Chapter 5:

Intentional and Natural Outbreaks of Infectious Disease

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Objectives

- Explain the general principles of surveillance for intentional and natural outbreaks of infectious disease.
- Describe the clinical presentation of category A and category B agents and the related diagnostic tests, treatment, and infection-control measures.
- Describe the clinical presentation of other potential emerging diseases and the related diagnostic tests, treatment, and infection-control measures.

Case Study

A 47-year-old male postal worker who worked in the mail-sorting area developed nausea, abdominal pain, and flulike symptoms. He attributed his symptoms to food poisoning and continued to work despite ongoing symptoms. Over the next several days he developed worsening nausea, vomiting, and abdominal pain and profuse sweating. On Day 5, while in church, he had a brief, self-limited syncopal episode. By the time paramedics arrived, he felt better. He went home, did not eat, and immediately went to bed. At 2 AM on Day 6, while at work, he developed worsening nausea, vomiting, abdominal pain, and profuse sweating. He then drove himself to the emergency department.

In the emergency department, the patient's temperature was 36.1°C (96.9°F), blood pressure was 82/59 mm Hg, pulse 95/min, respirations 18/min, and oxygen saturation 99% in room air. Physical examination was unremarkable. Laboratory data revealed mild leukocytosis and hemoconcentration. Chest radiograph showed a subtle and ill-defined area of increased density in the right subhilar region.

The following day his wife found him slumped in the bathroom. He was taken to a hospital by ambulance. On arrival, he reports nausea, vomiting, and lightheadedness. He denies dyspnea or chest pain but is ill-appearing and in respiratory distress. His vital signs are temperature 35.5°C (95.9°F), blood pressure 76/46 mm Hg, pulse 152/min, respiratory rate 28/min, and oxygen saturation 96% in room air. (Reported in *JAMA*. 2001;286:2554-2559.)

Your differential diagnosis includes inhalational anthrax.

- What diagnostic test should you order?

- What empiric treatment should be given?

- What needs to be done for the healthcare workers caring for this patient?

I. INTRODUCTION

When patients with new complaints seek healthcare, it is usually for common illnesses. However, it is imperative that healthcare providers also consider uncommon presentations of common diseases as well as uncommon diseases. While there are many categories of uncommon diseases, one category of increasing concern over the last several years is infections caused by new, emerging, or bioterrorism agents. Such infections may occur in several situations:

- A natural outbreak of a newly emerging disease (such as severe acute respiratory syndrome [SARS])
- An outbreak of a disease known to occur elsewhere but not in the local geographic area (such as Crimean-Congo hemorrhagic fever)
- An epidemic that started elsewhere but is not yet active in the local geographic area (such as pandemic influenza)
- The intentional or accidental release of a biological weapon (such as smallpox)
- The natural occurrence of agents used in bioterrorism (such as anthrax from animal skins)

Healthcare workers are in the front position to recognize and treat diseases caused by new, emerging, or bioterrorism agents. Some patients will present with unusual symptom complexes; however, many may have presenting symptoms and signs consistent with common illnesses. The following should prompt the healthcare provider to consider illnesses caused by emerging or bioterrorism agents:

- Widened mediastinum of thoracic radiographs
- Influenzalike illness in the summer months
- Pneumonia death in an otherwise healthy adult
- Vesicular rash that starts on the extremities

! *Healthcare workers are in the front position to recognize and treat diseases caused by new, emerging, or bioterrorism agents. Some patients will present with unusual symptom complexes; however, many may have presenting symptoms and signs consistent with common illnesses.* !

- Hemorrhagic fever syndrome
- Unexplained critical illness in otherwise healthy adults

Additionally, global political situations, worldwide sentinel healthcare events (ie, outbreaks elsewhere in the world), and patient-specific exposures and travels may suggest that increased suspicion of emerging or bioterrorism agents is warranted.

Healthcare workers should be familiar with the basic presentation, diagnosis, and treatment of infections caused by common emerging and bioterrorism agents. The United States Centers for Disease Control and Transmission (CDC) have categorized biological agents on the basis of their potential adverse impact on public health and potential for large-scale dissemination. The primary agents currently in each CDC category are discussed later in the chapter. It should be kept in mind, however, that new agents capable of causing worldwide outbreaks may be seen in the future (eg, SARS was not known prior to 2003).

