


Recognized since the 1800s and is primarily transmitted through contact with infected animals, contaminated food and water, or arthropod bites. Tularemia has been listed as a category A bioterrorism agent (3), defined as follows:

- Can be easily disseminated or transmitted from person to person
- Result in high mortality rates and have the potential for major public health impact
- Might cause public panic and social disruption; and require special action for public health preparedness.

### Epidemiology

The incidence of tularemia in the United States has declined since the 1950s and is currently less than 200 per year (4,5). Most cases in the United States occur in the western and southwestern states in small sporadic clusters. Tularemia primarily occurs during the summer months, most likely due to the increased exposure to biting arthropods. Cases also occur during the fall and winter and are linked to hunting and handling infected animals. Perhaps because of a greater likelihood of exposure to animals and arthropods, there is a 3-to-1 preponderance of male-to-female cases. The most recent cases in the United States have been young adults, although a significant percentage of cases occurs among children younger than the age of 14 years (6). Inhalational exposures have occurred in Martha's Vineyard in Massachusetts and were associated with mowing grass and cutting brush (7).

In the United States, ticks and biting flies are the most important arthropod vectors. Major animal reservoirs are lagomorphs (rabbits and hares), as well as rodents including prairie dogs, squirrels, and rats. Mosquitoes were implicated as a primary vector in Scandinavia in one large outbreak (8). Direct contact with infected animals is another significant mode of transmission (9). Hunting, trapping, butchering animal carcasses, and handling meat are all risk factors for tularemia. The organism survives well in cold, moist conditions and can withstand freezing. Finally, cats and other carnivores may transiently carry organisms in their mouths or claws and can thereby transmit infection to humans (10). Pets may also increase the likelihood of tick-borne transmission to humans.

Inhalational exposure may occur in the laboratory or as the consequence of a deliberate release of weaponized Francisella cultures. Human-to-human transmission of tularemia is not known to occur.

### Clinical Presentation

Tularemia has been classically described as presenting in one of six syndromes: ulceroglandular, oculoglandular, glandular, pharyngeal, pneumonic, and typhoidal (11). However, it is clear that individual patients may have symptoms of several of these types simultaneously. After initial entry into the host—either through cutaneous inoculation, ingestion, or inhalation—Francisella organisms multiply at the site of infection (11). A vigorous inflammatory response ensues, leading to subsequent necrosis. The organism multiplies within macrophages and travels to regional lymph nodes, kidney, liver, lung, and spleen (12). The meninges and pericardium are occasionally involved secondarily in untreated tularemia. Inhalation or cutaneous inoculation of 10 to 50 organisms is sufficient for infection (13,14). Symptoms usually begin 3 to 5 days after infection, although longer incubation periods are possible (15).

Differences in clinical presentation may be partly attributable to the type and route of infection. Thus tick-borne infection is more likely to result in skin lesions on the head and neck, trunk, and perineum, whereas animal-associated infections more commonly result in upper extremity lesions (16). Ingestion of contaminated water or food is more likely to cause pharyngeal infection. Inoculation into mucous membranes of the eye results in the oculoglandular syndrome, an ocular lesion with local lymphadenopathy. Inhalation of the organism leads to the pneumonic form of tularemia, although other forms of tularemia can also cause prominent pulmonary involvement through hematogenous dissemination. A typhoidal form of tularemia occurs in less than 30% of cases, in which there are no characteristic localized mucocutaneous or glandular signs or symptoms. The distinction between typhoidal and nontyphoidal infections appears to reflect differences in the host’s immune response. In nontyphoidal forms, there is a vigorous inflammatory reaction, and the prognosis is good compared to typhoidal infection, which has a higher mortality and in which pneumonia is more common (16).

In general, the onset of systemic symptoms in tularemia is abrupt and includes fever, headache, myalgia, cough, malaise, and chest pain or tightness. In mucocutaneous infection, the presenting complaint is usually painful lymphadenopathy, which may precede or follow the skin lesion. In the purely glandular form, there is no apparent skin lesion. Skin lesions usually begin as erythematous painful papules, which progress to necrotic ulcers that are slow to heal. Enlarged lymph nodes are also slow to resolve and may suppurate. In ocular infection, a painful conjunctivitis occurs. Pharyngeal tularemia presents as an exudative pharyngitis with adenopathy that is unresponsive to standard therapy. Tularemia pneumonia is characterized by fever, cough, and pleuritic pain, but sputum production and hemoptysis are unusual. A relative bradycardia, with a normal pulse despite an elevated temperature, is common (40%) in tularemia and may be a useful diagnostic finding (16). Chest radiographic findings include hilar adenopathy, patchy or less commonly lobar infiltrates, and pleural effusions.

Although there has not been a documented biologic attack with weaponized tularemia organisms, several probable aspects of such a scenario are worth noting to allow early recognition and management. If an aerosolized release of organisms were to occur, cases are likely to be pneumonic,
although aerosolized tularemia would also likely result in ocu-
lar and cutaneous forms (2). Occurrence of tularemia in urban set-
tings and among healthy individuals should alert the practi-
cer to the possibility of bioterrorism. Tularemia is a reportable
condition in many cases. Tularemia is caused by exposure to the
bacterium Francisella tularensis, which is found naturally in a
number of wildlife species in the United States. Exposure to the
bacterium occurs through contact with infected animals, includ-
ing ticks, deer, and small rodents. Tularemia can also be trans-
mitted to humans through aerosolization, which occurs when
large numbers of bacteria are dispersed through the air.

