doses causes fever, malaise, hair loss, leukopenia, and thrombocytopenia. These effects are reversible once therapy ceases.

Agents such as prednisone, interferon gamma, thymosin, levamisole, suramin, foscarnet, didanosine, adenosine arabinoside, acyclovir, zidovudine, and fialuridine inhibit hepatitis B virus replication; however, their lackluster efficacy and toxicity have limited their use.[428,430] Ganciclovir has been shown to reduce hepatitis B virus replication after liver transplantation.[431] A number of new nucleoside analogues, such as famciclovir, lamivudine, lobucavir, and adefovir dipivoxil, show promise in the treatment of chronic hepatitis B. Of these, famciclovir and lamivudine have been studied most extensively.[428] In a preliminary trial of 32 patients with chronic hepatitis B infection, 12 weeks of lamivudine therapy were well tolerated, and daily doses of 100 mg and 300 mg reduced HBV DNA to undetectable levels. In most patients, HBV DNA reappeared after therapy was complete, but 19% of patients had sustained suppression.[432] (See addendum at the end of the chapter.)

Hepatitis C

The therapy for hepatitis C is equally complex, controversial, and unsatisfactory. In acute hepatitis C, interferon alpha appears to decrease the chronicity rate. Interferon remains the only approved therapy for chronic hepatitis C,[433] although the low rate of sustained remissions and the significant side effects have mandated a search for ways to improve the efficacy of interferon and for new and more potent agents. Therapy is recommended for patients with elevated serum aminotransferase levels, anti-HCV in serum, and chronic hepatitis as shown by liver biopsy.[428] Current research shows a general trend toward the use of interferon in combination with other agents, such as ribavirin,[434] azidothymidine,[435] or recombinant human granulocyte colony-stimulating factor (rhG-CSF).[436] The response to interferon therapy in chronic hepatitis C may depend in part not only on the dose administered but also on host factors such as the hepatitis C genotype of the infection, the levels of HCV RNA, the fibrosis score of the histologic activity index, the iron concentrations in liver tissue, and the source of the infection.[428,437] (See addendum at the end of the chapter.)

Hepatitis D

Interferon alpha has been used in the treatment of chronic hepatitis D but with marginal success. Hepatitis D virus is inhibited by interferon alpha-2b, although permanent control of the disease is not achieved.[438] In the patient with chronic hepatitis B, it is important to determine whether hepatitis D is present because patients with combined infection respond more poorly to treatment and the recommended regimen of interferon is different (higher dose given for a more prolonged time).[401]

Liver transplantation has become the treatment of choice for fulminant hepatic failure since the advent of cyclosporin A in the early 1980s. Currently more than 2,500 transplants are done annually in the United States. Approximately 7% of these patients undergo transplantation for fulminant or subacute liver failure. Sixty to ninety percent survive 1 to 2 years.[439] The decision for transplantation needs to be made before complications of the hepatic failure are present; patients with incipient hepatic failure should be referred promptly to a liver transplant center.

Recommendations for Control and Prevention

The control and prevention of hepatitis are inextricably intertwined, and both are directly related to the specific epidemiology of each agent. Patients with jaundice thought to be caused by an unidentified hepatitis virus should be placed on contact and standard (formerly known as universal) precautions

pending further elucidation of the specific virus.

The advent of hepatitis vaccines has enhanced the ability to control and prevent these diseases. Hepatitis vaccines have two purposes: (1) to prevent the morbidity and occasional mortality associated with acute infection and (2) to reduce the occurrence of chronic liver disease and hepatocellular carcinoma. For the first aim, the principal targets are hepatitis A and B; for the second, the targets are hepatitis B and C. Hepatitis A and B can both be prevented by immunization. The increasing use of immunization for hepatitis A and B prevention will gradually obviate the need for IG prophylaxis.

