

# Chapter 13

## BACTERIAL SKIN DISEASES

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### INTRODUCTION

#### PYODERMAS

- Etiology
- Clinical Features
- Prognosis
- Treatment

#### PLAGUE

- Etiology
- Epidemiology
- Clinical Features
- Laboratory Findings
- Diagnosis
- Treatment

#### TULAREMIA

- Etiology
- Epidemiology
- Clinical Manifestations
- Diagnosis
- Treatment

#### DIPHTHERIA

- Etiology
- Epidemiology
- Clinical Manifestations
- Diagnosis
- Treatment
- Immunization

#### MENINGOCOCCAL INFECTIONS

- Etiology
- Epidemiology
- Clinical Manifestations
- Diagnosis
- Treatment
- Chemoprophylaxis of Carriers
- Vaccines

#### LYME DISEASE

- Epidemiology
- Clinical Manifestations
- Diagnosis
- Treatment

### SUMMARY

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## INTRODUCTION

Bacterial pyodermas are among the most common disabling skin conditions that occur in wartime. Secondary infections of various superficial wounds may lead to cellulitis, abscess formation, or lymphangitis. Cuts from coral in the Pacific Ocean during World War II<sup>1</sup> and fungal infections in Vietnam<sup>2</sup> were common precursors to pyodermas. Other bacterial diseases such as plague, meningococemia, and diphtheria can occur in epidemic

forms during wartime because of crowding and common exposures to insect vectors. These diseases have had major influences on military conflicts.<sup>3-5</sup>

Lyme disease is relatively newly recognized. It is not uncommon for present-day U.S. military troops to develop erythema chronicum migrans, the early skin manifestation of Lyme disease, after maneuvers in Germany.

## PYODERMAS

Pyodermas due to *Staphylococcus aureus* and *Streptococcus pyogenes* are common in army troops. There are several reasons for this: irregular bathing habits, poor access to facilities for personal hygiene, irritation of the skin by rough clothing and equipment, minor traumatic abrasions, scabies, insect bites, mingling with native populations, and crowded living conditions for large numbers of troops.

These infections have played a major part in combat ineffectiveness among troops. During World War I, bacterial infections (furuncles, abscesses, and cellulitis) and secondarily infected scabies were by far the two most common causes for hospital admission for skin disease among U.S. troops: as the primary diagnosis, they comprised almost two thirds of all hospital admissions of U.S. troops in the Great War.<sup>6</sup> During World War II, bacterial skin infections were the most common source of morbidity in a check of representative hospitals<sup>1</sup>:

- In a 3-week spot check of three American divisions in 1944, cutaneous bacterial infections were found to be responsible for 70% of lost man-days.
- In the Mediterranean theater, two chief groups, cellulitis and furunculosis, comprised most of the bacterial skin infections.
- In the Pacific theater, pyodermas were more common. For example, in the Philippines, excluding combat injuries, 70% to 80% of troops attending sick call complained of ecthyma. Impetigo was also common in the Pacific theater.

Although most of these lesions were likely due to *Staphylococcus aureus* or *Streptococcus pyogenes* or

both, some were culture-positive for *Corynebacterium diphtheriae*.<sup>1</sup>

During the Vietnam conflict, bacterial skin infections were second only to fungal infections in their frequency of occurrence and the disability they produced for U.S. troops. These were primarily ecthymatous ulcers due to *Streptococcus pyogenes* and were frequently referred to as "jungle sores." The importance of recognizing and treating these infections was documented in the U.S. Army Medical Department's official history, *Skin Diseases in Vietnam, 1965-72*:

With respect to pyoderma, the most important advance made during the Vietnam war was the recognition that these apparently trivial infections are a major military problem in the Tropics. Those who attempted to prevent and treat pyoderma found that simplistic solutions were of little avail and that lesions tended to grow in size and number despite the most strenuous efforts at control. Progress was made not only in recognizing the problem but also in better defining these infections both clinically and epidemiologically.<sup>2(pp89-90)</sup>

Pyodermas such as impetigo and ecthyma were more frequent and more severe in infantrymen than they were in support troops in Vietnam. This was explained by increased exposure to environmental stresses (eg, insect bites, cuts, and scratches) among infantrymen. Black soldiers had fewer pyodermas than white soldiers.<sup>2</sup>

### Etiology

For years, it has been dogma that most bacterial pyodermas were due to *Streptococcus pyogenes* occasionally complicated by *Staphylococcus aureus* infec-

tion. In a study of pyoderma in Vietnam,<sup>2</sup> 60 of 86 cases (70%) grew both *S aureus* and  $\beta$ -hemolytic streptococci. An additional 14% of cases cultured pure  $\beta$ -hemolytic streptococci, and another 10%, pure *S aureus*.<sup>2</sup> Within the past 10 years, most studies<sup>7-9</sup> of pyodermas show *S aureus* to be their primary cause.

It is not uncommon for tropical ulcers to contain several organisms of interest. A recent report on tropical ulcers in civilians found *S aureus* in only 2% and streptococci in only 15%. Coliform bacteria were found in 60%, fusobacteria in 35%, and bacteroides in 20%. All specimens grew a mixture of organisms.<sup>10</sup>

Folliculitis, furuncles, and carbuncles represent a continuum of severity of an infection centered about a hair follicle.<sup>11</sup> Although usually attributed to *S aureus*, one study<sup>12</sup> found this organism in only 24% of cutaneous abscesses. Another study<sup>13</sup> found *S aureus* in only 19% of vulvar furuncles; it suggested that although *S aureus* was usually believed to be the cause of furunculosis, it was not the only cause, especially if the lesion was around the genitals or the perianal region.

Erysipelas is almost always due to infection with  $\beta$ -hemolytic streptococci. Cellulitis is usually due to infection with  $\beta$ -hemolytic streptococci or *S aureus*.<sup>14</sup>

### Clinical Features

The characteristic sign of impetigo is superficial, stuck-on-appearing, honey-colored crusts (Figure 13-1). This is dried exudate from the underlying



**Fig. 13-1.** This thick yellow crust is typical of impetigo. Exudate from underlying denuded tissue dries, and patients present with this characteristic clinical sign.



**Fig. 13-2.** In bullous impetigo, the vesicles and bullae quickly rupture and form a thin, dry, varnishlike veneer. Annular lesions are not uncommon. These were positive on culture for *Staphylococcus aureus*.

eroded tissue. While impetigo often occurs on the face, any break in the skin can become secondarily infected. In the field, exposed skin of the arms and legs will be involved frequently, as most insect bites, dermatophytoses, allergic contact dermatitides, and traumatic sores commonly become secondarily infected. Impetigo heals without scarring because it does not penetrate the epidermis.

Bullous impetigo is usually due to pure *S aureus*, which manufactures a toxin, exfoliatin, that produces a subcorneal split in the epidermis.<sup>15</sup> Bullous impetigo is characterized by a flaccid blister that rapidly ruptures and makes the lesion appear varnished (Figure 13-2). Often a collarette of scale is also seen. Lesions tend to occur in the axillae or groin in adults (Figure 13-3).

Ecthyma presents as a punched-out ulceration, which may not be noted until a thick, overlying crust is removed (Figure 13-4). The condition is often tender or painful. Ecthyma was the most common pyoderma noted among U.S. troops in Vietnam<sup>2</sup> and was seen primarily on the hands, ankles, or lower extremities. There was often a zone of induration or erythema surrounding the ulcer, and multiple lesions were common. It heals with scarring because the epidermis is penetrated by the infection.

Furunculosis is an infection of the hair follicle that forms an inflammatory nodule with a pustular center (Figure 13-5).<sup>15</sup> Cellulitis is a more serious lesion that usually affects the lower extremities (Figure 13-6), face, or ear. It is red, painful or tender, and warm to the touch. If a palpable edge is present, the term *erysipelas* is used. Diagnosis is based on



**Fig. 13-3.** A superficial pustule is noted anterior to the axilla. A Gram's stain of the contents revealed neutrophils and Gram-positive cocci in clusters. Culture was positive for *Staphylococcus aureus*. In the axillary vault, the pustules have ruptured, leaving collarettes of scale, which are characteristic of bullous impetigo.



**Fig. 13-5.** This erythematous papule with a pustular center is centered about a hair follicle. A furuncle is best treated with local heat and drainage.



**Fig. 13-4.** This punched-out ulceration above the ankle is typical of the "jungle sores" seen in Vietnam and the South Pacific during World War II. It had been present for several weeks without change. A culture was positive for  $\beta$ -hemolytic streptococci, group A. This lesion of ecthyma rapidly responded to appropriate antibiotics.



**Fig. 13-6.** This erythematous lesion above the ankle has been slowly worsening for several days. It is hot to touch. No raised, palpable edge is noted. In severe cases, such as this one, scaling is often seen over the surface. This location is classic for cellulitis.

physical examination. Both entities may be associated with rigors, fever, leukocytosis, and malaise.

### Prognosis

Under combat conditions, ecthyma can last for weeks unless properly treated. In Vietnam, it was not uncommon to find soldiers on light duty for a month or more due to these skin ulcerations. Frequently, a new crop of lesions appeared as the old lesions healed. Cellulitis, erysipelas, and lymphangitis are well-known complications of impetigo and ecthyma. Acute glomerulonephritis can also complicate skin infections caused by *Streptococcus pyogenes*, but this was uncommon in Vietnam.<sup>2</sup>

### Treatment

The treatment of choice for pyodermas is an antistaphylococcal penicillin such as dicloxacillin given in a dose of 250 mg orally four times daily for 10 days. The dose is often doubled the first 3 days in more severe infections. Erythromycin and clindamycin are suitable alternatives if the patient is allergic to penicillin. Cephalosporins or combinations of amoxicillin and clavulanate may also be used, but are much more expensive and seldom offer an advantage over antistaphylococcal penicillins.

Topical antibiotics are generally not helpful or necessary when appropriate oral antibiotics are

given. Mupirocin is an exception to this.<sup>16</sup> Applied thrice daily for 1 week, it will heal most simple pyodermas and may avoid the need for systemic antibiotics. Debridement of the lesions is helpful but soaking in hexachlorophene or other antibacterial soaks retards rather than enhances healing.