**PLAGUE**

**Epidemiology**

Plague is primarily a rural disease that occurs in all continents
except Australia (19). Although most common in rural settings
in developing nations, sporadic clusters occur regularly in the
United States. For example, in 1990 and 2005, 13 cases of plague
were reported in the first 10 months of the year (6), however, in
2006, 13 cases were reported in the first 10 months of the year (6).
Most cases occur between spring and autumn in the Western states
where the disease is enzootic in wild rodents. Humans are infected via
bites from infected rodents or by handling infected animals,
either domestic pets or wild animals. Worldwide, the most im-
portant reservoir is the domestic rat, but as in the United States,
sylvatic foci (in wild animals) also exist (21). Human-to-human
transmission can occur in pneumonic plague but requires close
contact. The last known case acquired in this manner in the
United States was reported in 1923 (22).

**Clinical Manifestations**

The three main types of plague are bubonic, septiemic, and
pneumonic. Although there is no current experience with pneu-
monic plague acquired from a biologic attack, the clinical pre-
sentation is expected to differ from that of natural infection and
is discussed below.

**Bubonic Plague**

Bubonic plague is the most common type of plague, occurring in
76% of the cases reported in the United States between 1990
and 2005 (6). Large numbers of bacteria are inoculated at the
site of the flea bite and multiply locally, followed by rapid repli-
cation in nearby lymph nodes (21). The incubation period is
between 2 and 7 days. There is abrupt onset of fever, chills,
and headache. The characteristic bubo typically develops as a
smooth, firm oval mass which is extremely tender. The over-
lying skin is warm and erythematous, but suppuration is rare.
The primary lesion is often inapparent but can develop into an
ulcer. The most common site of the buboes is in the femoral
lymph nodes, but they are also seen in inguinal, cervical, and
axillary locations depending on the location of the inoculation.
Bacteremia occurs in about 25% of cases, and in untreated cases,
the mortality is approximately 50% (6,21). In untreated cases,
TABLE 117.1

TREATMENT RECOMMENDATIONS FOR TULAREMIA

<table>
<thead>
<tr>
<th>Contained casualty setting</th>
<th>Adults</th>
<th>Preferred choices:</th>
<th>Gentamicin, 5 mg/kg IM or IV once daily</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Alternative choices:</td>
<td>Doxycycline, 100 mg IV twice daily</td>
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<td></td>
<td></td>
<td></td>
<td>Chloramphenicol, 15 mg/kg IV 4 times daily</td>
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<td></td>
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<td></td>
<td>Ciprofloxacin, 400 mg IV twice daily</td>
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<tr>
<td></td>
<td>Children</td>
<td>Preferred choices:</td>
<td>Streptomycin, 15 mg/kg IM twice daily (not to exceed 2 g/d)</td>
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<td></td>
<td></td>
<td>Alternative choices:</td>
<td>Doxycycline</td>
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<td></td>
<td></td>
<td></td>
<td>If weight 45 kg or more, 100 mg IV twice daily</td>
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<td></td>
<td>If weight less than 45 kg, 2.2 mg/kg IV twice daily</td>
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<td></td>
<td></td>
<td></td>
<td>Chloramphenicol, 15 mg/kg IV 4 times daily</td>
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<td></td>
<td></td>
<td></td>
<td>Ciprofloxacin, 15 mg/kg IV twice daily</td>
</tr>
<tr>
<td></td>
<td>Pregnant women</td>
<td>Same as adults above except chloramphenicol is not recommended.</td>
<td></td>
</tr>
<tr>
<td>Mass casualty setting</td>
<td>Adults, including pregnant women</td>
<td>Preferred choices:</td>
<td>Doxycycline, 100 mg orally twice daily</td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td>Preferred choices:</td>
<td>Ciprofloxacin, 500 mg orally twice daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Doxycycline</td>
<td>If 45 kg or more, 100 mg orally twice daily</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>If less than 45 kg, 2.2 mg/kg orally twice daily</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Ciprofloxacin, 15 mg/kg orally (twice daily)*</td>
</tr>
</tbody>
</table>


*Ciprofloxacin dosage should not exceed 1 g/d in children.

deterioration is usually rapid, with progression of typical signs of shock and death occurring as early as 2 to 3 days.

Septicemic Plague

Septicemic plague is defined as plague in the absence of an apparent bubo. As with other systemic infections without clear localization, diagnosis of septicemic plague is often delayed, and the prognosis is thus poorer. In the United States from 1990 to 2003, 18% of reported plague cases were defined as septicemic, although 38% of the cases in 2006 were of this variety (6). A useful clue to the diagnosis of septicemic plague is that gastrointestinal symptoms of nausea and vomiting, diarrhea, and abdominal pain were prominent in several recent cases (6). Disseminated intravascular coagulation may develop rapidly with cutaneous and visceral hemorrhage. Rapidly progressive gangrene may also develop in this setting. Both septicemic plague and pneumatic plague are fatal if untreated. Even with treatment, mortality rates of 33% in septicemic plague were reported from New Mexico in the 1980s (23).