Hepatitis A

Since hepatitis A is transmitted primarily by the fecal-oral route, good sanitation and handwashing are paramount in the control of this disease. This is especially important for food handlers, whether in garrison or in the field. Detection of the ill food handler and restriction of his or her activities are essential in prevention and control. The field offers an excellent setting for transmission of this disease via food handling if appropriate care is not exercised and the involved military personnel have not been immunized. The advent of active immunization for hepatitis A will further reduce its impact on military forces, but even so, a foodborne outbreak of hepatitis A during a field training exercise that resulted in 22 ill soldiers and more than 300 lost work days was recently described.[420] In this outbreak, the secondary attack rate was nearly 20%. The index case was a cook's aide, who complained of fatigue, anorexia, and dark urine after 12 days in the field. Poor personal hygiene, inadequate sanitation, crowded conditions, and lack of immunization (vaccine was not available at that time) all facilitated this outbreak of hepatitis A. Food handlers should be repeatedly encouraged to report illness, and a work environment should be created where food handlers are not penalized or made uncomfortable when they do so. Food handlers should be prospectively immunized against hepatitis A. As the immunization of military personnel continues, the threat of hepatitis E may be larger as US forces deploy into areas of the world where this other enterically spread pathogen is common.[440,441]

Infection with hepatitis A is endemic in developing countries. Travelers to such destinations, whether they are deploying or traveling for pleasure, should be advised to seek immunization prospectively and to take specific precautions. Only well-cooked, hot food should be ingested. Only bottled beverages should be drunk and those without ice. Eating uncooked vegetables, fruit not peeled by the consumer, and shellfish is associated with risk. Hepatitis A vaccine is now recommended for all military personnel.

Nosocomial spread of hepatitis A is rare, even when patients share the same room and toilet facilities. Standard precautions are all that is required for the hospitalized patient with hepatitis A.

Use of Immune Globulin. Before the hepatitis A vaccine, pooled IG was the mainstay of immunoprophylaxis. In the absence of prior hepatitis A vaccination, all household and sexual contacts of persons with hepatitis A should receive 0.02mL/kg of IG as soon as practical after exposure. Serologic testing of contacts is not recommended as it may delay administration of IG and add cost. The use of IG more than 2 weeks after exposure is of no benefit.

Careful handwashing and meticulous environmental hygiene are essential in a daycare setting, particularly after changing diapers and preparing or handling food. Increased education and surveillance of employees and families are necessary for interrupting an outbreak. Outbreaks of hepatitis A in such settings must be reported to local public health officials, as well as to military preventive medicine units as applicable. Currently available hepatitis vaccines are not licensed for use in children under 2 years of age. Adult care takers should be immunized prospectively against hepatitis A. Recommendations for the use of IG for an outbreak of hepatitis A in a daycare setting are complex and vary depending on the ages of the children cared for, whether they are toilet trained, whether household contacts are involved, and how long a delay has elapsed before recognition of the disease. All recommendations involve the use of IG (0.02mL/kg). For further specifics, see a standard reference.[442,443] Schoolroom exposure generally does not pose a risk for transmission, and IG administration is not indicated.

If an outbreak occurs in institutions for custodial care, such as prisons, institutions for the mentally disabled, and nursing homes, residents and staff in close contact with infected persons should receive IG (0.02 mL/kg). Emphasis should be placed on careful handwashing and good personal hygiene. Generally, immunoprophylaxis is not required in a barracks setting unless conditions of poor handwashing, hygiene, sanitation, and crowding are present and transmission is likely.

In foodborne or waterborne outbreaks of hepatitis A, generally the source is recognized too late for IG to be effective. IG may be effective if it is administered to exposed persons within 2 weeks of the last exposure to hepatitis A–contaminated food or

water. Experiences in the field suggest that standard recommendations are too stringent for such settings. In the field, confirmation of a case of hepatitis A may be difficult and therefore the *presumptive* diagnosis should prompt aggressive epidemiologic investigation. When any person working in a mess tent is presumptively diagnosed with hepatitis A, aggressive use of IG is warranted if laboratory confirmation is unavailable. At a minimum, all cooks should receive IG and consideration should be given to administering IG to all who eat at the mess tent. Clinical decisions should be driven by the aggressive epidemiologic investigation. Ultimately, control and prevention in the field setting depend on good sanitation and effective vaccination of all personnel.[420]