Treatment of pyoderma in a combat situation remains a problem. For most of these drugs to work, they must be given four times daily, which is impossible in combat. The combination of amoxicillin and clavulanate requires dosing thrice daily as does topical mupirocin, but in combat even this may be too much. Benzathine penicillin may be helpful as a single dose of 1.2 million units, administered intramuscularly. No further therapy for *Streptococcus pyogenes* would be required; however, this is poor coverage for *Staphylococcus aureus*.

Furuncles are best treated with local heat. When there is superficial fluctuance, they can be drained. Antibiotics are usually not required unless systemic symptoms are present.<sup>13</sup>

Cellulitis and erysipelas are more serious infections. Intravenous antibiotics are usually the best therapy. Penicillin is usually adequate for erysipelas, but coverage with an antistaphylococcal penicillin is indicated for cellulitis. If the patient is allergic to penicillin, intravenous vancomycin or erythromycin may be used. Elevation is important if a lower leg is involved.<sup>14</sup>

## PLAGUE

Plague is a zoonotic disease caused by the bacterium *Yersinia pestis*, which is usually transmitted to humans by rodents and their fleas but can also be transmitted via the respiratory route. When transmitted by a flea bite, the disease is characterized by an early sign known as a *bubo* (ie, a mass of lymph nodes in the groin, axilla, or neck that become matted together and drain purulent material). Three days after these buboes appear, the patients develop high fever and delirium. Black splotches develop due to hemorrhages into the skin. It is these black areas that gave this disease its common name: Black Death. Systemic and pneumonic forms of plague can also occur; these forms of the disease and their transmission, which are discussed later in this section, are far rarer than bubonic plague.

Plague is a disease of antiquity. During the second millennium BC, the Philistines were smitten with plague after capturing the Ark of the Covenant from the Israelites. During the 6th century AD, the

Justinian plague (ie, the first plague pandemic) was described in the area of Constantinople.<sup>3</sup> During the 14th century, 70% to 80% of those who contracted the disease died from it. During the year 1346, Europe and the lands around the Mediterranean had a population of approximately 100 million people. An outbreak of plague lasting from 1346 to 1352 and known as the Great Dying or the Great Pestilence (ie, the second pandemic) killed approximately one fourth of this population. Europe alone sustained a loss of approximately 20 million people.<sup>17</sup>

After the second great pandemic, plague recurred in Europe over the next few centuries. London's last experience with plague ended with the Great Fire of 1666.<sup>17</sup> The disease was subsequently seen in the armies of Frederick the Great, Catherine the Great, and Napoleon's troops in Egypt.<sup>3</sup>

The third pandemic began in China and rapidly spread to most of Asia during the period 1894 through 1920. In India alone, an estimated 12 mil-

lion people died. Several important epidemiological discoveries were made during this period<sup>3</sup>:

- During 1894, Kitasato and Yersin independently isolated and described the plague bacillus.
- From 1903 to 1905, Liston of the Indian Plague Commission demonstrated the association with rats and fleas. The vital concepts of rat and flea control emerged from this commission.
- Haffkine, working in Bombay during this same period, developed an effective plague vaccine.
- Territorial spread of this disease was reduced by the development of rat-proof ships, together with fumigation of premises and vessels.

During World War II, a killed plague vaccine was developed and administered to U.S. troops in endemic areas. Dichlorodiphenyltrichloroethane (DDT) was developed and introduced during the war, and plague control became synonymous with flea control. Plague was not a significant problem for U.S. troops during World War II. Following the war, plague control rapidly improved. The sulfonamides and, especially, streptomycin and tetracycline proved effective in the treatment of all clinical forms of the disease. Plague foci were found in both commensal and wild rodents via improved bacteriological and serologic techniques. These foci were reduced by new insecticides and rodenticides. Promising new vaccines were introduced.<sup>3</sup>

Plague has never been a significant problem to the U.S. military, thanks to an understanding of the epidemiology of the disease. Effective control measures have been rapidly incorporated into preventive medicine programs. Plague is endemic in Vietnam, and during the conflict in the 1960s and 1970s, more than 10,000 cases occurred per year in the Vietnamese population.<sup>18</sup> Still, there were relatively few cases of this disease in American servicemen.<sup>3</sup>

## Etiology

*Yersinia pestis* is a plump, Gram-negative, pleomorphic bacillus (0.8 × 1.5 μm; range 0.5–2.0 μm). A bipolar (ie, safety-pin) appearance is best demonstrated in smears of infected animal tissues stained by either the Giemsa or the Wayson method. Preparations stained with Gram's stain do not dependably render this classic appearance. It does not ferment lactose.<sup>19</sup>

Plague bacilli are aerobic and facultatively anaerobic. They are not fastidious and grow readily in most bacteriological culture mediums. Growth is satisfactory at 35°C to 37°C, but slow. Even at the optimum growth temperature of 28°C, about 48 hours are necessary before colonies are readily discernible on plain agar.<sup>19</sup>

The fluorescent antibody test is used for rapid identification of this bacterium. It tests for bacterial envelope fraction 1, which is produced most readily at 37°C but not at temperatures below 28°C. This test is best used on smears of animal tissues, aspirates of exudates from buboes or other tissues, sputum specimens, and cultures incubated at 37°C. Clinical specimens that were frozen or refrigerated after collection are suitable for immediate fluorescent antibody testing. Cross-reactions with *Y pseudotuberculosis* may occur, and occasional strains of *Y pestis* exhibit weak or no staining. A positive fluorescent antibody test supported by epidemiological and clinical evidence is good evidence for this diagnosis.<sup>19</sup>

## Epidemiology

The ecology of plague is complex. Infection occurs primarily in rodents and is usually spread to people and pets by the bite of an infected rodent flea. The oriental rat flea, *Xenopsylla cheopis*, has been considered the traditional vector in urban outbreaks; however, multiple species of fleas have been associated with plague.<sup>20</sup>

In the *X cheopis* flea, *Y pestis* infection leads to a blockage of the midgut by fibrinoid material and masses of these bacilli. The flea, in effect, cannot ingest a blood meal, and it makes repeated attempts to feed. Unable to pass the meal through the blockage, it regurgitates several thousand bacilli onto the bite site with each attempt. If infected *X cheopis* is maintained at temperatures over 27°C, this blockage will spontaneously clear. Plague epidemics have long been known to subside spontaneously when ambient temperatures remain above 27°C to 30°C, probably due to this phenomenon.<sup>20</sup> Epidemics of plague are distinctly seasonal: bubonic plague is a disease of the cooler months in hot climates and of the warmer months in cool climates.<sup>3</sup>

## Typical Mode of Transmission

The two most important reservoirs of plague bacillus throughout the world are two commensal rodents, *Rattus rattus* (the domestic rat) and *Rattus norvegicus* (the urban rat). Throughout history,

plague epidemics have occurred when huge numbers of susceptible rats died, which forced their infected fleas to seek other hosts. Rats are not the only host, however: more than 200 species of rodents are susceptible,<sup>20</sup> including prairie dogs, chipmunks, marmots, and deer mice. In the Rocky Mountain states, where plague is endemic, epizootics among rock squirrels are often the source of infection in humans. The infected fleas can seek out humans who are hunting, camping, or living in these areas.<sup>19</sup> The fleas can also be transported to humans through pets such as dogs and cats.

### Other Modes of Transmission

Pets can also acquire the disease via the ingestional route, by devouring the sick animals, which are easy prey. Although in dogs plague is usually a mild illness, it causes a higher than 50% mortality in cats.<sup>20</sup> Cats can transmit the disease to humans by bite or scratch<sup>21</sup> as well as via fleas. Cats have also been associated with the transmission of pneumonic plague.<sup>22</sup> Exposure to domestic cats was associated with 3% of plague in the United States during the 1970s, ranking third behind bites of infected fleas (82%) and direct exposure to wild animals (15%).<sup>23</sup>

Plague can also be rapidly spread through the air, and about 5% of bubonic plague patients will develop the potential for airborne transmission. Most severe epidemics have occurred in areas where the climate is relatively cool. *Y pestis* cannot survive in aerosol clouds at high temperature and humidity. Hence, primary plague pneumonia is rare in the tropics. Conversely, low humidity is also associated with rapid death of the plague bacillus in the air. Epidemics of primary plague pneumonia are favored by cool weather, moderate humidity, and close personal contact between individuals.<sup>3</sup>

The transportation of infected rodents and fleas from endemic areas may introduce the disease into new areas. The rat-proofing of ships has greatly reduced the risk of transporting infected rats and fleas to distant seaports. The technique of shipping by containers, however, may present a special hazard because the containers can harbor rats.<sup>3</sup>

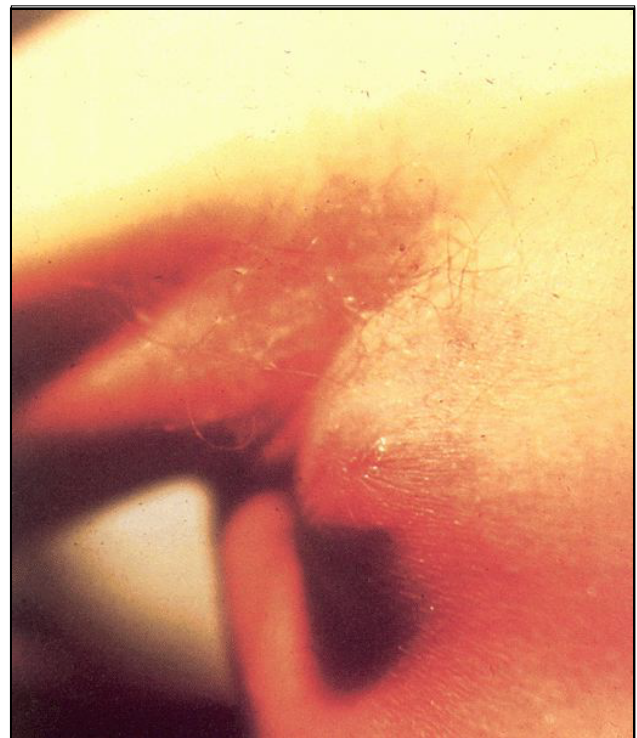
### Clinical Features

Plague begins abruptly and, unless early therapy is initiated, can cause death in hours to a few days in 60% to 90% of cases. Only cholera and meningococemia can overwhelm a previously healthy body's defenses so rapidly.<sup>3</sup> Plague usually

occurs in three forms: bubonic, septicemic, and pneumonic. Complications such as meningitis and endophthalmitis can arise from hematogenous spread of *Y pestis*.