Pneumonic Plague

Pneumonic plague may develop secondary to either bubonic or septicemic plague. The incidence of secondary pulmonary involvement is approximately 12% (19). Recent cases of primary pneumonic plague in the United States have occurred either from laboratory accidents or from exposure to cats (24). Pneumonic plague is similar to other acute pneumonias, with abrupt onset of fever and dyspnea. Watery or purulent, and bloody sputum is produced and is highly infectious. Transmission is via respiratory droplets, and therefore simple respiratory isolation with droplet precautions is sufficient. The chest radiograph usually reveals bronchopneumonia and multifocal consolidation, or cavitation may be seen (25).

Clues to plague arising as the result of a biologic attack include cases outside areas of known enzootic infection; occurrences in an area without associated rodent die-offs, and numerous cases of pneumonia in otherwise healthy patients (25). In general, routine laboratory tests are not markedly different from those seen in other causes of fulminating pneumonia and
### Diagnosis

Specialized laboratory tests to definitively and rapidly identify Y. pestis are not widely available. When plague is suspected, coordination with state public health officials and the Centers for Disease Control and Prevention will allow more specialized tests and susceptibility testing to be performed. Blood, sputum, lymph node aspirates, and lesion swabs should be examined by Gram or Wright-Giemsa stain for the presence of bipolar-staining Gram-negative bacilli, which have the appearance of safety pins. The laboratory should be alerted to the possibility of plague so that appropriate biosafety procedures can be followed.

### Treatment

The recommendations for therapy of plague provided here are derived from the recommendations of the Working Group on Civilian Biodefense and the CDC (25). Treatment recommendations for plague are complicated by the lack of clinical efficacy trials, lack of experience with widespread pneumonic plague, and potentially unpredictable clinical responses in infections due to a biologic attack. Although some recommendations are not FDA-approved uses of the antibiotics, they are the consensus recommendations for the best alternatives for therapy in various situations and clinical scenarios.

The historically proven, effective antibiotic therapy for plague has been streptomycin. Because of the limited availability of streptomycin, gentamicin—used successfully to treat plague—is the recommended alternative. Both tetracycline and doxycycline are effective against plague and are also recommended. For pregnant women and children, the use of tetracyclines and quinolones carries the risk of potential side effects. Nevertheless, given the high mortality of plague, these agents are recommended as acceptable alternatives if aminoglycosides cannot be administered or are not available. In the setting of a mass casualty, oral regimens are recommended, as these allow treatment of large numbers of people and are also useful in settings where parenteral therapy may not be possible.

The recommended duration of therapy for plague (Table 117.2) is 10 days, and oral therapy should be substituted when the patient’s condition improves. Duration of postexposure prophylaxis to prevent plague infection is 7 days. For full details regarding usage in pregnant women and children as well as in special settings including renal failure, please consult the CDC Web site where the most current recommendations may be found (27).

### ANTHRAX

Anthrax was an extremely rare disease in the United States until the bioterrorism attacks of 2001. The disease is caused by a Gram-positive, spore-forming bacillus, Bacillus anthracis. However, anthrax was tested as a biologic weapon by the United States in the 1960s and by several other countries until at least the 1970s. The technology to produce highly infectious anthrax spores and disseminate them widely as an aerosol exists and is known to have been developed for use as a biologic warfare agent (28). It is therefore important for all physicians to be aware of the manifestations of anthrax and especially of the expected characteristics of an outbreak due to a biologic attack.

### Epidemiology

There are three major modes of infection with anthrax: inhalational, cutaneous, and gastrointestinal. Cutaneous anthrax is the most common type of anthrax. However, it is still extremely rare in the United States, with 224 cases having been reported in the 30 years from 1944 to 1994 (29). Barring exposure to intentionally produced anthrax, inhalational anthrax is even less common and occurs primarily in those with occupational or laboratory exposure. Prior to 2001, there were only 18 cases of inhalational anthrax reported from 1900 to 1978 (30). Gastrointestinal anthrax is most commonly reported where improperly cooked meat contaminated with large numbers of anthrax bacilli has been consumed (31).

### Clinical Manifestations

The presentation of anthrax due to a biologic attack is still incompletely characterized. Most of the information relevant to inhalational anthrax from anthrax manufactured as a biologic weapon is from the 2001 U.S. attacks and an unintentional release in Sverdlovsk, Russia, in 1979 (32). There were 11 cases of inhalational anthrax resulting from the exposures in 2001. Several aspects of the pathophysiology of inhalational anthrax are highly relevant to the clinician. Infection occurs after spores are inhaled and deposited in the alveoli. The spores are phagocytosed by macrophages and transported to regional lymph nodes where they germinate and replicate vegetatively (33). There may be a period of extended latency in the lymph node because of spores that remain dormant. Therefore, although the usual period of incubation is 2 to 6 days, cases have occurred as late as 6 weeks after exposure to aerosolized anthrax (32). When replication does occur, toxin production leads to edema, necrosis, and hemorrhage. Typical symptoms are fever and chills, chest discomfort and dyspnea, severe fatigue, and vomiting. Two stages may occur, with an initial period of improvement followed by rapid deterioration. The initial finding on chest radiograph is a widened mediastinum due to mediastinal lymph node involvement (34). A hemorrhagic mediastinal lymphadenitis ensues, often accompanied by bloody pleural effusions. Eight of 11 patients in 2001 developed bloody pleural effusions, and 10 of 11 had radiologic evidence of mediastinal adenopathy (35). Although anthrax does not cause a typical bronchopneumonia, pulmonary infiltrates or consolidation were observed in 8 of 11 cases. In addition, in an autopsy series from the Sverdlovsk outbreak, primary focal hemorrhagic necrotizing pneumonia was described in 11 of 42 cases (36).