II. GENERAL PRINCIPLES OF INFECTIOUS DISEASE

A. Epidemics

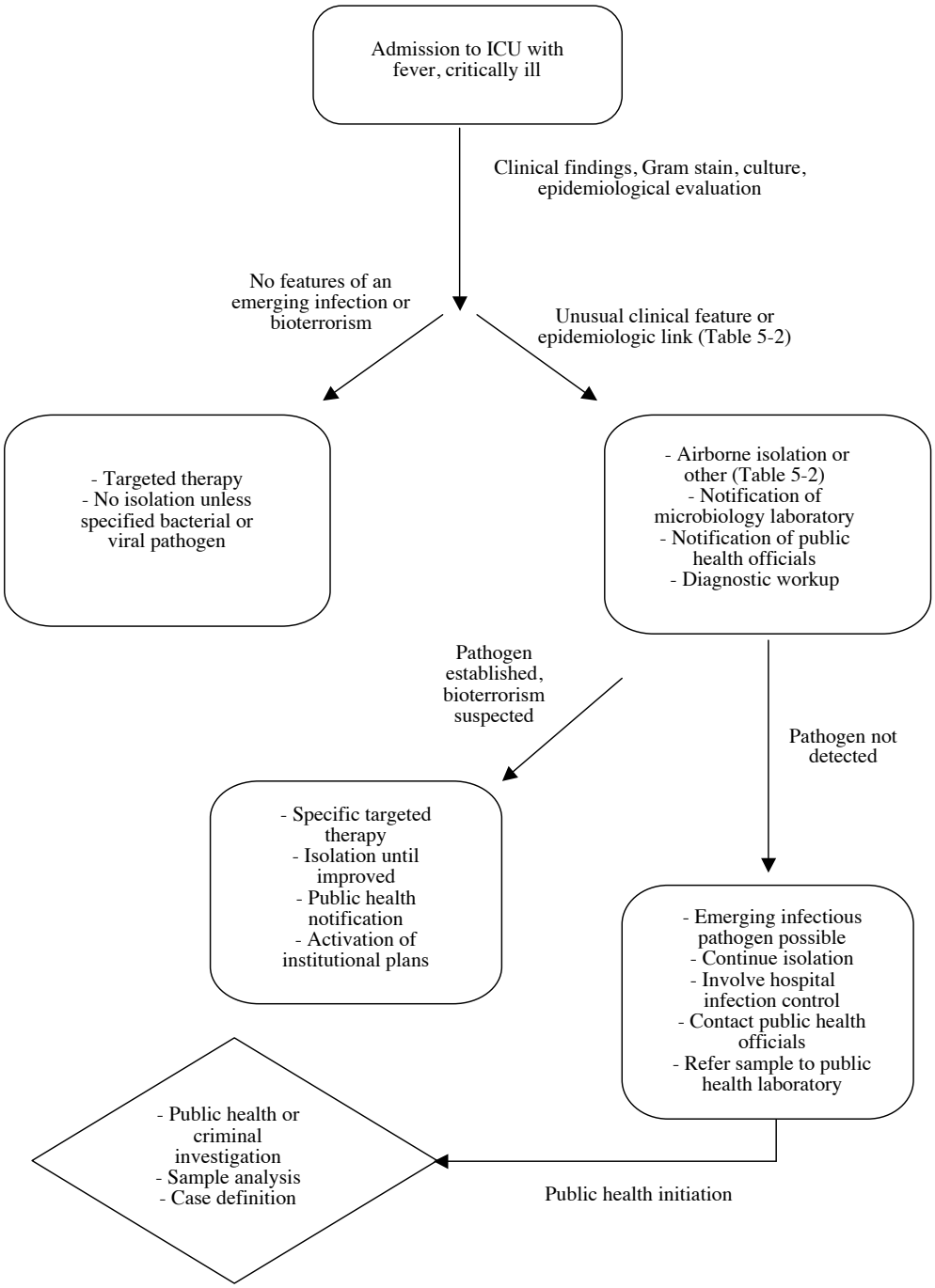
Epidemics occur in a variety of settings and with a multitude of infectious diseases. In order to determine if an epidemic is occurring, a baseline assessment of the disease must be made. As with influenza and other infectious diseases, seasonal variations may occur, with more cases seen in the winter or summer months. Additionally, more cases are often seen in certain at-risk populations (such as people exposed to anthrax from animal skins), which results in a baseline that reflects that population. Once the baseline risk and disease rate are determined, the basic endemic nature of the disease is established. If cases then occur in increased numbers and/or outside of the at-risk population, an outbreak is established.