### Bubonic Plague

The bubonic form of plague is the most common. After the flea bite, the organisms proliferate in the lymph nodes. After an incubation period of 2 to 8 days, the typical patient has the sudden onset of chills, fever, weakness, and headache. At the same time or by the next day, the patient notices the bubo.<sup>18</sup> Intense pain usually heralds the onset of a bubo with the lesion itself becoming visible or palpable within 24 hours. Buboes may occur anywhere there are lymph nodes. Occasionally, intraabdominal buboes have presented as acute surgical abdomens, and operations for this have occurred on numerous occasions. The most common location, accounting for over half of all buboes, is in the groin. Involvement in this location is felt to be secondary to a flea bite on the leg. Buboes are also common in the axillae (Figure 13-7) and then the



**Fig. 13-7.** This painful, swollen axillary lymph node occurred in a prostrate, febrile patient with bubonic plague. Buboes most frequently occur in the groin, as flea bites are most common on the legs.

neck. Intense pain is characteristic of these buboes.<sup>3</sup>

The patient is typically prostrate and lethargic in uncomplicated bubonic plague. The temperature is in the range of 38.5°C to 40°C, with a pulse rate of 110 to 140 beats per minute and a low blood pressure of approximately 100/60. The liver and spleen are often palpable and tender.<sup>18</sup>

Early bubonic plague is typically not associated with skin lesions.<sup>24</sup> In Vietnam, about 25% of patients had papules, pustules, vesicles, or eschars near the bubo or in an anatomical area that drained to the bubo. Presumably, these were the sites of flea bites. White blood cells and plague bacilli were found on opening these lesions. Systemic disease may also lead to purpura and gangrene of the distal extremities.<sup>15</sup>

### **Septicemic Plague**

Plague also has a septicemic form in which buboes do not occur. In this small subset (about 10%) of patients, the mode of transmission is the same as in the bubonic form; however, blood stream invasion occurs prior to regional lymph node involvement. Older patients, who seem to be particularly susceptible to this aggressive form of plague, become acutely ill. In fact, there may be so many bacteria in the blood that they are readily seen on a blood smear. This is a grave prognostic sign.<sup>19</sup>

### **Pneumonic Plague**

One of the feared complications of bubonic plague is secondary pneumonia, which occurs by spread of the plague bacillus through the blood stream to the lungs. Intermittent bacteremia is common in plague. Single blood cultures taken at the time of admission of Vietnamese patients were positive in 27% of cases.<sup>18</sup> Plague pneumonia presents with cough, chest pain, hemoptysis, and purulent sputum loaded with bacilli. It is highly contagious with an incubation period of less than 3 days in new patients.<sup>19</sup> In fact, healthy patients have reportedly been exposed, become ill, and died on the same day. Pneumonic plague is invariably fatal when treatment is delayed more than 1 day after the onset of the illness.<sup>18</sup> Patients with plague may also present with pharyngitis.<sup>18</sup>

### **Laboratory Findings**

The white blood cell count is typically elevated in the range of 10,000 to 20,000/mm<sup>3</sup>. Severely ill

patients tend to have higher counts. Platelet counts are normal to low. Disseminated intravascular coagulation is common, with the laboratory abnormalities typical for this. Liver function tests are often elevated, as are renal function tests.<sup>18</sup>

### **Diagnosis**

Plague should be considered in all patients who present with buboes. It should also be seriously considered in febrile patients who have been exposed to rodents and fleas in endemic areas of the world. When a patient presents with a bubo, the best way to make the diagnosis is by needle aspiration. (It may be necessary to inject a small amount of saline to get an adequate specimen.) The specimen is sent for culture, but a small amount is air-dried and stained with Gram's and Wayson or Giemsa stains. The Gram's stain reveals pleomorphic, Gram-negative bacilli and coccobacilli. The typical safety-pin appearance is seen on either the Wayson or Giemsa stain. The fluorescent antibody test will give rapid confirmation.<sup>18</sup>

Blood, purulent sputum, and skin lesions (if present) should all be inoculated onto blood, MacConkey agar plates, and infusion broth. Appropriate stains should also be done on these specimens.<sup>18</sup>

For definitive identification, cultures can be mailed in double containers to the Centers for Disease Control and Prevention Plague Branch, P.O. Box 2087, Fort Collins, Colorado 80522 (telephone 303-221-6450). This laboratory can also perform acute and convalescent serologic testing to confirm the diagnosis.<sup>18</sup> The differential diagnosis should include tularemia, staphylococcal and streptococcal infections, lymphogranuloma venereum, and chancroid.<sup>19</sup>

### **Treatment**

Untreated, the case-fatality rate of bubonic plague is about 60%. In septicemic or pneumonic plague, it is probably 100%. The prognosis in pneumonic plague is poor if therapy is delayed more than 1 day after the onset of the symptoms. With early therapy, the fatality rate in bubonic plague should approach zero, but recently it was listed at 16%.<sup>19</sup>

All patients with bubonic plague should be isolated until 48 hours after specific therapy has been instituted because of the possibility of secondary plague pneumonia. Purulent discharges should be handled with rubber gloves. Face masks, including



eye protection, are indispensable in caring for patients with pulmonary plague. Nonspecific therapy includes management of shock, dehydration, high fever, and convulsions.<sup>19</sup>

Antibiotic therapy should be started promptly, without awaiting laboratory confirmation, after specimens have been obtained for diagnosis. The drug of choice, intramuscular streptomycin, was first demonstrated in 1948.<sup>25</sup> No drug investigated since then has proved more efficacious or less toxic. It is injected at a dose of 30 mg/kg/d in two<sup>18</sup> or four<sup>19</sup> equal portions for 10 days. Most patients improve rapidly and become afebrile within 3 days. The drug should be used cautiously in pregnant women. The risk of hearing loss and vestibular dysfunction is minimal, but this should be considered in patients with preexisting hearing loss and in the elderly. In such patients, the course could be reduced to 3 days following the disappearance of fever. Renal injury due to streptomycin is rare, but renal function should be monitored.<sup>18</sup> Gentamicin has also been reported to be effective and has the advantage that it can be given intravenously. Mobilization of intramuscular streptomycin may be compromised in hypotensive patients.<sup>24</sup>

Tetracycline is a satisfactory alternative, to be given orally in a daily dose of 2 to 4 g/d in four divided doses for 10 days. This drug is contraindicated in young children, pregnant women, and in patients with renal failure. Tetracycline has also been used to complete a 10-day course after 5 days of intramuscular streptomycin, to minimize the side effects of the latter.<sup>18</sup>

Chloramphenicol is especially good for the treatment of plague meningitis or endophthalmitis because of its excellent penetration in these areas. It is also good in patients with hypotension, in whom intramuscular injections would be poorly absorbed. The drug is given intravenously in the

above cases, but it can also be given orally. The intravenous loading dose is 25 mg/kg, followed by 60 mg/kg/d in four divided doses. After clinical improvement, the drug may be given orally to complete 10 days of therapy. The dose may be reduced to 30 mg/kg/d in four divided doses to lessen the effects of bone marrow suppression, which should be monitored.<sup>18</sup>

Co-trimoxazole, a combination of trimethoprim and sulfamethoxazole, has also been effective in the treatment of plague,<sup>26,27</sup> but it does not appear to be as effective as the aforementioned drugs.

In an asymptomatic person who has had close (ie, within 2 m or less) or face-to-face contact with a patient with pneumonic plague, prophylaxis should be considered. Oral tetracycline (30 mg/kg/d in divided doses every 6 h) is the best choice of drugs.<sup>18,28</sup> If the asymptomatic patient (a) cannot tolerate tetracycline, (b) is a child, or (c) is pregnant, then oral co-trimoxazole is recommended, although it is not optimal therapy for treating active disease. Reliable contacts who are not placed on drug prophylaxis can be instructed to take their temperature twice daily. They are to seek medical attention immediately if they develop fever or respiratory symptoms, including a sore throat, as this could be a manifestation of plaque pharyngitis.<sup>29</sup> In such cases, hospitalization, isolation, and more aggressive therapy are indicated. A 4-fold rise in titer of *Y pestis*-specific antibody when comparing acute and convalescent sera may establish whether actual infection has occurred.<sup>19</sup>

There is a vaccine available for those who might come in contact with plague. Two injections are given initially with an interval of 1 to 3 months between them. Thereafter, it must be given every 6 months.<sup>18</sup> This vaccine is given to members of the U.S. armed forces who are to deploy to regions where plague is endemic (eg, Southeast Asia).

## TULAREMIA

Tularemia (also called deer fly fever and rabbit fever) is a disease caused by the bacterium *Francisella tularensis*, which is usually transmitted to humans by exposure to rabbits and ticks (direct inoculation), but which can also be transmitted via infectious aerosol. Soldiers can be exposed to tularemia while on maneuvers in areas where the disease is prevalent. The typical ulceroglandular form of the disease is characterized by a cutaneous ulcer, regional lymphadenopathy, fever, and

constitutional symptoms; however, tularemia also takes typhoidal, oropharyngeal, and oculoglandular forms.

In 1911, McCoy described a plaguelike illness of rodents while studying plague among California ground squirrels.<sup>30</sup> Subsequently, he recovered the organism from rodents in Tulare County, California<sup>31</sup> (rabbits, now classified zoologically as members of the order Lagomorpha, were at that time classified with the Rodentia). In 1914, Wherry and

Lamb described the first bacteriologically confirmed case of tularemia in a human patient.<sup>32</sup>

### Etiology

*F tularensis* is a small, Gram-negative coccobacillus. It tends to be pleomorphic in culture. On most ordinary culture media, it grows poorly or not at all. It does grow well on glucose cysteine blood agar, thioglycolate broth, and in other media containing enough cysteine (specifically, sulfhydryl groups). Optimal growth occurs at 37°C under aerobic conditions, with small colonies occurring at 24 to 48 hours. The organism is identified on the basis of its growth requirements, morphology, fluorescent staining, and agglutinins with specific antisera.<sup>33</sup>

There are two types of *F tularensis*. Type A is distributed solely in North America and is virulent for humans and rabbits. It is also positive for citrulline ureidase, and it ferments glycerol. Type B is found in North America, Europe, and Asia. It causes a milder form of disease in humans and is avirulent for rabbits. It is negative for citrulline ureidase and does not ferment glycerol.<sup>34</sup>

### Epidemiology

*F tularensis* is distributed throughout the northern hemisphere between 30° and 71° north latitude. It has been recovered from numerous wild and domestic animals. Outbreaks are generally attributed to rabbits, hares, and muskrats. It has also been isolated from fish, amphibians, birds, ticks, deerflies, mud, and water.<sup>33</sup> Large outbreaks of gastroenteritis, which were traced to contaminated water, occurred in Europe during World War II.<sup>35</sup>

Humans most commonly acquire the disease via direct inoculation from a tick bite, or after exposure to the bite, body fluids, tissues, or pelt of an infected animal (eg, a rabbit). *F tularensis* has been reported able to penetrate intact skin but probably enters via small, open skin lesions—or, of course, via the bite. Most rabbit exposure cases have occurred in the winter, while most tick-bite cases occur in the spring or summer.<sup>33</sup>

Tularemia is an occupational hazard for rabbit hunters, butchers, cooks, those who process frozen rabbit meat and pelts, and laboratory technicians.<sup>34</sup> Laboratory workers can acquire the disease via two mechanisms: (1) direct inoculation and (2) aerosolization of *F tularensis* from cultured organisms.