An important point emphasized by Lucey is that while there are three known modes of exposure—inhalational, cutaneous, and gastrointestinal—anthrax may actually present as meningitis, which was the initial presentation of the index case in 2001.
TABLE 117.2

RECOMMENDATIONS FOR TREATMENT OF PATIENTS WITH PNEUMONIC PLAGUE IN CONTAINED AND MASS CASUALTY SETTINGS AND FOR POSTEXPOSURE PROPHYLAXIS

<table>
<thead>
<tr>
<th>CONTAINED CASUALTY SETTING</th>
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<tbody>
<tr>
<td><strong>Adults</strong></td>
<td>Preferred choices:</td>
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<tr>
<td></td>
<td>Streptomycin, 1 g IM twice daily</td>
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<tr>
<td></td>
<td>Gentamicin, 5 mg/kg IM or IV once daily or</td>
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<tr>
<td></td>
<td>2 mg/kg loading dose followed by 1.7 mg/kg IM or IV three times daily</td>
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<td></td>
<td>Alternative choices:</td>
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<tr>
<td></td>
<td>Doxycycline, 100 mg IV twice daily or</td>
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<tr>
<td></td>
<td>200 mg IV once daily</td>
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<tr>
<td></td>
<td>Ciprofloxacin, 400 mg IV twice daily</td>
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<tr>
<td></td>
<td>Chloramphenicol, 25 mg/kg IV 4 times daily</td>
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<tr>
<td>Children</td>
<td>Preferred choices:</td>
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<tr>
<td></td>
<td>Streptomycin, 15 mg/kg IM twice daily (maximum daily dose, 2 g)</td>
</tr>
<tr>
<td></td>
<td>Gentamicin, 2.5 mg/kg IM or IV 3 times daily</td>
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<tr>
<td></td>
<td>Alternative choices:</td>
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<tr>
<td></td>
<td>Doxycycline</td>
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<tr>
<td></td>
<td>If 45 kg or more, give adult dosage</td>
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<tr>
<td></td>
<td>If less than 45 kg, give 2.2 mg/kg IV twice daily (maximum, 200 mg/d)</td>
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<tr>
<td></td>
<td>Ciprofloxacin, 15 mg/kg IV twice daily</td>
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<tr>
<td></td>
<td>Chloramphenicol, 25 mg/kg IV 4 times daily</td>
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<tr>
<td></td>
<td>In children, ciprofloxacin dose should not exceed 1 g/d, and chloramphenicol should not exceed 4 g/d. Children younger than 2 y should not receive chloramphenicol.</td>
</tr>
<tr>
<td>Pregnant Women</td>
<td>Same as adults above except chloramphenicol is not recommended.</td>
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<thead>
<tr>
<th>MASS CASUALTY SETTING AND POSTEXPOSURE PROPHYLAXIS</th>
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<tbody>
<tr>
<td><strong>Adults, including pregnant women</strong></td>
<td>Preferred choices:</td>
</tr>
<tr>
<td></td>
<td>Doxycycline, 100 mg orally twice daily</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin, 500 mg orally twice daily</td>
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<td></td>
<td>Alternative choice:</td>
</tr>
<tr>
<td></td>
<td>Chloramphenicol, 25 mg/kg orally 4 times daily</td>
</tr>
<tr>
<td><strong>Children</strong></td>
<td>Preferred choices:</td>
</tr>
<tr>
<td></td>
<td>Doxycycline</td>
</tr>
<tr>
<td></td>
<td>If 45 kg or more, give adult dosage</td>
</tr>
<tr>
<td></td>
<td>If less than 45 kg, give 2.2 mg/kg orally twice daily</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin, 20 mg/kg orally twice daily</td>
</tr>
<tr>
<td></td>
<td>Alternative choice:</td>
</tr>
<tr>
<td></td>
<td>Chloramphenicol, 25 mg/kg orally 4 times daily (maximum 200 mg/dL)</td>
</tr>
</tbody>
</table>

(28). Furthermore, as many as 50% of inhalational anthrax cases may develop meningitis (36). Anthrax causes a rapidly progressive hemorrhagic meningitis with characteristic large Gram-positive bacilli in the cerebrospinal fluid (CSF). Similarly, although the portal of infection is the lung, hemorrhagic submucosal lesions may develop in the gastrointestinal tract along with mesenteric infection; such lesions were seen in 39 of 42 of the autopsy cases reported in the Sverdlovsk outbreak (36) and in one 2001 case. Importantly, this patient presented with primarily gastrointestinal symptoms (37).

The diagnosis of inhalational anthrax may be difficult, especially in the early stages. In addition to the signs and symptoms listed above, tachycardia and severe diaphoresis may be present. Rhinorrhea or sore throat are common in viral respiratory infections but were uncommon in inhalational anthrax (38). A high index of clinical suspicion should be maintained, especially since the risk of exposure may be unknown in the early stages of a biologic attack. Blood cultures are invariably positive if obtained prior to antibiotics.

Cutaneous anthrax is also expected to occur as a result of a biologic anthrax attack. Cutaneous cases occurred up to 12 days after the exposure in the Sverdlovsk outbreak (32). The initial lesion is a papule or macule, leading to ulceration at the site of inoculation within two days, followed by vesiculation. The lesion is painless, although it may be highly pruritic, and the vesicular fluid contains large amounts of bacteria. The characteristic depressed black eschar that subsequently develops is painless. Surrounding edema is often a prominent feature of cutaneous anthrax lesions. In the one case of cutaneous anthrax that developed in a 7-month-old infant in 2001, microangiopathic hemolytic anemia and renal insufficiency occurred (39).