In the absence of previous vaccination, IG prophylaxis for the prevention of hepatitis A is recommended for travelers to developing countries. Those travelers staying less than 3 months should receive 0.02 mL/kg. Those staying longer than 3 months should receive 0.06 mL/kg every 5 months. Vaccination of susceptible prospective travelers is an alternative if sufficient lead time exists. Alternatively, one dose of IG and hepatitis A vaccination may be given if no lead time exists, but this strategy may reduce the immunogenicity of the vaccine.[444]

Vaccine. Two killed-virus hepatitis A vaccines have been approved for use in the United States (HAVRIX, developed by SmithKline Beecham Pharmaceuticals, Philadelphia, Penn, and VAQTA developed by Merck & Co, West Point, Penn). Each has been shown to have protective efficacy exceeding 90% and low levels of adverse reactions in trials in children.[445,446] Within 15 days of primary injection, up to 98% of adults and 96% of children and adolescents develop protective levels of antibody against hepatitis A. See Table 38-9 for doses and administration schedules. The most commonly reported adverse events after immunization are soreness at the injection site and headache. Research at the Walter Reed Army Institute of Research has shown that immunization by jet gun confers immunity equivalent to immunization by needle and syringe. Additionally, hepatitis A vaccine is just as effective when given with hepatitis B vaccine as it is when given alone.[447]

Hepatitis A vaccine is likely to be universally recommended for pediatric use, but its current high cost may be a problem.[448] Adults targeted for immunization include international travelers to areas of high endemicity, staff members of daycare centers and custodial institutions, military personnel, food handlers, members of population groups with a high level of endemic infection, persons whose sexual practices place them at increased risk (eg, male homosexuals, persons with multiple sexual partners), handlers of nonhuman primates, and hemophiliacs[449] and other regular recipients of blood products. Hepatitis A vaccination should replace IG for use in preexposure prophylaxis. Vaccine may be combined with IG for either postexposure prophylaxis or situations where immediate and long-term protection are required. Hepatitis A vaccination is recommended for all Department of Defense personnel[450,451]; however, the implementation of this policy is likely to be delayed by the expense. The most current recommendations for candidates for hepatitis A vaccination from the Advisory Committee on Immunization Practices are listed in Exhibit 38-16.

Hepatitis B

Standard precautions should be followed for patients with acute or chronic hepatitis B infection. Infants born to HBsAg-positive mothers should

TABLE 38-9

DOSAGE AND ADMINISTRATION SCHEDULES FOR TWO HEPATITIS A VACCINES*

	HAVRIX†	Intervals	VAQTA‡	Intervals
Children	2-18 y		2-17 y	
	0.5 mL	0 and 6-12 mo	0.5 mL	0 and 6-18 mo
	or			
	0.5 mL	0,1, and 6-12 mo		
Adults	1 mL	0 and 6-12 mo	0.5 mL	0 and 6-12 mo

* See package inserts for updated information
† SmithKline Beecham Pharmaceuticals, Philadelphia, Penn
‡ Merck and Company, Inc., West Point, Penn

EXHIBIT 38-16

CANDIDATES FOR HEPATITIS A IMMUNIZATION

For Routine Immunization

Children living in states, counties, and communities with rates that are twice the 1987-1997 national average or greater (ie, ≥ 20 cases per 100,000 population)*

Those at Increased Risk

Travelers to endemic regions
Men having sex with men
Users of illicit injection drugs
Persons working closely with nonhuman primates
Persons with occupational risk (eg, researchers, military personnel)
Persons with chronic liver disease
Persons who receive clotting factor concentrates

* Consideration of routine vaccination should be given for children in states, counties, and communities with rates exceeding the 1987-1997 national average (ie, ≥ 10 but < 20 cases per 100,000 population).