An outbreak takes place when the frequency (incidence) of an infectious disease increases. For example, a short outbreak of hospital-acquired infections may occur and subsequently subside without sustained cases and spread. Many outbreaks are short lived, but an outbreak that lasts over a prolonged period is considered an epidemic. The features of an epidemic include the following:

- An increase in the number of cases of a particular agent above the baseline by at least 2 standard deviations from the mean
- An increase of cases in the at-risk population and usually an increase in new or lower-risk populations as well
- The number of cases increases rapidly when compared to prior baseline cases
- The increase is sustained beyond a few cases (usually lasting months or longer)

Recent epidemics of infectious agents of bioterrorism have included the anthrax cases in 2001, SARS, botulism in black tar heroin users, and viral hemorrhagic fever cases in Africa. See **Figure 5-1** for an algorithm for evaluation of a suspected emerging pathogen.

Figure 5-1. Algorithm for Evaluation of a Suspected Emerging Pathogen [a]



[a] Adapted with permission from Sandrock C, Stollenwerk N. Acute febrile respiratory illness in the ICU. *Chest.* 2008;133:1221.

B. Detection and Surveillance

To determine the baseline number of cases of an infectious agent, surveillance for that disease is required. Surveillance may take the form of a cross-sectional study, such as a prevalence study, or a longitudinal study for incidence. Determining the incidence of a disease is the main type of surveillance performed, and the most valuable. Incidence studies typically take one of the following forms:

- Passive surveillance is the reporting and tracking of diagnosed cases within the healthcare system. It is the predominant way that baseline incidence is determined. Cases are reported after diagnosis.

- Active surveillance is the active testing and evaluation of an infectious agent in at-risk groups. This approach requires frequent testing and is labor-intensive but may detect a number of cases that passive surveillance misses.

- Syndromic surveillance is the reporting of a cluster of syndromes that may be closely related to a disease, but the disease itself does not necessarily require diagnostic confirmation. Defining an illness as influenzalike rather than testing for influenza is a classic example.

- Environmental surveillance is the detection of agents in an at-risk environment with programs such as BioWatch.

Detection can be performed a number of ways. During passive surveillance, diagnosis is established and may be performed by culture, serology, or polymerase chain reaction (PCR). However, with active surveillance, a rapid test with good sensitivity and specificity is often needed and usually consists of antigen or PCR testing. Once detection is established, strain specificity is often required to further determine connection. For example, the multiple cases of tularemia detected during an outbreak may be due to a single strain or multiple strains. Thus, under PCR or gel electrophoresis, strain similarity is determined in addition to detection. This will further support the evidence reported during surveillance.

C. Infection Control, Isolation, and Quarantine

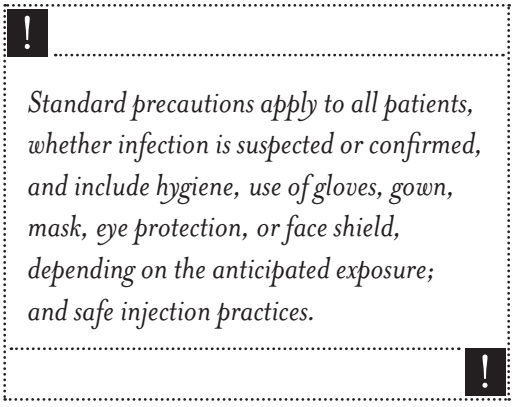
The diseases discussed in this chapter are contagious; that is, they are capable of being spread from one person to another. While the cornerstone of a public health response to epidemics and bioterrorism is early detection and therapeutics and vaccinations when available, public health authorities at many levels (hospital, regional, national) can implement measures to decrease the ability of diseases to spread from affected individuals to the healthy population.