**Diagnosis**

Blood cultures should be obtained promptly if anthrax is suspected. Blood smears should be examined for the presence of organisms. Chest radiograph and chest CT scans should be...
obtained to look for evidence of mediastinal widening, pleural effusions, and parenchymal abnormalities. Thoracentesis of any pleural effusions should be performed, and lumbar puncture should be done as indicated. The clinical microbiology laboratory and the state public health department should both be notified of the possibility of anthrax. If indicated, specimens can be sent to specialized laboratories participating in the Laboratory Response Network for specific testing such as immunohistochemical staining or polymerase chain reaction (PCR). Cutaneous lesions, especially vesicle fluid, should be swabbed for stain and culture. Punch biopsy of the periphery of lesions may also be performed and analyzed by immunohistochemistry or PCR if the Gram stain is negative. Nasal swabs are not sensitive indicators of exposure or infection and should not be used to diagnose or rule out infection in individual patients (40); Sputum culture is generally negative in inhalational anthrax.

**Treatment**

The current recommendations for therapy of anthrax provided here are derived from the Working Group on Civilian Biodefense (41) and the CDC guidelines (Table 117.3). As with recommendations for plague, these are based on expert opinion and a risk–benefit calculation that takes into account the extremely high mortality of inhalational anthrax. As such, the recommendations include therapy with drugs that are not specifically FDA-approved for anthrax and drugs that may have potential side effects in pregnant women and children.

Several factors are important in choosing an empiric regimen for inhalational anthrax. The 60% survival rate in the 2001 cases, which were treated with multidrug regimens, was superior to historical experience. Partly because of these data, the CDC has recommended the use of ciprofloxacin and at least one or two other drugs for the initial treatment of inhalational anthrax. Other factors to be considered are the penetration of drugs into the central nervous system (CNS) in cases where meningitis may be present, as well as the possibility of engineered or primary drug resistance. Although penicillin is FDA-approved for anthrax, the presence of inducible beta-lactamases dictate against the use of penicillin alone. Parenteral therapy is recommended initially. In a mass exposure setting or for postexposure prophylaxis, ciprofloxacin as an oral agent is recommended.

The duration of therapy is an important consideration both in treatment and in postexposure prophylaxis. Although the longest period of latency in the Sverdlovsk episode was reported to be 43 days, viable spores have been demonstrated in the mediastinal lymph nodes of monkeys as late as 100 days after exposure, and disease has occurred 98 days after exposure (42,43). In addition, antibiotic treatment may prevent not only disease, but also the development of an effective immune response; therefore, treatment regimens are recommended for 60 days, with close follow-up after discontinuation of antibiotics. Postexposure vaccination, if available, was also used as an option in addition to antibiotic prophylaxis. Treatment summary guidelines are as follows:

- Recommendations for a mass exposure setting—for both treatment and prophylaxis, where parenteral or multidrug therapy may be problematic—essentially consist of oral ciprofloxacin, 500 mg every 12 hours or 10 to 15 mg/kg twice daily for children.

**TABLE 117.3**

**INHALATIONAL ANTHRAX TREATMENT PROTOCOL IN THE CONTAINED CASUALTY SETTING**

| Adults (including pregnant women) | Ciprofloxacin, 400 mg every 12 h or Doxycycline* 100 mg every 12 h and one or two additional antimicrobials | IV treatment initially. Switch to oral antimicrobial therapy when clinically appropriate. Continue for 60 days (IV and PO combined) |
| Children | Ciprofloxacin, 10–15 mg/kg every 12 h or Doxycycline* Older than 8 y and greater than 45 kg: 100 mg every 12 h Younger than 8 y or 45 kg or less: 2.2 mg/kg every 12 h and One or two additional antimicrobials | Same as adult |

*If meningitis is suspected, doxycycline may be less optimal because of poor central nervous system penetration.

*Other agents with in vitro activity include rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, and clarithromycin. Because of concerns of constitutive and inducible beta-lactamases in *Bacillus anthracis*, penicillin and ampicillin should not be used alone.

*The ciprofloxacin dosage in children should not exceed 1 g/d.
For cutaneous anthrax, the recommendations are ciprofloxacin or doxycycline alone at the same doses as in inhalational anthrax.

The recommended duration of treatment is a minimum of 60 days after exposure because of the risk of latent spores that may cause reactivation.

Based on the experience with other bacterial types of meningitis, the use of adjunctive steroids may be considered in anthrax meningitis.

Initial therapy may be altered based on the clinical course of the patient; one or two first-line antimicrobial agents—ciprofloxacin or doxycycline—may be adequate as the patient improves.

**VIRAL HEMORRHAGIC FEVER**

The major diseases that will be considered in this section are Marburg, Ebola, and Lassa fevers. Marburg and Ebola viruses are filoviruses, whereas Lassa virus is an arenavirus with different clinical characteristics. Nevertheless, they have the potential to create similar problems in hospital management because of the sometimes dramatic nature of the illness and the potential for human-to-human transmission.