### Clinical Manifestations

The incubation period is usually 3 to 5 days. A skin papule develops at the site of entry and within 2 to 4 days, an ulcer forms. The patient experiences an abrupt onset of fever, chills, headache, malaise, and fatigue. Painful regional lymphadenopathy follows, and buboes can occur. This is the typical ulceroglandular form of tularemia, which occurs in more than 75% of cases. In rabbit-associated cases, the ulcer is located on the patient's hand or fingers in more than 90% of cases (Figure 13-8). In tick-associated ulcers, the lesions tend to occur on the patient's lower extremities, perineum, or trunk. Multiple ulcers may occur in patients who came in contact with many infected animals.<sup>33</sup>

Of rabbit-associated cases of tularemia, 80% to 90% of patients have axillary or epitrochlear adenopathy; of tick-borne cases, 60% to 70% have inguinal or femoral adenopathy. Glandular tularemia occurs in 5% to 15% of cases and is characterized by lymphadenopathy without skin ulceration. In the typhoidal form (approximately 5% of cases), fever, weight loss, and prostration occur without lymphadenopathy. The protean manifestations of tularemia, including oropharyngeal and oculoglandular forms, and the often-negative history make diagnosis difficult.<sup>33</sup>



**Fig. 13-8.** This ulceration on the hand is typical of tularemia in a rabbit hunter, one who skinned an infected rabbit and in so doing, infected his hand. He will subsequently develop distal nodes in his axilla that will likely suppurate. He will also develop profound malaise, chills, and fever. Cultures are typically negative, even if special media are used. Diagnosis is usually made on the basis of serologic testing.

Pleuropulmonary complications are not infrequent in tularemia. Pneumonia is seen in 30% to 80% of the typhoidal cases and in 10% to 15% of the ulceroglandular cases. It is characterized by non-productive cough, few findings on physical exam, and ill-defined infiltrates in one or more lobes on chest radiographs.<sup>33</sup>

A nonspecific skin eruption has been reported in about 20% of cases. In a few cases, erythema nodosum and, less commonly, erythema multiforme have been reported. Some patients develop hepatomegaly and elevated liver function test values. Transient renal failure, rhabdomyolysis, pericarditis, peritonitis, meningitis, and osteomyelitis rarely occur.<sup>33</sup>

### Diagnosis

Tularemia may be immediately suspected in the typical case of ulceroglandular tularemia with a characteristic skin lesion, lymphadenopathy, fever, and a history of exposure to rabbits or ticks. The diagnosis is much more difficult when other forms of the disease are seen and when the history is negative, as is frequently the case. *F tularensis* is seldom seen on Gram's stain of sputum, skin ulcerations, or node aspiration. Because the organism does not grow on most ordinary media, cultures are usually negative. Many laboratories are reluctant to grow this organism because infectious aerosols can be created.<sup>33</sup>

Most cases of tularemia are diagnosed serologically. A 4-fold rise in the tube agglutination or microagglutination titer is diagnostic of infection. A single convalescent titer of 1:160 or greater is diagnostic of past or current infection. Titers are usually negative in the first week of illness but are positive in 50% to 70% of cases after 2 weeks of illness. Maximum titers are reached in 4 to 8 weeks and may remain elevated at diagnostic levels for many years.<sup>33</sup>

### Treatment

Before the introduction of streptomycin therapy in 1947, the natural course of tularemia was a prolonged illness with most patients unable to work for the first month of illness; many could work only part time for 3 months after the disease began. Some illnesses lasted 14 to 15 months.<sup>35</sup> Untreated, the mortality of tularemia has been low, cited at 5% to 7%.<sup>36</sup> With antibiotics, mortality is about 2%.<sup>33</sup> If the patient has a serious underlying medical disorder or if treatment is delayed, mortality may rise to 6%.<sup>36</sup>

The drug of choice is streptomycin, administered intramuscularly in an adult dose of 0.5 g (15–20 mg/kg/d in divided doses) twice daily for 7 to 14 days.<sup>33</sup> In those with more severe infections (eg, pneumonic involvement or the typhoidal form), it may be wise to double the dose for the first 2 to 3 days.<sup>34</sup> Most patients' fevers decrease during the first 48 hours. Relapses are uncommon.<sup>35</sup>

Gentamicin is an acceptable alternative to streptomycin. The dose is 3 to 5 mg/kg/d in three divided doses every 8 hours, administered intramuscularly. (This dose may require adjustment depending on the patient's serum creatinine.) Gentamicin is a particularly useful drug when the diagnosis is unknown and additional Gram-negative coverage is desired.<sup>33</sup>

Tetracycline has also been used, but relapses are more common. A loading dose is given: 30 mg/kg, administered orally, followed by 30 mg/kg/d in divided doses for 14 days.<sup>33</sup> Tetracycline should not be given to pregnant or lactating women, young children, or patients with renal or hepatic insufficiency.

A live attenuated vaccine is available. It does not provide complete protection but does ameliorate the course of the disease. Candidates for receiving the vaccine include laboratory workers who are routinely exposed to *F tularensis* and persons whose vocations require repeated exposure to rabbits.<sup>33</sup> Soldiers are not routinely vaccinated against tularemia.

## DIPHTHERIA

Diphtheria, a disease of the pharyngeal mucous membranes, is caused by a toxin produced by the bacterium *Corynebacterium diphtheriae*. Locally, this toxin produces a tough pseudomembrane, which can cause death by asphyxiation. This same toxin can profoundly affect distal targets—especially the heart and nerves. In the United States, infection more commonly causes skin lesions than upper-

respiratory tract involvement.<sup>37</sup>

Early in the 1700s in New England, an epidemic of diphtheria killed 2.5% of the population, including one third of the children. Thereafter, epidemics occurred about every 25 years throughout the 18th and 19th centuries.<sup>4</sup>

In France in 1821, Bretonneau first described the unique clinical characteristics of diphtheria, nam-

ing it for the Greek word for leather, after its tough pseudomembrane. In 1883, Klebs described the bacillus in diphtheritic membranes. In Berlin in 1884, Loeffler first isolated the organism in pure culture. He then reproduced the disease in guinea pigs. He also demonstrated that healthy persons could carry the disease in an asymptomatic fashion. In 1888, Roux and Yersin demonstrated that bacteria-free filtrates of the organism could kill guinea pigs, thus demonstrating the production of a toxin. In 1890, Von Behring showed that antiserum against this toxin protected infected animals from death. Horses were found in 1894 to be the most efficient producers of antiserum.<sup>4</sup>

In 1913, Schick demonstrated that a person's susceptibility to diphtheria could be proven by injecting toxin into his skin. A positive reaction indicated the absence of protective antibodies. In 1923, Ramon found that the toxin could be rendered nontoxic by exposing it to formalin and heat, yet the nontoxic form could induce an antibody response. Between 1930 and 1945, most western countries introduced large-scale childhood immunization against diphtheria.<sup>4</sup>

About 5,700 cases of diphtheria occurred in the U.S. Army from 1942 to 1945. (In comparison, 150,000 cases of diphtheria, with nearly 14,000 deaths, had occurred in 41 states in 1920. And 30,000 cases of diphtheria, with 2,600 deaths, occurred in the entire United States in 1938.) The British Royal Army had recognized that cutaneous diphtheria was common in the desert sores of their troops in Palestine and Egypt during World War I, and this lesson was relearned later with the jungle ulcers of the Pacific and the China, India, and Burma theaters. There was no widespread immunization of U.S. troops during World War II because (a) the number of cases was relatively low and (b) reactions to the vaccine were feared. An important consideration in the decision not to immunize troops routinely was based on the knowledge that injection of diphtheria toxoid would be followed by moderate-to-severe reactions in an appreciable number of cases: 10% of those injected developed incapacitating febrile reactions.<sup>38</sup>

After World War II, during the occupation of Germany, the incidence of nasopharyngeal diphtheria increased tremendously among the civilian population living in bombed-out areas, often in association with overcrowding. As rules against fraternization with the civilian population were relaxed, diphtheria increased among the military population. During 1945, there were 2,240 cases of diphtheria, with 67 deaths, among U.S. troops

in Europe.<sup>38</sup> In April 1946, all susceptible military personnel under the age of 35 were required to be immunized before traveling to the European theater.<sup>39</sup>

## Etiology

*C diphtheriae* is an irregularly staining, pleomorphic, Gram-positive bacillus with clubbed ends. In Loeffler's medium (consisting of a heat-coagulated mixture of 75% serum and 25% broth), it initially outgrows other throat flora. The agar plates should be inspected for growth at 12 to 18 hours. Direct smears from clinical exudates do not demonstrate the characteristic metachromatic granules and "Chinese character" palisading morphology as well as smears that are taken from colonies grown on Loeffler's medium. Tellurite medium inhibits much of the normal throat flora and identifies *C diphtheriae* as gray-black colonies, subdivided into *gravis*, *intermedius*, and *mitis*, based on their hemolytic potential, fermentation reactions, and differing colonial morphology.<sup>4</sup>

*C diphtheriae* is not a very invasive organism, tending to remain in the superficial portion of the skin or mucous membranes. Its major virulence is due to the production of a potent exotoxin that inhibits protein synthesis in mammalian, but not bacterial, cells. The toxin affects all cells in the body but especially the heart, nerves, and kidney. This is an extremely potent toxin, in that one molecule causes cessation of protein synthesis in one cell within several hours. Exotoxin production is dependent on the presence of a lysogenic  $\beta$  phage, which may or may not be present in *C diphtheriae*. Antitoxin can neutralize the toxin before it reaches its target, but antitoxin is useless once the toxin is inside the cell.<sup>4</sup>

## Epidemiology

Humans are the only known reservoir of *C diphtheriae*. The organism can be spread by means of airborne droplets or from infected skin lesions. Most upper respiratory infections occur in the colder months in temperate climates and are associated with overcrowding. Convalescent or healthy carriers and those incubating the disease are most important in spreading the disease.<sup>40</sup>

In endemic conditions, *C diphtheriae* can be found in 3% to 5% of the population,<sup>4</sup> but in North America and Europe, the bacterium has recently become very rare. This is curious because in many parts of the United States, a large proportion of the popula-

tion is susceptible to the toxin. For example, among 183 urban adults in Minnesota, only 26% of men and 21% of women showed an overall protective level of antibody.<sup>41</sup> Despite this, the disease is quite rare in the United States at present.