1. Infection Control

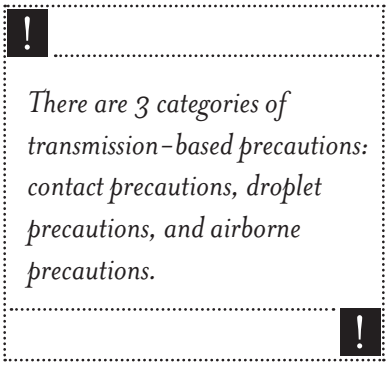
Infection control is the use of measures to prevent the transmission of infectious agents in healthcare settings. Although a thorough discussion of infection control exceeds the scope of this chapter, disease-specific infection controls are discussed with the individual agents presented

below. Please refer to local, CDC, or other national infection-control guidelines for up-to-date information and a more detailed discussion.

Standard precautions apply to all patients, whether infection is suspected or confirmed, and include hygiene; use of gloves, gown, mask, eye protection, or face shield, depending on the anticipated exposure; and safe injection practices. When the transmission of an agent is not interrupted using standard precautions, transmission-based precautions are implemented.



There are 3 categories of transmission-based precautions: contact precautions, droplet precautions, and airborne precautions.



- Contact precautions are intended to prevent transmission of infectious agents that are spread by direct or indirect contact with an affected patient or the patient's environment. They include wearing a gown and gloves for all interactions that may involve contact with the patient or potentially contaminated areas in the patient's environment.

- Droplet precautions are intended to prevent transmission of pathogens spread through close respiratory or mucous membrane contact with respiratory secretions. They include wearing a mask in addition to taking contact precautions. (A high-filtration mask or respirator is not necessary.)

- Airborne precautions prevent transmission of infectious agents that remain infectious over long distances when suspended in the air. In addition to observing contact precautions, healthcare workers wear a high-filtration (N-95 or better) mask or respirator, depending on the disease-specific recommendations.

Higher levels of precaution may be warranted for higher risk procedures. See **Table 5-1** for a list of procedures considered to be higher risk.

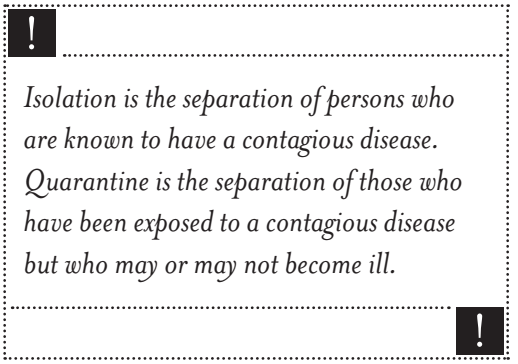
Table 5-1. Respiratory Care Procedures That Carry an Increased Risk for Disease Transmission

- Nebulization of medication
- Endotracheal intubation
- Nasotracheal suctioning
- Noninvasive positive-pressure ventilation
- Bag-mask ventilation
- Bronchoscopy
- Humidified oxygen delivery
- Non-rebreather mask without expiratory filter

2. Isolation and Quarantine

Public health authorities may also use isolation and quarantine to physically separate affected individuals from the rest of the population. Isolation is the separation of persons who are known to have a contagious disease. Quarantine is the separation of those who have been exposed to a contagious disease but who may or may not become ill.

A quarantine may extend beyond people. The CDC applies this term to any situation in which a person, building, conveyance, cargo, or animal thought to have been exposed to a dangerous contagious disease agent is closed off or kept apart from others to prevent disease spread.



III. NATURAL EPIDEMICS VERSUS BIOTERRORISM

The primary difference between natural epidemics and epidemics caused by bioterrorism is that in bioterrorism the release of a contagious disease agent is intentional. In both instances a disease agent may be transmissible from person to person, as is smallpox, or nontransmissible, as is anthrax. By and large the approach to controlling the event depends on the agent, not on the initial cause. The strains on healthcare resources and other systems (eg, food supply) are related more to the breadth of impact than to the type of epidemic.

A. Bioterrorism: CDC Category A Agents

Category A agents have both a high potential for adverse public health impact and a serious potential for large-scale dissemination and are thus the highest priority agents. The Category A agents are

- Anthrax
- Smallpox
- Plague
- Botulism
- Tularemia
- Viral hemorrhagic fevers

Clinical features of these agents are summarized in **Table 5-2**, and guidelines for controlling the infections are outlined in **Table 5-3**.