**Epidemiology**

Since 1976, there have been approximately a dozen outbreaks of Ebola in Africa, with mortality generally ranging from 53% to 88% (44). There have also been eight cases of documented human infection in the United States from contact with imported monkeys from the Philippines. Infections with this Reston strain of Ebola virus have been subclinical. Marburg virus has been associated with six outbreaks since the disease was recognized in 1976 in German and Yugoslav laboratory workers infected by African green monkeys of Ugandan origin (45). Since then, there have been six other clusters of infection in Africa, the most recent in Angola and the Democratic Republic of Congo. Involving more than 400 people, the mortality was 83% and 90%, respectively, in these last two outbreaks.

Both infections are transmitted by exposure to infected primate blood or cell culture (46). Secondary transmission occurs from exposure to blood and body fluids, as well as by intimate contact. Ebola transmission has ranged from 3% to 17% in household contacts (47). Droplet and, possibly, small-particle aerosol transmission is thought to have occurred in the Reston outbreak but has not been documented in human-to-human transmission (46). Nosocomial transmission is associated with percutaneous exposure and mucous membrane or cutaneous exposure to infected body fluids. The skin of patients is also infected and may serve as a source of secondary transmission (46).

Lassa virus causes a chronic infection of rodents, and is endemic throughout West Africa (48). Transmission to humans is through exposure to infected rodents, primarily through contact with urine (49). Person-to-person transmission is thought to be primarily via contact with infected body fluids, although aerosol transmission may also occur. Incubation is between 3 and 16 days. Other arenaviruses are present worldwide in rodent reservoirs and are a potential source of new clinical syndromes (48).

**Clinical Manifestations**

The clinical pictures of Ebola and Marburg infection are similar (46). The incubation period ranges between 3 and 10 days. Abrupt onset of fever, myalgias, and headache is typical. Nausea and vomiting, abdominal pain, diarrhea, chest pain, and pharyngitis are common. Photosphobia, lymph node enlargement, jaundice, and pancreatitis are all manifestations of widespread organ involvement. CNS involvement may manifest as obtundation or coma. A bleeding diathesis is seen in at least 50% of patients. A characteristic maculopapular rash is described by day 5 of the illness. By the second week, there is either a period of defervescence and improvement, or further deterioration with multisystem failure. Disseminated intravascular coagulation, as well as hepatic and renal failure may ensue; convalescence is often protracted. Mortality is estimated at 25% for Marburg, 50% for Ebola-Sudan, and 90% for Ebola-Zaire (46). As described above, Ebola-Reston has not led to any known human deaths. There is viremia with infection of all organs, leading to necrosis in areas of viral replication (50). Pathogenesis is thought to be also due to cytokine release, leading to increased vascular permeability and hemodynamic instability (51).

Lassa fever presents with relatively nonspecific signs and symptoms, making recognition of cases in the initial stages difficult (48, 52). A combination of fever, retrosternal pain, pharyngitis, and proteinuria has been suggested to be indicative of Lassa fever (52). A diffuse capillary leak syndrome in the second week of illness is a cardinal manifestation of this disorder. Mortality of hospitalized cases ranges from 15% to 25%. Seventh cranial nerve deafness is a common sequela of Lassa infection, occurring in approximately one-third of cases (53). Persistent vertigo is another reported side effect (54). The pathogenic mechanism of Lassa fever is not well understood, but there is variable necrosis in affected organs, and the systemic manifestations of vascular dysfunction may be due to soluble macrophage-derived factors.

**Diagnosis**

A history of travel to endemic areas and a clinical syndrome compatible with viral hemorrhagic fever (VHF) are key elements of making a diagnosis. Nevertheless, a cluster of cases with signs and symptoms indicative of VHF may be the first clue of a biologic attack. Specialized testing for Marburg and Ebola, including PCR and direct antigen visualization in clinical samples, is available through reference laboratories. Contact with local public health authorities and the CDC will allow testing via mobile laboratory facilities. BSL-4 level containment facilities are required for attempts to isolate virus and BSL-3 facilities for routine testing.

Lassa virus is easily cultured, as the levels of viremia are usually high; reverse transcription-PCR (RT-PCR) may also be used to identify Lassa virus.

**Treatment**

Treatment of Marburg and Ebola virus is primarily supportive, as there is no effective specific therapy, and interferon is
felt not to be useful. Unnecessary movement or manipulation of the patient should be avoided. Contact and respiratory isolation of the patient is necessary, including use of goggles and face shields to prevent exposure to body fluids (55). Thorough disinfection of all materials that have come into patient contact should be performed, and containers of biologic waste should be externally disinfected (55).

In cases of Lassa fever, where the aspartate transaminase levels exceed 150 IU/L, early treatment with intravenous ribavirin has been reported to be beneficial in tapering doses over 12 days (56).

**SMALLPOX**

Smallpox is caused by infection with variola, a double-stranded DNA orthopoxvirus. Smallpox, one of the most feared and lethal diseases known to man, was virtually eliminated as a natural threat by vaccination (57). By 1980, the World Health Organization declared it to be eradicated worldwide, with the last case known to have occurred naturally in 1977. In the United States, universal childhood vaccination ended in 1972, and thus, most people in the United States today are susceptible to smallpox infection. The anthrax attacks in 2001 again raised the possibility of smallpox being used as a biologic weapon. Smallpox is classified as a category A bioterrorism agent, a high-priority organism that poses a risk to national security (see above under Tularemia for full definition of Category A agents) (3) and should be considered one of the most dangerous agents because of its high infectiousness, capability for rapid spread, lack of effective treatment, and capacity to induce mass social disruption and overburden the public health system.