Person-to-person spread from skin infections is more efficient than from the respiratory tract. Skin infections were once thought to occur primarily in the tropics, but several recent outbreaks have occurred in Europe and North America among alcoholics and poverty-stricken groups.<sup>4,37</sup>

### Clinical Manifestations

The incubation period for *C diphtheriae* is usually 2 to 4 days. Pharyngitis is the most common presentation of diphtheria and is characterized by abrupt onset, fever (usually < 103°F), mild pharyngeal injection, pharyngeal pain, a uniquely fetid breath, and the development of a membrane. This membrane may be on one or both tonsils, but it may also extend to involve the posterior pharynx, soft palate, larynx, and nasopharynx, which indicates more severe disease (Figure 13-9). Initially white, the membrane evolves into a dirty gray color with patches of necrosis. Cervical adenopathy and swelling may cause the patient to have a “bull-neck” appearance, with respiratory stridor. Involvement of the larynx, trachea, and bronchi may produce airway obstruction. This may require intubation and mechanical removal of the membrane, or the patient may rapidly become exhausted and die. Indeed, in the late 19th century, the most common



**Fig. 13-9.** This febrile patient with pharyngeal diphtheria has erythema, edema, and a gray membrane on the tonsils and posterior pharynx.



**Fig. 13-10.** Hemorrhagic pustules on the digits are often indicative of septicemia with *Candida albicans* or Gram-negative organisms. In this patient, *Corynebacterium diphtheriae* was the cause.

cause of death in children was suffocation. *Streptococcus pyogenes* is a common cause of secondary infection, which is usually manifested by a bright red pharynx and fever above 103°F.<sup>4,40</sup>

Cutaneous diphtheria occurs in patients of low socioeconomic status who have poor personal hygiene. Hemorrhagic pustules lead to ulcerations, which are frequently slow to heal (Figures 13-10 and 13-11). They are often infected with *Staphylococcus aureus* and *Streptococcus pyogenes* as well as *C diphtheriae*. Systemic toxicity is unusual, as is heart and nerve involvement.<sup>4</sup> Other sites for diphtheria infection include the ear, the conjunctiva, and the genitalia.<sup>40</sup>

Systemic complications of respiratory diphtheria are secondary to *C diphtheriae*'s production of toxin. The toxin may affect all tissues but is particularly toxic to the heart and nerves. Characteristically, myocarditis (*a*) is noticed when the respiratory disease is improving, usually 1 to 2 weeks after the onset of the disease and (*b*) is responsible for about half the mortality of diphtheria. Clinically significant cardiac abnormalities occur in about 20% of cases.<sup>40</sup> The onset of myocarditis may be acute or gradual. It is important to routinely monitor all diphtheria patients with electrocardiograms. The patient may appear clinically well, but the electrocardiogram may show significant abnormalities. Patients with electrocardiographic evidence of myocarditis have a mortality rate 3- to 4-fold higher than those with normal tracings. Patients with atrioventricular dissociation and left bundle branch block have a mortality of 60% to 90%; survivors may



**Fig. 13-11.** Diphtherial ulcerations characteristically have a purplish rolled border and involve the feet or legs.

have permanent conduction defects. The serum aspartate aminotransferase level closely parallels the intensity of the myocarditis and may be used to follow its course.<sup>4</sup>

Neurological abnormalities occur more commonly in those patients with severe disease. They usually occur late, often a month after the onset of the disease. Cranial nerves are usually affected first. Paralysis of the soft palate and posterior pharyngeal wall may lead to regurgitation of ingested fluids through the nose. Aspiration may also occur. Neurological involvement can affect the peripheral motor nerves, beginning proximally and advancing distally; it especially affects the dorsiflexors of the feet. Involvement varies from weakness to total paralysis.<sup>4</sup> Slow, but complete, recovery of neurological function is the norm.<sup>40</sup>

### Diagnosis

The diagnosis of diphtheria is based on cultural isolation and bacterial identification of the organism with laboratory proof of the toxicogenicity. The laboratory must be notified of the possibility of diphtheria so that the culture specimens may be

placed in appropriate media (ie, tellurite and Loeffler's). An immunofluorescence test can rapidly identify *C diphtheriae*, but it will not establish toxicogenicity. This determination requires either guinea pig inoculation or an agar gel-diffusion technique.<sup>40</sup>

The presence of the pharyngeal membrane, electrocardiographic abnormalities, and cranial nerve palsies all point to the diagnosis of diphtheria. Diagnosis is most difficult in mild cases.<sup>40</sup>

### Treatment

For nearly a century, the cornerstone of treatment has been diphtheria antitoxin. Diphtheria was the first disease in which treatment with specific antibody was shown to be of therapeutic value. Diphtheria antitoxin only neutralizes toxin before it enters the cell, so it is crucial to give it as soon as a presumptive diagnosis is made. Recommendations by the Committee on Infectious Disease by the American Academy of Pediatrics include the following:

- 20,000 to 40,000 units of diphtheria antitoxin for pharyngeal or laryngeal infection of 48 hours' duration,
- 40,000 to 60,000 units for nasopharyngeal disease, and
- 80,000 to 100,000 for extensive disease of 3 or more days' duration or brawny edema of the neck.

Intravenous administration is recommended to rapidly inactivate toxin. Before systemic doses are given, the patient must be tested for sensitivity with 1:10 antitoxin solution (for conjunctival testing) or 1:100 dilution (for intradermal testing). Antitoxin is probably of no value for cutaneous disease, but some authorities use 20,000 to 40,000 units of antitoxin because toxic sequelae have been reported.<sup>37,42</sup>

The diphtheria antitoxin is produced in horses and up to 10% of patients will show some allergy to horse protein. The patient must be questioned about sensitivity to horse protein prior to starting therapy. Epinephrine should be available for immediate administration. If an immediate reaction occurs, the patient should be desensitized with progressively increasing doses of diphtheria antitoxin.<sup>42</sup>

Antibacterial therapy serves three purposes:

1. It shuts down toxin production.
2. It treats the local infection and covers a

possible secondary infection with *Streptococcus pyogenes*.

3. It curtails the spread of the disease to other persons.

Untreated, 1% to 15% of persons recovering from diphtheria become carriers.<sup>40</sup>

The drug of choice in diphtheria for active infection is erythromycin, with an adult dose of 500 mg every 6 hours by mouth for 2 weeks. If the patient cannot swallow, erythromycin may be given intravenously as 30 mg/kg/d in three divided doses every 8 hours. Thrombophlebitis is common with intravenous usage.<sup>40</sup>

Penicillin is usually effective in active diphtheria but is not as effective in carriers as erythromycin. The adult dose of penicillin is 600,000 units (given in the procaine form) administered intramuscularly every 12 hours for 2 weeks. Clindamycin and rifampin have also been effective,<sup>37</sup> but generally only erythromycin and penicillin are recommended.<sup>40</sup>

The patient should be maintained in strict isolation during therapy and should have three consecutive negative cultures at 24-hour intervals at the conclusion of therapy to document eradication of the organism. This is to assess for the carrier state.<sup>4</sup>

Regarding cutaneous diphtheria, the patient should be placed in contact isolation until two cultures of skin lesions, taken at 24-hour intervals, are negative.<sup>42</sup>

The treatment of choice for the carrier state is 7 days of oral erythromycin.<sup>4</sup> However, in one study,<sup>43</sup> 21% of patients treated with erythromycin cultured positive for *C diphtheriae* 2 weeks after the conclu-

sion of therapy. An alternative for adults is 2,400,000 units of benzathine penicillin G, administered intramuscularly in one dose. Carriers should also be cultured for *C diphtheriae* 2 weeks after chemotherapy is concluded.<sup>40</sup>

Supportive care is also important. Airway and cardiac complications may occur early. The membrane can extend into the larynx or break off and occlude the airway, causing breathing difficulties or death by asphyxiation. Many experts recommend intubation or tracheostomy early, particularly if the membrane involves the larynx. This allows access so that the membrane can be mechanically removed. Cardiac monitoring is also important.<sup>4</sup>

### Immunization

Diphtheria is prevented by active immunization using toxoid (formalin-detoxified diphtherial toxin). Preschool immunization is undoubtedly effective, but this protection wanes with age. When toxicogenic diphtheria was common, reinforcement of immunization was also common owing to overcrowding and high carrier rates. In the United States, reinforcement no longer occurs, and large numbers of women and the elderly are now believed to be at risk. Hence, it is now recommended that adults be reimmunized every 10 years.<sup>41</sup> This is done usually with the highly purified tetanus-diphtheria toxoid for adults. Diphtheria immunization is the standard practice in the U.S. Army, and consequently, diphtheria should not be a problem for soldiers; however, diphtheria may well be a problem in local populations where overcrowding and poor hygiene are the rule.

## MENINGOCOCCAL INFECTIONS

Meningococcal infections usually begin with the growth of *Neisseria meningitidis* in the human oropharynx. Occasionally, this proliferation will give rise to systemic infection, usually meningitis and bacteremia (ie, meningococemia).