Table 5-2. Features of the CDC Category A Agents

	Anthrax	Smallpox	Plague	Botulism	Tularemia	Viral Hemorrhagic Fever
Agent	Spore-forming bacteria	Virus	Bacteria	Toxin	Bacteria	Virus
Species	*Bacillus anthracis*	Variola major	*Yersinia pestis*	Toxin of *Clostridium botulinum*	*Francisella tularensis*	Filovirus, Bunyaviridae, arenavirus
Inoculation	Inhalation, contact	Inhalation, contact	Inhalation, bite	Ingestion, inhalation	Inhalation, bite	Inhalation, contact
Clinical Presentation	Rapid pneumonia and sepsis	Febrile prodrome, rash, multiorgan failure	Regional lymphadenitis (bubo), then rapid sepsis and also pneumonia	Descending paralysis involving cranial nerves first	Ulcero-glandular, or rapid pneumonia	Rapid onset of sepsis and hemorrhage
Clinical Hallmark	Widened mediastinum	Poxlike lesions	Rapid pneumonia and sepsis in 24 h	Rapid onset of cranial nerve palsy	Rapid onset of pneumonia	Bleeding syndrome
Diagnosis	Culture in blood	Clinical, viral detection by PCR or isolation in culture	Culture, serology, RT-PCR of body fluid	Toxin detection in serum or stool	Serology	Clinical syndrome and antigen testing by ELISA
Treatment	Ciprofloxacin, doxycycline	Supportive, cidofovir is experimental	Gentamicin	Antitoxin, supportive	Gentamicin	Supportive, ribavirin for some agents

Abbreviations: PCR, polymerase chain reaction; RT-PCR, reverse transcriptase polymerase chain reaction; ELISA, enzyme-linked immunosorbent assay.

Table 5-3. Infection Control and Respiratory Protection for Category A Bioterrorism Agents and Select Naturally Occurring Infections

Agent	Isolation	Baseline Protection	Protection in Higher-Risk Procedures
Botulism	None	None	None
Viral Hemorrhagic Fever	Airborne and contact	N-95 respirator	N-95 or PAPR
Smallpox	Airborne and contact	N-95 respirator	N-95 or PAPR
Plague	Droplet and contact [a]	N-95 respirator	N-95 or PAPR
Tularemia	None	None	Surgical
Anthrax	None	None	Surgical
Influenza (novel strain)	Airborne and contact	N-95 respirator	N-95 or PAPR
SARS	Droplet and contact	Surgical mask	N-95 or PAPR

Abbreviations: PAPR, powered air-purifying respirator; SARS, severe acute respiratory syndrome.
[a] Isolation can be stopped after 48 h of appropriate antibacterial therapy.

1. Anthrax

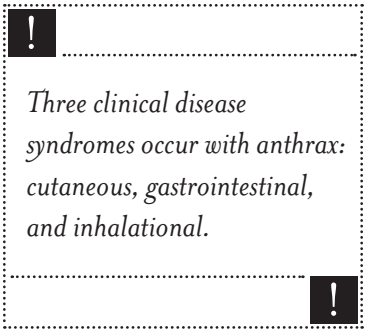
Anthrax is caused by *Bacillus anthracis*, a sporulating gram-positive rod. There are 3 distinct stages to its ecology, including a soil stage, animal infection, and human infection. Anthrax is part of the normal soil flora, but local multiplication may occur under certain soil conditions. In such situations, anthrax converts to a spore form that is resistant to decontamination and environmental influences. Herbivores, such as cattle, come into contact with infectious soil through grazing. Human disease largely occurs through contact with animal products, such as animal skins.

In 2001, 22 cases of anthrax occurred in the United States due to intentional dissemination through the postal system. This act placed anthrax on the forefront of bioterrorism. Despite this outbreak in 2001, anthrax remains relatively rare in the United States, with most endemic and epizootic cases occurring the Middle East. Most cases in the United States occur through handling of animal products, such as the infections in 2006 associated with African animal-hide drum skin. Anthrax as a bioterrorism and zoonotic agent remains a threat.

a. Clinical Presentation

Disease occurs when the spore form of anthrax is introduced subcutaneously or via inhalation, becomes the vegetative (bacillus) form, and starts replication. Endotoxin secretion, along with a thick capsule that avoids phagocytosis, leads to local spread, edema, hemorrhage, and tissue necrosis. The anthrax capsule, edema factor toxin, and lethal factor toxin act in concert to drive disease.