**Epidemiology**

Smallpox is spread by direct close contact via large droplet inhalation (58); there are no known animal reservoirs. Spread can also occur by contact with lesions or infected fomites. Household spread has been reported to range from 30% to 80% (59). Smallpox outbreaks were most common during the winter and early spring (60). All ages are susceptible although, historically, vaccination rates and prior infections modulated the attack rates among different groups. Patients are most contagious when they have a rash, although they may be infectious during the symptomatic prodrome prior to the development of skin lesions (see below). Incubation is from 7 to 17 days, during which period the patient is not infectious.

**Clinical Manifestations**

During the prodromal phase, the patient experiences high fever with back pain and prostration (57). The rash follows within a day or two, with more lesions on the face, oral mucosa, and extremities than on the trunk—termed a centrifugal pattern. The lesions begin as macules, progress to vesicles, and become pustules over the first week. Fever is usually persistent throughout the period of rash development. The lesions are deep seated, firm, painful, and important for the diagnosis—all lesions are at the same stage of development at each phase. All of these characteristics of the rash serve to differentiate it from the rash of chickenpox, which is superficial, appears in crops, is centrifetal in distribution, and is associated with a relatively mild prodrome. The extent of the smallpox rash correlates with mortality, which may range from 10% to 75%. In fatal cases, death usually occurs by the second week. The lesions begin to crust over after 7 to 9 days, and the patient is noninfectious only after all scabs have fallen off. Scarring and pitting result in the characteristic pox-marked appearance of survivors. The pathologic damage in smallpox is generally confined to the skin and mucous membranes, although virus is present throughout the internal organs (57). The systemic manifestations and fatalities are attributed to toxemia and antigenemia.

Vaccine-modified smallpox presents as a milder illness with fewer lesions and mortality less than 10% (57). A hemorrhagic form of smallpox may occur in which there is diffuse erythema, followed by petechial hemorrhages; it is reported to have mortality approaching 100% (61). In malignant or “flat” smallpox, discrete lesions do not develop, but confluent bloody lesions are present (62). A form of smallpox known as variola minor, with much milder symptoms and mortality less than 10%, is now known to be due to a genetically distinct strain of the virus (63).

**Diagnosis**

Specimens of vesicular or pustular fluid should be obtained for culture and electron microscopic examination; these are transported in double-sealed, leakproof containers designed for transport of body fluids. Specimens should be handled only in BSL-4 laboratories, and public health authorities should be notified to assist with specimen handling if a case of smallpox is suspected. The diagnosis of orthopoxvirus infection can be performed by molecular techniques such as PCR and DNA sequencing.

**Treatment and Prevention**

Although a full discussion of infection control and vaccination protocols is beyond the scope of this text, the following principles should be followed (64). The patient should be isolated, and contact and airborne precautions should be instituted when a case of smallpox is suspected. All personnel who had face-to-face contact with the patient should be vaccinated, as should all personnel who had contact with the patient while the latter was febrile. Local health authorities should be contacted immediately, and the CDC will provide assistance with prioritizing contacts for vaccination and monitoring. It should also be noted that contraindications to vaccinations do not apply to high-risk exposures. Treatment is primarily supportive and is aimed at maintaining hemodynamic stability and treating secondary infections.

**MONKEYPOX**

Monkeypox is a disease clinically similar to smallpox that has been sporadically reported in Africa since 1960. Pronounced lymphadenopathy is an additional sign of monkeypox that may help differentiate it from smallpox (65,66). Monkeypox
Malaria, the fourth largest killer of children younger than 5 years of age, causes over 350 million clinical episodes and one million deaths per year. Although a comprehensive discussion of the management of malaria will not be possible here, we will cover the recognition and treatment of severe malaria, which may be encountered in the critical care setting in a nonendemic setting. As such, this chapter will focus on infection with Plasmodium falciparum, the strain of the parasite that is most likely to cause high-level parasitemia and severe life-threatening malaria.

**Epidemiology**

Malaria is endemic throughout much of the world, with the greatest number of cases in Africa and Asia (69). Malaria has been officially eradicated in the United States since 1970, but approximately 1,200 cases are reported annually (70), most in travelers from endemic areas. Other cases are due to local transmission from infected mosquitoes (so-called airport malaria), congenital malaria, and malaria acquired from blood transfusion. Local transmission of malaria in the United States has occurred at least 11 times since 1970, with 20 probable cases (71). In a recent outbreak in Florida, seven cases were verified as being caused by the same strain of P. vivax (71). Thus, domestic transmission of malaria is possible, especially in warmer regions of the United States.

In endemic areas, many adults are partially immune to malaria and, although infected, may even be asymptomatic. Children are particularly prone to infection and to developing severe disease. Other high-risk groups include pregnant women, asplenic individuals, and other immunocompromised hosts.

**Clinical Manifestations**

Malaria typically has an incubation period of 1 to 3 weeks. However, this may be extended by partial immunity or chemoprophyaxis. Therefore, it has been suggested that any traveler returning from an endemic area should be considered at risk for development of malaria for as long as 3 months (72). The clinical presentation is usually nonspecific. Fever and headache are universally present, and myalgia, sweats, and weakness are common. Paroxysmal and cyclical fever, although classically associated with malaria, are not consistently present. Especially in the case of falciparum malaria, the fever is often continuous.