In 1805, Vieusseaux described epidemic cerebrospinal fever (meningococcal meningitis) in Geneva. Weichselbaum isolated meningococcal organisms from cerebrospinal fluid in 1887. Healthy persons were noted to be carriers of the organism by Kiefer in 1896 and Albrecht and Ghon in 1901. In 1909, Dopter first recognized serotypes of meningococcus. This laid the basis for Flexner's serum therapy of infection in 1913. Sulfonamides were

found to be effective in 1937. Sulfonamides also eradicated the carrier state and were given as prophylaxis to prevent epidemics in areas of crowded living conditions. Subsequently, other antibiotics were found to be more effective in treating meningococcal infections, and mortality and morbidity declined further. In 1963, the resistance of *N meningitidis* to sulfonamide became a clinically significant problem. This has led to the development of safe and effective vaccines against serogroups A, C, Y, and W-135.<sup>44</sup>

Military records indicate that the U.S. Army has had significant outbreaks of meningococcal disease in the War of 1812, the Mexican War, the Civil War, World War I, and World War II.<sup>5</sup> Hospital admis-

sion rates have always been negligible except during periods of rapid mobilization of new personnel. During World War II, the Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army issued an interim report, which contained this statement from its Commission on Meningococcal Meningitis:

[A] field laboratory was set up on September 28, 1942, [at Jefferson Barracks, Missouri]. The purpose of the study [was] to determine if possible the factors influencing the continued occurrence of meningitis at this station.... [The report emphasized] the three factors which aid the occurrence of meningococcal meningitis: crowded quarters, a high meningococcus carrier rate, and the continued addition of susceptibles (unseasoned recruits).<sup>45(p36)</sup>

Of 5,000 cases reported to the Commission on Meningococcal Meningitis during World War II, 67% of the soldiers had been in service less than 3 months and 93% in service less than 1 year.<sup>5</sup>

The incidence of this disease is low compared with that of other respiratory diseases. During World War I, meningococcal disease ranked only 76th as a cause of admission to a hospital; however, 40% of the cases were fatal and the disease ranked sixth as a cause of death.<sup>5</sup> Meningococcal disease is one of the few that can kill a healthy young adult in a matter of hours to a few days.

## Etiology

*N meningitidis* appears as a Gram-negative diplococcus with the adjacent sides flattened. It is oxidase positive and typically metabolizes both glucose and maltose. *N gonorrhoea*, in contrast, does not metabolize maltose.<sup>44</sup>

The organism is fastidious in terms of growth media and conditions. It is aerobic, grows best at temperatures of 35°C to 37°C with a 5% to 10% atmosphere of carbon dioxide, and requires enriched media such as chocolate agar.<sup>44</sup>

Meningococci are surrounded by a polysaccharide capsule and are divided into serogroups on the basis of differences in their capsular polysaccharides. Groups A, B, C, W, and Y cause the most serious disease.<sup>46</sup>

## Epidemiology

There is no known reservoir for meningococci other than humans. The bacteria are usually spread from person to person by respiratory droplets from the

nasopharynx of asymptomatic carriers. Usually this gives rise to immunity that is serospecific for the organism; serious infection will occasionally result.<sup>46</sup>

The carrier rate in the United States is estimated to be 5% to 10%. High carriage rates also consistently develop in military recruits whether or not actual disease has occurred. In this situation, the prevalence of meningococcal carriage has ranged from 40% to 80%. In household contacts of a case of meningococcal meningitis, 17% to 50% are found to carry the same strain as the index case.<sup>47</sup>

Major outbreaks of meningococcal disease have been documented at 7- to 10-year intervals in the United States during the 20th century, and large epidemics (in both the indigenous population and in the military) occurred during World War I, World War II, and the Korean and Vietnam conflicts. Significant outbreaks, usually of the group A serotype, are regularly reported in Africa and South America.<sup>48</sup>

Most epidemic disease in the United States was also caused by the group A serotype until the 1960s.<sup>48</sup> Then group B emerged and has remained the predominant serotype since: the B serotype currently causes more than 50% of the meningococcal meningitis in the United States.<sup>47</sup> Group C is the second-most-common serotype and is especially common in closed populations (eg, military training centers). Increasingly, Groups Y and W-135 are being reported in Western Europe and the United States. Group Y is also commonly associated with pneumonia.<sup>48</sup>

Most meningococcal disease in the United States occurs in two populations: infants and children under the age of 4, and military recruits, but sporadic disease may occur in any age group.<sup>48</sup> The highest frequency of cases is in the winter and early spring; the lowest in the summer.<sup>46</sup>

Several factors predispose to meningococcal disease:

- prior viral respiratory disease,
- complement defects in C5, C6, C7 and C8,<sup>49</sup>
- properdin deficiencies,<sup>50</sup> and
- immunoglobulin deficiencies.<sup>46</sup>

In addition,

- patients with a terminal complement deficiency frequently have recurrent disease in association with low mortality, a high incidence of group-Y disease, and initial infection during the teenage years<sup>49</sup>; and
- properdin deficiency predisposes to fatal disease.<sup>50</sup>



## Clinical Manifestations

The signs and symptoms of meningococcal disease can vary from bacteremia and transient fever to death within a matter of hours. Of patients with meningococcal disease, 90% to 95% present with either meningococemia or meningitis or both. The typical patient has nonspecific prodromal symptoms of headache, cough, and sore throat followed by the sudden development of spiking fever, chills, myalgias, and arthralgias.<sup>46</sup>

Although a transient maculopapular eruption associated with generalized myalgias has been described in meningococcal disease, the more typical eruption is petechial. It may remain sparse or progress to widespread purpura (Figure 13-12). The petechial eruption is manifested as 1- to 2-mm lesions on the trunk, lower extremities, and conjunctivae. They commonly occur on the skin where elastic from underwear or stockings applies pressure to the skin. Petechiae correlate with the extent of thrombocytopenia. Increasing numbers and enlarging lesions indicate progression of the bleeding complications due to disseminated intravascular coagulation.<sup>44</sup>

Postmortem studies<sup>44</sup> have found varying degrees of myocarditis in over 50% of patients who die of meningococcal disease. There may be clinical evidence of heart failure, which cardiac glycosides have successfully reversed.



**Fig. 13-12.** This patient, a young man with meningococemia, developed a stiff neck and fever several days before these purpuric macules developed. These lesions progress by coalescence into angulated, confluent, reticulated patches with central necrosis.

## Fulminant Meningococemia

Fulminant meningococemia, also known as the Waterhouse-Friderichsen syndrome, is meningococemia associated with shock and vasomotor collapse. The onset is abrupt, and profound prostration occurs within hours. Extensive ecchymoses are common. With the onset of shock, the blood pressure falls, mentation decreases, and coma may develop.<sup>46</sup> Global mortality for all meningococcal disease among civilians has remained constant at 10% to 19% for the past few decades, but the mortality for fulminant meningococemia is 40% to 57%.<sup>51</sup> Recovering patients may have extensive sloughing of skin or loss of digits due to gangrene.<sup>46</sup>

## Arthritis–Dermatitis Syndrome

The arthritis–dermatitis syndrome consists of fever, rash, and joint pain (or any combination) in a young, sexually active patient. This syndrome has primarily been caused by *Neisseria gonorrhoea*. However, a recent report of 62 such patients noted blood or synovial cultures, or both, positive for gonococci in 9 and meningococci in 5. This suggests that *N meningitidis* should be given more consideration in the differential diagnosis of arthritis–dermatitis syndrome in the future, although *N gonorrhoea* still predominates.<sup>52</sup>

## Meningitis

The other common form of meningococcal disease is meningitis. This occurs primarily in children aged 6 months to 10 years with symptoms of vomiting, fever, headache, and confusion or lethargy. Typically, the patient has signs of an upper respiratory infection followed by an illness that progresses over a few days. Onset may also be sudden and rapidly progressive. A presumptive diagnosis of meningococcal disease should be made whenever meningitis occurs in association with a petechial or purpuric eruption because this is rarely seen in other infections.<sup>46</sup>

Signs of meningeal irritation are common except in the very young or very old, but focal signs and seizures are less common than in infections due to *Haemophilus influenzae* or pneumococcus. The levels of consciousness are about the same in all three diseases.<sup>44</sup>

## Meningococcal Pneumonia

Meningococcal pneumonia has been recognized for decades. This type of infection usually has no

associated skin findings. It is most commonly caused by group Y. A study of U.S. Air Force recruits reported that a history of cough, chest pain, chills, and previous respiratory infection occurred in more than half of the cases. Rales and fever occurred in almost all patients, and pharyngitis occurred in over 80%. Forty-two percent of the patients had involvement of more than one lobe, and 29% had pleural involvement. Bacteremia is uncommon, so blood cultures are usually not helpful. Transtracheal cultures appear to be the best way of making the diagnosis in meningococcal pneumonia.<sup>53</sup>

### Diagnosis

The diagnosis of meningococcal disease is usually made from positive blood and cerebrospinal fluid cultures. About half of patients with meningococcal disease have positive blood cultures, and 58% to 94% of patients have positive cerebrospinal fluid cultures or positive Gram's stains for Gram-negative diplococci in the cerebrospinal fluid. Several cases of meningococemia with no evidence of meningitis have had positive cerebrospinal fluid cultures. The cerebrospinal fluid in meningococcal meningitis has elevated leukocytes (predominantly neutrophils), low glucose, and elevated protein.<sup>44</sup>

Counterimmunoelectrophoresis and latex agglutination assays may also be helpful, especially early in the course of the disease or when the patient has been treated with antibiotics before cultures were obtained.<sup>46</sup>

### Treatment

The current recommended treatment for meningococcal meningitis, meningococemia, and chronic meningococemia is penicillin G, administered intravenously at a dose ranging from 300,000 units per kg per day to 24 million units per day in divided doses. If the patient is allergic to penicillin, the second drug of choice is chloramphenicol, administered intravenously at a dose of 100 mg/kg/d up to 4 g/d in divided doses. A 7- to 10-day course of therapy is usually adequate.<sup>44</sup>

Penicillin-resistant *N meningitidis* has recently been reported in Europe.<sup>54</sup> These bacteria were sensitive to third-generation cephalosporins such as ceftriaxone and cefotaxime.

In every case of meningococcal disease, the potential for shock should be considered and

treated as necessary. The patient should be placed on respiratory isolation to minimize nosocomial spread.