Three clinical disease syndromes occur with anthrax: cutaneous, gastrointestinal, and inhalational. Cutaneous anthrax is the most common form worldwide and follows an incubation period of 7 to 14 days after inoculation of spores into the subcutaneous space. This is followed by a small, painless papule that can be pruritic. This papule quickly enlarges and develops a central vesicle, followed by erosion into a painless black eschar. Edema surrounds the tissues, and regional lymphadenopathy may also occur along with systemic symptoms of fever and malaise. The hands, arms, face, and neck are the most common areas affected.



With inhalational anthrax, spores that reach the distal airways are brought into the mediastinal lymph nodes, where replication occurs. The incubation period averages 1 to 7 days, followed by clinical symptoms of a nonspecific febrile illness, often mimicking influenza. However, within 24 hours, disease rapidly progresses with the development of respiratory failure, hemorrhagic mediastinitis, necrotizing pneumonia, shock, multiorgan failure, and death. The development of shock and multiorgan failure can occur rapidly.

Gastrointestinal anthrax is rare and occurs after the consumption of undercooked meats of infected animals, usually in family clusters. Bowel edema, followed by mesenteric lymphadenitis and necrosis occur, with rapid progression to shock and death.

b. Diagnosis

The diagnosis of anthrax is best performed by culture of the blood, sputum, pleural fluid, cerebrospinal fluid, or skin. Clinicians should notify the laboratory of suspected anthrax because if samples are not properly handled, spore formation can occur during culture, leading to infection in laboratory workers. Additionally, any suspected case of anthrax should be referred to the public health laboratories for confirmation and strain typing. Rapid PCR and enzyme-linked immunosorbent assays (ELISA) exist and have good sensitivity and specificity.

c. Treatment and Prophylaxis

Treatment of anthrax includes ciprofloxacin, doxycycline, and penicillin, if the agent is susceptible. In the 2001 bioterrorism attacks rifampin, clindamycin, or vancomycin was used in combination with ciprofloxacin, and penicillin was not used due to resistance. Appropriate pleural space drainage or the use of a central nervous ventricular shunt may be called for in individual cases.

In the 2001 attacks only inhalational cases of anthrax were managed in the ICU. Respiratory failure along with shock and multiorgan failure occurred.

An anthrax vaccine made from cell-free filtrates of avirulent, nonencapsulated strains and containing several proteins, including the protective antigen, is available. However, its use in humans has been limited due to the need for frequent dosing, side effects, and poor immunogenicity. Its use is currently reserved for military personnel. Exposure to aerosolized anthrax spores requires prophylaxis with either ciprofloxacin or doxycycline in adults and with amoxicillin as a second line in children and pregnant women.

In treated patients, the mortality for cutaneous anthrax remains low at less than 1%, but in untreated patients, the mortality is 20%. Although inhalational anthrax may carry a mortality of 80-90%, the inhalational cases from 2001 in the United States had a lower mortality of 45%.

d. Infection Control

Anthrax is not contagious in the vegetative bacillus form found during clinical infection. Contact with infected animals and animal products increases the likelihood of disease spread, so limiting contact or wearing the appropriate personal protective equipment (PPE), particularly in endemic areas, is indicated.

2. Smallpox

Anytime smallpox is suspected, public health officials should immediately become involved. The causative agent of smallpox is variola virus, a member of the family Poxviridae. Smallpox was eradicated worldwide in 1977 but now has regained interest as a potential bioterrorism agent. Smallpox was endemic worldwide, and at one point accounted for over 10% of all deaths worldwide, until the last endemic case in Somalia in 1977. It occurs in 2 forms, variola major and

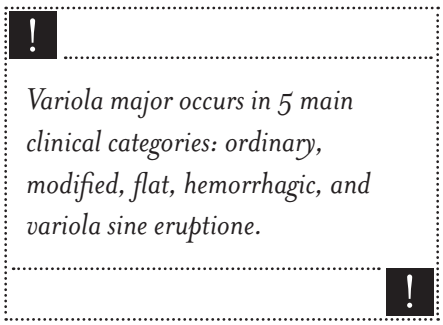
variola minor. Variola major is the most common form of smallpox, has more severe disease with an extensive rash and fever, and carries a higher mortality (around 20% in the unvaccinated). Variola minor is less common and severe, with mortality historically under 1%.