Although other infections are common in malaria-endemic areas, malaria should be considered one of the most likely diagnoses in any patient with a consistent clinical picture and travel history. If malaria is suspected, prompt infectious disease consultation is indicated to help with management and assess the likelihood of alternate diagnoses.

The pathogenesis of malaria is complex and related to both the direct effects of the parasite on erythrocytes and the vascular and indirect effects on cytokine production, tissue oxygen consumption, and other systemic effects (72). Several aspects of the biology of *Plasmodium falciparum* are relevant to the development of severe malaria. *P. falciparum* sequesters itself in the venous microcirculation of virtually all tissues, including the brain. Hypoglycemia is common during *P. falciparum* infection and is thought to be due to oxygen consumption by replicating parasites, as well as a result of increased tissue metabolism. Severe anemia may occur and is due to lysis of infected erythrocytes and the clearance of uninfected erythrocytes and decreased erythrocyte production. Thus, the anemia in severe malaria is often normochromic and normocytic. This combination of factors aggravates tissue hypoxia and leads to metabolic acidosis. A capillary leak syndrome due to parasite sequestration and cytokine production may lead to pulmonary edema. Renal failure in malaria is multifactorial and is more common in adults than children. Hemolobinuria may be severe enough to cause dark urine, termed, when present, black-water fever.

**Diagnosis**

The gold standard for diagnosis of malaria remains the microscopic identification of parasites on the blood smear. Examination of thick and thin blood smears should be performed immediately by trained personnel. If the initial examination is negative, smears should be repeated every 12 to 24 hours for a total of 48 to 72 hours (70). When parasites are detected, the percentage of parasitemia can be calculated by counting the number of infected and noninfected red blood cells (RBCs). The number of white blood cells (WBCs) in the microscopical field can also be used as an internal standard to aid in estimated parasite density and percentage when thick smears are examined. Malaria is a nationally notifiable disease, and the state health authorities should be notified when a diagnosis of malaria is made. The Centers for Disease Control and Prevention maintains a 24-hour malaria hotline to assist clinicians with the management of suspected and confirmed malaria cases. The numbers to call are at the time of this publication: 770-488-7788 Monday to Friday, 8:00 a.m. to 4:30 p.m. Off-hours, weekends, and federal holidays, call 770-488-7100 and ask to have the malaria clinician on call to be paged (73).

**Treatment**

It should be emphasized that patients, particularly those who are nonimmune, may deteriorate rapidly. Thus hospitalization of patients during the initial phase of treatment is prudent. Furthermore, nonimmune patients may have severe illness before manifesting high degrees of parasitemia. Therefore, patients who manifest any of the symptoms or signs of severe malaria and have any degree of parasitemia on blood smear should be
RMSF is caused by *Rickettsia rickettsii*, an intracellular bacterium that is transmitted in the United States primarily by the dog tick, *Dermacentor variabilis*, in the Eastern states, and the wood tick *Dermacentor andersoni*, in the Rocky Mountain States; ticks are also the primary reservoir for *R. rickettsii*. Despite the name, most cases of RMSF occur in the southeastern United States, and more than half of all reported cases are from North Carolina, South Carolina, Tennessee, Oklahoma, and Arkansas. However, cases have been reported in all 48 continental states except Vermont and Maine (77). Most cases occur between April and September. Children are at highest risk of RMSF, and the peak incidence is between 5 and 9 years of age (77). Although males are reported to be at higher risk, a recent study of children with RMSF found more cases among girls than boys (78). Most bites are unnoticed, and the tick remains attached for 6 to 10 hours for feeding and infection to take place.

### Clinical Manifestations and Pathogenesis

The rickettsial organisms primarily target and infect endothelial cells (79). The primary pathology consists of diffuse cell injury and increased vascular permeability caused by cell-to-cell spread of the organisms after initial hematogenous and lymphatic seeding. Infection occurs in virtually all internal organs, and vascular injury occurs in lung, heart, brain, gastrointestinal tract, and skin as well as other sites. Symptoms typically begin 2 to 14 days after the tick bite. Virtually all patients experience the classical triad of fever, headache, and rash (78,80,81). However, it should be emphasized that the rash is present in only about 50% of cases within the first 3 days. Rash usually appears by the second to fifth day, but is absent in about 10% of patients. The rash is often faint in the initial stages and may be more difficult to detect in patients with dark skin (81). It begins as a blanching, pink maculopapular exanthem, most commonly beginning at the wrists and ankles, and develops into palpable lesions that spread centrally. The rash often becomes petechial and may involve the palms and soles. Commonly associated symptoms occurring in more than 50% of patients are myalgias, nausea, vomiting, and abdominal pain. The serum AST (aspartate aminotransferase) is often elevated, and thrombocytopenia and hyponatremia occur in up to 50% of cases (81).

CNS abnormalities occur in about 25% and carry a poor prognosis. CSF abnormalities are observed in one third of patients and consist of pleocytosis and elevated protein levels,
although the CSF glucose is usually normal and a fungal infection is associated with meningitis in RMSF. Factors that are likely to lead to delay in diagnosis include absence of rash or delayed appearance of the rash, no history of tick bite, and presentation early in the course of disease ($1,84,8.5$). R. rickettsii can be isolated in culture or demonstrated by immunohistochemistry in tissue specimens. However, these methods are not routinely available, and empiric therapy should not await the result of laboratory testing. Serology is likewise useful for confirmation of diagnosis. Diagnosis should therefore be made on the basis of epidemiologic and clinical findings described above.

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