### Chemoprophylaxis of Carriers

Household contacts of patients with meningococcal disease are 500- to 800-fold more likely to contract the infection than the general population. Military barracks, college dormitories, chronic-care hospitals, and nursery schools also have high-risk populations. These people should receive prophylactic therapy. Hospital personnel and medical staff are not recommended for prophylaxis unless they have had intimate contact with a patient (eg, mouth-to-mouth resuscitation).<sup>44</sup>

Initially, sulfadiazine was highly effective in eradicating the carrier state. However, the bacteria became resistant during the mid-1960s, and it is no longer used unless the meningococcus is known to be sensitive. The current choice for chemoprophylaxis in adults is rifampin, administered orally, 600 mg every 12 hours for four doses. The patient should be forewarned about red urine. Rifampin-resistant meningococci also occur.<sup>44</sup> Minocycline can also be used for prophylaxis but this drug has a high incidence of vertigo and staining of tooth enamel in young children. Recently, a single dose of ceftriaxone (250 mg, administered intramuscularly) was reported as effective in eradicating pharyngeal carriage of group A *N meningitidis*.<sup>55</sup> This could be particularly helpful if other serogroups are sensitive. It would also be especially useful in pregnant women. Ciprofloxacin (250 mg every 12 h for 2 d) has also been effective.<sup>56</sup>

### Vaccines

A quadrivalent vaccine that is effective against serotypes A, C, Y, and W-135 is licensed for use in the United States. It is recommended for high-risk patients with terminal complement defects and functional or anatomical asplenia. It is also recommended for travelers to high-risk areas, such as the meningitis belt in Africa.<sup>46</sup>

There is no effective vaccine for group B meningococcus, the predominant serotype in the United States. Group C is a poor immunogen for children under the age of 2 years—the age group usually affected by this serotype.<sup>44</sup>

Recruits into the U.S. Army are routinely given the quadrivalent vaccine.

## LYME DISEASE

Lyme disease (Lyme borelliosis) is a multisystem infection caused by the spirochete *Borrelia burgdorferi*, which is transmitted by ticks of the genus *Ixodes*. The characteristic skin lesion and earliest manifestation of this disease is erythema chronicum migrans (ECM, also known as erythema migrans). This may be followed by localized involvement of the nervous system, heart, or joints.<sup>57</sup> Some patients recover spontaneously without treatment,<sup>58</sup> but others will have disabling arthritis, neurological impairment, or cardiac conduction abnormalities.

Lyme disease is not only the most commonly reported tick-borne disease in the United States,<sup>58</sup> according to T. E. Woodward, former president of the Armed Forces Epidemiology Board, it is also

potentially of massive importance to both the military and the public in many areas of the continental United States. Many epidemiologists believe that, were it not for the advent of [acquired immunodeficiency syndrome], Lyme disease would now be the nation's primary infectious disease problem. Incidence of the disease is steadily rising in the United States, more commonly among males, and with widespread distribution.<sup>59(p269)</sup>

In Lyme, Connecticut, in 1975, a cluster of patients with presumed juvenile rheumatoid arthritis prompted an investigation by Steere<sup>60</sup> into a disorder now recognized as Lyme disease.<sup>57</sup> The rural setting of the case cluster and the identification of ECM as a feature of the disease suggested that it was passed by an arthropod vector. In 1982, Burgdorfer et al<sup>61</sup> reported the isolation of the causative spirochete, subsequently named *Borrelia burgdorferi*, from an *Ixodes scapularis* tick. In retrospect, it is clear that the borelliosis we now call Lyme disease had been seen and treated earlier<sup>57</sup>:

- In Sweden in 1909, Afzelius<sup>62</sup> described a patient with migrating annular skin lesions presumed to be caused by the tick *Ixodes reduvius*. He coined the term erythema chronicum migrans.
- In 1948, Lennhoff<sup>63</sup> described spirochetes in lesions of ECM. This received little attention.
- In 1951, Hollstrom<sup>64</sup> reported successful treatment of ECM with penicillin, and during the 1950s, ECM was widely treated in Europe with penicillin.

### Epidemiology

In this country, Lyme disease is most prevalent from April to October in the three geographical areas where the tick vector is endemic: in the Northeast, from Maryland to Massachusetts; in the Midwest, in Wisconsin and Minnesota; and in the West, in northern California and Oregon. Lyme disease was reported in 47 states during 1991.<sup>65</sup> Thousands of new cases are estimated to occur every summer in Europe, especially in Germany, Austria, France, Switzerland, and Sweden. In Russia, Lyme disease has been reported from the Baltic to the Pacific. The disease has also been found in Australia, China, and Japan.<sup>57</sup>

Ticks, particularly the genus *Ixodes*, are the major vectors for *Borrelia burgdorferi*. In the United States, *Ixodes scapularis* is the most common vector in the East and Midwest and *I pacificus* in the West; in Europe, the vector is *I ricinus*.<sup>58</sup>

The risk of contracting Lyme disease depends on both the density of the tick population and their degree of infection by *Borrelia*. In the eastern United States, as many as 60% of the *Ixodes scapularis* may be parasitized with *B burgdorferi*; in the West, only 1% to 2% of *I pacificus* are parasitized.<sup>58</sup>

All stages (larva, nymph, adult) of the *Ixodes* tick are capable of passing the disease, the nymphal being the most common. The nymph is so small that it is difficult to recognize (beware the freckle that moves!). The bite is painless and often unnoticed. The tick must remain attached for 1 to 3 days to pass the disease.<sup>58</sup>

Many organisms may serve as a reservoir for *B burgdorferi*, but the most common are the deer and white footed mice. *Ixodes* ticks feed on many species of song birds. Migration of birds infested with these ticks may be one means through which new endemic areas develop. The illness of Lyme disease is not known to occur in wild animals but is well known to occur in domestic animals, including dogs, horses, and cattle.<sup>66</sup>

### Clinical Manifestations

Lyme disease has three major clinical stages: (1) localized ECM, (2) disseminated infection, and (3) persistent infection. These stages are arbitrary, and systemic progression from one stage to another is frequently not seen. In fact, a patient may present

with manifestations of two stages or may present in the third stage without evidence of preceding findings. A revised classification also recognizes three stages of disease but groups them differently: (1) early infection, which encompasses stages 1 and 2; and (2) late infection, encompassing stage 3, which usually begins a year or more after the onset of the disease.<sup>57</sup>

#### **Early Infection: Stage 1 (Localized Erythema Chronicum Migrans)**

Stage 1 begins 3 to 30 days after the tick bite, which only about one third of patients recall. This stage is characterized by nonspecific constitutional symptoms: fever, chills, malaise, fatigue, arthralgias, and headache. The most prominent manifestation is ECM, which is present in 60% to 83% of adults,<sup>67</sup> but in fewer than 25% of children.<sup>58</sup> ECM typically begins at the site of the tick bite as an erythematous papule that enlarges to an annular configuration (Figure 13-13). The edge may be raised and indurated or flat.



**Fig. 13-13.** This early lesion of erythema chronicum migrans developed 2 weeks after a tick bite to the patient's leg. The site of the tick's attachment is clearly seen in the center of the peripheral erythema.



**Fig. 13-14.** As the annular erythematous border of the eruption of erythema chronicum migrans advances away from the central bite site, very large lesions may develop.

The central portion partially clears, often leaving an erythematous central punctum, but may remain red and indurated or, rarely, become necrotic. These signs suggest a differential diagnosis of brown recluse spider bite, cellulitis, or tularemia (Figure 13-14).<sup>67</sup>

The lesion is frequently found where ticks characteristically feed: the axilla, popliteal fossa, thigh, groin, buttocks, and underwear lines. ECM is usually asymptomatic. The average size of the lesion is 15 cm, but lesions up to 68 cm in diameter are sometimes seen. When left untreated, ECM fades in weeks to months. The average duration is 1 month. With appropriate antibiotic treatment, ECM usually resolves within days.<sup>67</sup>

The histological findings of ECM are relatively nonspecific. Hence, the presence of *B burgdorferi* must be shown on silver stain, labeled-antibody staining, or culture for confirmation of the disorder. Spirochetes are most commonly found in the dermis of the advancing edge of the lesions.<sup>67</sup>

#### **Early Infection: Stage 2 (Disseminated Infection)**

Within days to weeks of inoculation, the spirochete spreads to many parts of the body. One or more secondary skin lesions may occur and have been reported in 6% to 48% of cases. These secondary lesions tend to be smaller than the originals and to migrate less. However, multiple lesions may become confluent and produce polycyclic or geographical patterns. If untreated they tend to disappear within a month but can persist for more than a year. In patients who are receiving appropriate

therapy, the lesions usually resolve in a few days. The differential diagnosis includes erythema multiforme, erythema annulare centrifugum, secondary syphilis, erythema marginatum, and drug eruption.<sup>67</sup>

In Europe, approximately 1% of cases develop a borrelia lymphocytoma, a form of B-cell pseudolymphoma, also known as Spiegler-Fendt lymphoid hyperplasia. (The borrelia organism has been found on silver stain and also on tissue culture.) This lesion (described as a firm, red, red-brown, or red-purple nodule or plaque) has been known to occur at the time of ECM or as late as 10 months after the tick bite. In children, the lesion tends to develop on the ear's pinna. In adults, it is found on the nipple or areola. This lesion has not been described in the United States.<sup>67</sup>

**Musculoskeletal Manifestations.** Disseminated infection is associated with characteristic symptoms related to involvement of the musculoskeletal system. Musculoskeletal pain is generally migratory, lasting only hours or days at a given location. The patients often appear quite ill with debilitating malaise and fatigue. A mean of 6 months after the onset of the disease (range: 2 wk–2 y), approximately 60% of patients in the United States begin to have brief attacks of asymmetric oligoarthritis in the large joints, especially the knee.<sup>57</sup>

**Neurological Manifestations.** The earliest neurological manifestation is seventh cranial nerve palsy (Bell's palsy). This is seen in 5% of patients with early untreated disease. Gradual resolution over several weeks is generally seen, even in untreated patients. In the United States, approximately 15% of untreated patients develop a spectrum of neurological abnormalities, including lymphocytic meningitis, meningoencephalitis, cranial nerve palsies, peripheral neuritis, and radiculoneuritis.<sup>66</sup>

The most common manifestation of central nervous system Lyme disease is meningitis, which is characterized by fluctuating symptoms mimicking those of aseptic meningitis. Complaints include severe headache (typically occurring in short attacks lasting over hours), irritability, neck stiffness without frank meningism, photophobia, and nausea and vomiting. Examination of the cerebrospinal fluid shows a lymphocytic pleocytosis of a few to a few hundred cells, a normal glucose level, and mild protein elevation. These findings are indistinguishable from those found in aseptic meningitis.<sup>66</sup>

Syndromes involving the peripheral nervous system include peripheral neuritis; sensory radiculitis; sensorimotor radiculoneuritis; and brachial, lumbar, or sacral plexitis. Several neurological manifestations may occur simultaneously or in sequence.