Smallpox is very contagious, with approximately half of all unvaccinated household contacts contracting disease. After worldwide eradication by 1977, routine vaccination of smallpox ceased. However, due to the ever-increasing unvaccinated population along with the variola virus's contagiousness and ability to be transmitted by aerosol, smallpox is a CDC Category A bioterrorism agent. Only 2 stockpiles of the virus are known to remain, 1 at the CDC and 1 at the Russian State Research Center.

a. Clinical Presentation

Smallpox infection occurs when the viral particles enter the respiratory tract, replicate locally, and then are carried to regional lymph nodes. Subsequent viremia occurs with spread to lymphoid organs, followed by further viral amplification and the progression of symptoms. Variola major occurs in 5 main clinical categories: ordinary, modified, flat, hemorrhagic, and variola sine eruptione.

Ordinary type infection used to account for more than 70% of smallpox cases. After an incubation period of 10 to 14 days, disease onset (preeruptive phase) occurs, signaled by high fever, severe headache, and malaise. The preeruptive phase can last 2 to 4 days and is followed by the eruptive phase, characterized by rash. The lesions first appear as small erythematous macules on the mucous membranes, tongue, and face (herald spots). Spread occurs in a centrifugal fashion, with macules evolving into papules, then vesicles, and finally the classic pustules (pox) by days 5 to 7 of the rash. Fever usually resolves during the eruptive phase but may recur after the pustules develop. Crusting and healing begin by day 14 of the rash.



The modified type of variola major was similar to the ordinary type; however, the rash was more rapid but less severe because this type was common in vaccinated individuals. The flat type, which had pustules that remained flat and confluent, often occurred in children. The hemorrhagic type of variola major was rare but very severe, with the lesions and mucous membranes becoming hemorrhagic. It was more common in pregnant women and rapidly led to multiorgan failure within a few days. Variola sine eruptione, an infection with fever but no rash, was often found in vaccinated individuals.

Mortality for ordinary type variola was around 20% from multiorgan failure and hypotension, with flat and hemorrhagic types carrying a higher mortality and the modified and sine eruptione types carrying a much lower mortality. Complications include secondary bacterial skin infections and pneumonia, along with encephalitis, orchitis, and extensive scarring of the skin and cornea.

b. Diagnosis

Diagnosis of smallpox is largely clinical, with the acute onset of fever followed by the characteristic rash of deep-seated vesicles or pustules. For laboratory diagnosis, virus isolation from a skin lesion with reverse transcriptase polymerase chain reaction confirmation is used and only performed at the CDC or World Health Organization (WHO) laboratory.

c. Treatment and Prophylaxis

Treatment is largely supportive. Cidofovir has activity in animal models, though human data are lacking. Vaccination after exposure or early in disease may lessen the severity of illness and is the mainstay for reducing spread and controlling disease in the community. Vaccination can be administered within 4 days of exposure to a known case to provide protection. Respiratory management in the ICU includes support with positive pressure ventilation as clinically required and other supportive therapy.

d. Infection Control

Because smallpox is spread through contact with infected lesions or respiratory secretions, full PPE, including gown, gloves, and face shield, are required (**Table 5-3**). Guidelines from the CDC recommend airborne isolation with use of an N-95 or powered air-purifying respirator (PAPR) for respiratory protection. In addition, all healthcare workers handling any smallpox patient should receive the vaccination. Public health officials should immediately become involved with any suspected case of smallpox.

3. Plague

Yersinia pestis, the etiologic agent of plague, has caused a number of pandemics throughout human history. Plague is a zoonosis that primarily affects rodents, with humans and other animals (domestic cats) being accidental hosts. The natural ecosystem of *Y pestis* depends largely on flea and rodent interaction, with seasonal variability noted based on environmental conditions. Infected fleas inoculate their rodent hosts by biting them. Mortality in rodents remains lower than in other mammals, and when the disease is passed from infected rodent to flea, the life cycle continues. Plague is transmitted to humans by bites from infected fleas, scratches or bites from infected animals, exposure to infected humans, and, potentially, bioterrorism. The most common mode of transmission is bites from infected fleas, and squirrels, rabbits, domestic cats, and prairie dogs. Large rodent or other animal die-offs, particularly in more susceptible species, may herald a large epidemic in nature. Plague is found worldwide, and in the United States endemic disease is found largely in the western states.

a. Clinical Presentation

! *Three clinical syndromes are associated with plague: bubonic plague (80%–90% of cases), septicemic plague (10% of cases), and pneumonic plague (very rare).* !