Source: Advisory Committee on Immunization Practices. Prevention of hepatitis A through active or passive immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR*. 1999;48(RR-12):1–37.

have maternal blood carefully removed at delivery by a gloved health care provider in addition to the subsequent administration of hepatitis B immune globulin (HBIG) and hepatitis B vaccine. The blood of these infants should be handled with standard precautions as 1% to 3% of such infants are HBsAg positive due to infection in utero.

The most effective hepatitis B immunoprophylaxis is the preexposure immunization of all susceptible individuals. Hepatitis B vaccine has been available since 1981 and is one of the most efficacious yet underutilized vaccines in the medical armamentarium. Vaccination is recommended for all infants as part of the routine childhood immunization schedule. Immunization of all adolescents is currently recommended by the American Academy of Pediatrics.[412] Universal immunization is desirable.

Postexposure prophylaxis with hepatitis B vaccine and HBIG can effectively prevent infection. HBIG provides temporary protection and is only indicated in specific instances. Hepatitis B vaccine is used for protection both before and after exposure and provides long-term protection. HBIG is prepared from plasma known to have a high titer of antibody to HBsAg and to be negative for antibodies to HIV. The initial hepatitis B vaccine was made from plasma from male homosexuals in San Francisco who were positive for HBsAg. This vaccine was carefully purified; at no time has there been any evidence of transmission of HIV from this vaccine. It is no longer used in the United States but is still used extensively in other countries.[452] The second generation of hepatitis B vaccines currently used in the United States is produced by recombinant DNA technology using common baker's yeast (*Saccharomyces cerevisiae*) modified to produce HBsAg in large quantities and hence HIV transmission is no longer even a theoretic issue.

The two vaccines currently in use are RECOMBIVAX (Merck & Co.) and ENGERIX-B (SmithKline Beecham Pharmaceuticals). Neither vaccine has been shown to be superior to the other when used as recommended. Three intramuscular doses are required to induce protective immunity in more than 90% of adults and 95% of adolescents, children, and infants. See Table 38-10 for doses and administration schedules. Immunocompromised and hemodialysis patients should receive larger doses. A booster dose may be given to all vaccinees 4 to 6 months after primary immunization is complete to produce higher titers and more lasting protection.[442]

High-risk candidates for hepatitis B immunization are listed in Exhibit 38-17; family members of HbsAg-positive adoptees from countries where hepatitis B is endemic are also candidates. The screening of pregnant women for evidence of

TABLE 38-10

DOSAGES AND ADMINISTRATION SCHEDULES FOR HEPATITIS B VACCINES

Population	Intervals	RECOMBIVAX*	ENGERIX-B†
Infants			
HBsAg - mother	0-2, 1-4, 6-18 mos	0.5 mL (2.5 μg)	0.5 mL (10 μg)
HBsAg + mother	birth (HBIG), 1-2 and 6 mos	0.5 mL (5 μg)	0.5 mL (10 μg)
Children			
1-10 y	0, 1-2, and 4-6 mos	0.5 mL (2.5 μg)	0.5 mL (10 μg)
11-19 y	0, 1-2, and 4-6 mos	0.5 mL (5 μg)	0.5 mL (10 μg)
Adults			
≥ 20 y	0, 1-2, and 4-6 mos	1 mL (10 μg)	1 mL (20 μg)
Immunocompromised	0, 1, and 6 mos	1 mL (40 μg)	2 mL (40 μg)

* Merck and Company, Inc., West Point, Penn
† SmithKline Beecham Pharmaceutical, Philadelphia, Penn

chronic hepatitis B infection (positive HBsAg/HBe Ag) is essential and allows for the use of HBIG and hepatitis B vaccine to interrupt vertical transmission. This effort alone is expected to prevent millions of cases of hepatocellular carcinoma worldwide. The Department of Defense mandates HBV immunization of all health care workers and those judged to be high-risk candidates.