The combination of radiculoneuritis and cerebrospinal fluid pleocytosis, known as Bannwarth's syndrome or tick-borne meningopolyneuritis, is particularly common in Europe and the countries of the former Soviet Union.<sup>66</sup>

**Myocardial Manifestations.** Fewer than 10% of untreated patients develop Lyme carditis, which appears, on average, 2 to 6 weeks after disease onset. Lyme carditis is generally seen in patients with minimal or no symptoms associated with the onset of the infection. Varying degrees of atrioventricular block occur, often changing from minute to minute or hour to hour. Even in untreated patients, these conduction abnormalities are usually brief. High-grade atrioventricular block frequently requires the insertion of a temporary pacemaker. Rarely, a permanent pacemaker may be required.<sup>66</sup>

### **Late Infection: Stage 3 (Persistent Infection)**

Episodes of arthritis, which is the characteristic sign of persistent infection, often become longer during the second and third years of illness. They last months rather than weeks, and chronic arthritis begins during this time. Only one or a few of the large joints are affected. Usually it is the knee.<sup>57</sup>

Acrodermatitis chronica atrophicans is a unique late complication of Lyme disease, which about 10% of patients in Europe develop. However, it has rarely been reported in the United States. Acrodermatitis chronica atrophicans occurs 6 months to 8 years after the initial infection and is more common in elderly patients. An initial, nonspecific, often bilaterally symmetrical, inflammatory state usually occurs on acral sites. Typically, this is an erythematous or violaceous discoloration in doughy or swollen skin with plaques or nodules. The lesions may wax and wane over weeks to years before atrophy occurs. In the atrophic stage, the skin resembles cigarette paper, with prominent blood vessels. There may be hypopigmentation or hyperpigmentation with scaling. The lesion may be associated with pain, pruritus, or paresthesias. Regional lymphadenopathy may be present. *B burgdorferi* may be demonstrated by special stains in these lesions. Early acrodermatitis chronica atrophicans does not resolve spontaneously but may respond to antibiotic therapy. Later lesions may not resolve even with antibiotics, but their progression can usually be halted.<sup>67</sup>

Other skin conditions rarely reported to be associated with *Borrelia* infection include benign lymphocytic infiltrate, morphea, lichen sclerosus et atrophicus, atrophoderma of Pasini and Pierini,

**TABLE 13-1**  
**RECOMMENDATIONS FOR TREATMENT OF ADULTS WITH LYME DISEASE**

Disease Stage	Recommended Treatment
Early infection, Stage 1	Doxycycline 100 mg PO b.i.d. for 10–21 d* Amoxicillin 500 mg PO t.i.d. for 10–21 d Tetracycline 250–500 mg PO q.i.d. for 10–21 d* Cefuroxime axetil 500 mg PO b.i.d. for 20 d Phenoxymethyl penicillin 250–500 mg PO q.i.d. for 10–21 d Erythromycin 250 mg PO q.i.d. for 14–21 d
Neurological manifestations	
Bell's Palsy or mild symptoms	Treat as above, but for at least 3 wk
Other neuropathies, meningitis, encephalitis	Ceftriaxone 2 g, IV, single daily dose for 14–21 d Penicillin G, 20 million U/d, IV, in divided doses for 14–21 d
Lyme carditis	
Mild disease (1st-degree heart block)	Doxycycline 100 mg PO b.i.d. for 14–21 d* Amoxicillin 500 mg PO t.i.d. for 14–21 d
More serious disease	Ceftriaxone 2 g IV single, daily dose for 14–21 d Penicillin G, 20 million U/d, IV, in divided doses for 14–21 d
Lyme arthritis	Doxycycline 100 mg PO b.i.d. for 30 d* Amoxicillin and probenecid, 500 mg of each PO q.i.d. for 30 d Penicillin G, 20 million U/d, IV, in divided doses for 14–21 d Ceftriaxone 2 g, IV, single daily dose for 14–21 d

\*Not recommended for use in pregnant women and children ≤ 8 years of age  
IV: intravenous; PO: by mouth; b.i.d.: twice daily; t.i.d.: three times daily; q.i.d.: four times daily; U: units  
Data sources: (1) Rahn DW, Malawista SE. Lyme disease: Recommendations for diagnosis and treatment. *Ann Int Med.* 1991;114:472–481. (2) Rahn DW, Malawista SE. Lyme disease. *West J Med.* 1991;154:706–714. (3) Nadelman RB, Luger SW, Frank E, et al. Comparison of cefuroxime axetil and doxycycline in the treatment of early Lyme disease. *Ann Int Med.* 1992;117:273–280. (4) Abele DC, Anders KH. The many faces and phases of borreliosis: Lyme disease. *J Am Acad Dermatol.* 1990;23:167–186; 401–410. (5) Rahn DW. Lyme disease: Clinical manifestations, diagnosis, and treatment. *Semin Arthritis Rheum.* 1991;20:201–218.

eosinophilic fasciitis, and progressive facial hemiatrophy. Only a minority of these lesions are believed to be caused by Lyme disease.<sup>67</sup>

In this third stage, the following neurological conditions have occurred: chronic encephalomyelitis, spastic paraparesis, ataxic gait, subtle mental disorders, chronic axonal polyradiculopathy, and dementia.<sup>57</sup>

**Diagnosis**

The diagnosis of Lyme disease is usually made by the observation of a typical ECM lesion and the history of its expanding character. In an endemic area, this is sufficient to treat the patient for Lyme disease. The history of a tick bite is helpful but present in only about one third of cases. More than one half the patients have other acute symptoms, especially fatigue, headache, fever, myalgias, arthralgias, and mildly stiff neck. Serologic tests

are often negative in early disease. Perhaps the best diagnostic test is a biopsy of the expanding edge of the lesion with a modified Steiner stain for organisms, but this is only positive in approximately half the cases.<sup>68</sup> Special cultures have made possible an isolation of 86% from 4-mm punch biopsies of the expanding edge of the lesions of erythema migrans.<sup>69</sup>

With chronic manifestations of Lyme disease, a serology test is much more likely to be helpful. These tests are not standardized and there may be significant variation between laboratories. Additionally, false positives from other conditions, such as syphilis, confuse the picture.<sup>70</sup> A significant percentage of patients in endemic areas may have positive serologic results with no evidence of Lyme disease.<sup>65</sup>

**Treatment**

Current recommended therapy<sup>71,72</sup> for early Lyme disease consists of

1. doxycycline, 100 mg, administered orally twice daily for 10 to 21 days, or
2. amoxicillin, 500 mg, administered orally thrice daily for 10 to 21 days (this is particularly useful when the patient is pregnant).

The duration of therapy depends on the rapidity of the clinical response.<sup>72</sup> Earlier regimens included tetracycline, 250 to 500 mg, administered orally four times daily for 10 to 21 days. Doxycycline is given only twice daily, is better absorbed and tolerated, and penetrates into the cerebrospinal fluid better than tetracycline. The major drawback with doxycycline is that it causes photosensitivity in many patients. It should also not be used in pregnant or lactating women or young children. Phenoxymethylpenicillin, 250 to 500 mg, administered orally four times daily for 10 to 21 days, has largely been supplanted by amoxicillin.<sup>71</sup>

For pregnant patients who are allergic to penicillin, and others who are allergic to or intolerant of

penicillins and tetracyclines, erythromycin remains a good alternative at a dose of 250 mg administered orally four times daily for 10 to 21 days. Erythromycin is less effective than doxycycline or amoxicillin. Cefuroxime axetil, 500 mg administered orally twice daily for 20 days, has been reported<sup>73</sup> to be effective in the treatment of early Lyme disease. Up to 15% of patients with early Lyme disease experience a Jarisch-Herxheimer reaction after the first or second dose of antibiotic therapy, particularly when penicillin or tetracycline is used.<sup>58</sup>

Late skin manifestations should be treated for 30 days. Other systemic late manifestations often require intravenous penicillin G or ceftriaxone. Ceftriaxone is particularly useful because it can be administered parenterally once a day.<sup>66,71</sup> The dose and duration of medications used for therapy are continually being refined. Lyme disease is a difficult one in which to define a cure from therapy, but Table 13-1 contains information that medical officers may find helpful.

## SUMMARY

Cutaneous bacterial infections have had a major impact on wars. Pyodermas (eg, furuncles, abscesses, impetigo, ecthyma), frequently caused by *Staphylococcus aureus* or *Streptococcus pyogenes*, are especially common in soldiers—probably due to poor hygiene in the field and the predisposition to superficial injuries to the skin. Pyodermas may be difficult to treat in deployed soldiers because local skin care and strict antistaphylococcal antibiotic administration can not be assured.

More lethal bacterial infections with cutaneous manifestations (eg, plague, tularemia, diphtheria, meningococcal infections) are fortunately much less common than are the pyodermas. Plague—the great scourge of the Middle Ages—is endemic in certain parts of the world today. (However, plague is a greater threat in its role as a biowarfare weapon.) Meningococcal meningitis was a curse of training bases in the past and still remains a threat today.

Meningococcal disease is one of the few that can kill a healthy young adult in a matter of hours to a few days. Medical officers should view with great seriousness a petechial rash in a recruit who also has a spiking fever, chills, and myalgia and arthralgias. Although penicillin remains the antibiotic of choice, the recent report of penicillin-resistant *Neisseria meningitidis* is worrisome.

Lyme disease, which is caused by a spirochete transmitted by a tick and is endemic to many parts of the continental United States, is becoming a public health problem of increasing importance. The occurrence of erythema chronicum migrans in a patient who goes on to develop protean symptoms involving the central nervous system, heart, and joints is highly suggestive of Lyme disease. In endemic areas, the presence of typical erythema chronicum migrans is sufficient to justify treatment with doxycycline or amoxicillin.

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