Complex algorithms exist for the management of potential hepatitis B exposure[442,443] in health care providers following needlestick or sharps injury, but comprehensive hepatitis B immunization of all health care providers obviates their need. Today, there is virtually no rationale for health care workers not to be fully immune to hepatitis B. Hepatitis B vaccines licensed in the United States are very safe vaccines. Anaphylaxis is rare. The only contraindication to vaccine administration is hypersensitivity to yeast or another component of the vaccine.[452]

EXHIBIT 38-17

CANDIDATES FOR HEPATITIS B IMMUNIZATION

For Routine Immunization

- All infants
- All adolescents

Those at Increased Risk

- Health care workers
- Clients and staff of custodial institutions
- Hemodialysis patients
- Patients who regularly receive blood products
- Household and sexual contacts of HBsAg carriers
- Travelers for more than 6 months in areas of high endemicity
- Sexually active homosexual or bisexual males
- Heterosexuals with multiple partners or a history of sexually transmitted diseases

Hepatitis C

Standard precautions are indicated for the hospitalized patient with hepatitis C. Frequently a patient is found to have hepatitis C as an incidental finding in the hospital, highlighting the need for standard precautions for every hospitalized patient regardless of known or suspected diagnosis.

No immunoprophylaxis of proven benefit exists for hepatitis C. Now that screening of plasma donors and exclusion of infected persons from the donor pool is recommended in the United States, IG manufactured in this country does not contain appreciable titers of antibodies to hepatitis C, and therefore is not expected to be of any benefit. No vaccine currently exists for hepatitis C. Formulation of such a vaccine is hindered by the extensive genetic

and antigenic diversity among different strains of hepatitis C and by the fact that HCV infection does not confer solid immunity against reinfection.[452]

Hepatitis D

Since hepatitis D can only be transmitted in the presence of hepatitis B infection, isolation precautions for hepatitis D are the same as those for hepatitis B. Similarly the same control and prevention methods apply. Immunization for hepatitis B will prevent acquisition of delta hepatitis. HBsAg carriers should be extremely careful to avoid exposure to hepatitis D because no immunoprophylactic measures currently exist to prevent hepatitis D superinfection.

Hepatitis E

Appropriate isolation for patients with hepatitis E is contact isolation with standard precautions routinely observed. Prevention involves good sanitation and not ingesting contaminated food or water. Passive immunoprophylaxis with IG prepared in the United States is not effective against hepatitis E. A study[453] in cynomolgus monkeys showed that immunization with a recombinant protein representing part of the hepatitis E capsid could confer immunity. This suggests that a vaccine may be developed in the future that would be useful for travelers and military persons who deploy outside the United States.

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ADDENDUM: ADDITIONAL DIAGNOSTIC AND UPDATED TREATMENT INFORMATION FOR HEPATITIS

Additional Diagnostic Information for Hepatitis B

Generally, patients with chronic hepatitis B display persistently positive HBsAg, anti-HBc (IgG), and HBeAg markers. Some patients with chronic hepatitis B are infected with a mutant strain of HBV, characterized by the presence of HBsAg, anti-HBc, and abnormal serum enzymes but the absence of HBeAg. This form of chronic hepatitis may sometimes be associated with more severe liver disease.

Updated Recommendations for Therapy: Hepatitis B

Because of the results in a recent study[1] among US patients showing that lamivudine administered for 1 year favorably affected liver histology, virology, and biochemical features in patients with chronic hepatitis B and appeared to be well tolerated, the drug is achieving greater popularity and is even considered by some to be the starting drug of choice. Unfortunately, long-term treatment with this drug appears to be associated with the increasing likelihood of development of mutant strains, probably necessitating extended or even life-long treatment.

Updated Recommendations for Therapy: Hepatitis C

A new form of interferon has been developed and is called pegylated interferon. This form of interferon is attached to the molecule polyethylene glycol (hence the prefix "peg") and has a delayed excretion after injection, thus maintaining a high and sustained interferon blood level. Accordingly, it is administered as a once weekly dose. First reports indicate that pegylated interferon on its own is approximately equivalent in efficacy to the combination of conventional interferon plus ribavirin.[2,3] Furthermore, preliminary reports indicate that pegylated interferon plus ribavirin is clearly superior to the prior recommended treatment regimen and is expected to be the treatment of choice for the immediate future.[4]

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