Three clinical syndromes are associated with plague: bubonic plague (80%-90% of cases), septicemic plague (10% of cases), and pneumonic plague (very rare). After an incubation period of 2 to 7 days, syndrome-specific symptoms usually occur. In bubonic plague, a sudden onset of fevers, chills, and headache is followed by pain and swelling in the regional lymph nodes proximal to the site of the bite or scratch. An affected lymph node (bubo) is characterized by intense tenderness with erythema and edema but without fluctuation. Without treatment, disease disseminates, leading to complications such as pneumonia, meningitis, sepsis, and multiorgan failure. The development of pneumonia becomes extremely concerning because these patients are highly contagious.

In septicemic plague, acute fever is followed by sepsis without the presence of a bubo. Additional symptoms such as nausea, vomiting, and diarrhea complicate septicemic plague. Sepsis, disseminated intravascular coagulation, and multiorgan failure develop quickly.

Most cases of pneumonic plague are secondary from bubonic or septicemic plague, but a primary pneumonic plague can occur after exposure to infected humans, animals, or aerosols in an intentional bioterrorist attack. Due to its high contagiousness, plague can spread rapidly, with primary pneumonia, as seen in past outbreaks, subsequently creating a sustained pandemic. Primary pneumonic plague's very short incubation period of hours to a few days is followed by sudden fever, cough, rapid onset of respiratory failure and acute respiratory distress syndrome (ARDS), and death.

b. Diagnosis

The clinical diagnosis of plague can be difficult, but in an endemic area a patient's exposure to animals may be the first clue. During intentional dissemination, multiple cases of severe, rapidly progressive pneumonia may raise suspicion. Laboratory diagnosis is primarily by culture of the sputum or blood as *Y pestis* grows well on most laboratory media. Serology and rapid diagnostic testing by enzyme-linked immunosorbent assay or PCR is also available but is used primarily in field testing.

c. Treatment and Prophylaxis

Streptomycin has been considered the treatment for plague, but due to its limited availability gentamicin or doxycycline is preferred. Most isolates are fully susceptible to gentamicin and doxycycline as well as to ciprofloxacin, which has been used in a more limited manner. Chloramphenicol is preferred for cases of meningitis due to its ability to cross the blood-brain barrier. Postexposure prophylaxis includes ciprofloxacin and doxycycline orally, with trimethoprim-sulfamethoxazole (if susceptible) or gentamicin for children and pregnant individuals. Pneumonic plague and septicemic plague in the

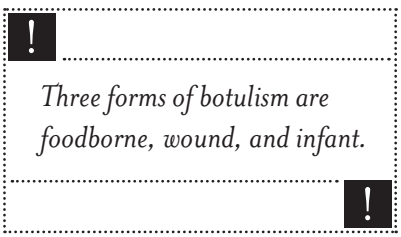
ICU will have multiorgan failure with ARDS, so management should include ventilation strategies appropriate for ARDS and other supportive care.

d. Infection Control

Due to the high rate of transmission of plague via aerosols, all patients should be on strict airborne isolation until antibiotics have been given for least 48 hours (**Table 5-3**). Infection-control measures include airborne isolation, including negative pressure isolation. Appropriate PPE, including an N-95 respirator or a PAPR, should be worn.

4. Botulism

Clostridium botulinum, the bacterium that produces and excretes botulinum toxin, is a gram-positive, spore-forming, obligate anaerobe. Its neurotoxin is responsible for the clinical disease botulism and is the only Category A agent that is a toxin. Seven serotypes of botulinum toxin exist, A through G, each produced by a different strain of *C botulinum*. All act on the presynaptic nerve terminal of the neuromuscular junction and the cholinergic autonomic synapses, disrupting neurotransmission and leading to the clinical findings. Serotypes A, B, and E predominate in clinical disease, although any serotype can cause disease. Botulinum toxin is extremely lethal, with an oral lethal dose estimated to be 1 ng/kg, although lethal inhalational disease requires 2 to 3 times that dose.



Three forms of botulism are foodborne, wound, and infant. Foodborne disease occurs in outbreaks and is often associated with consumption of improperly home-canned foods, such as fruits and vegetables. It also occurs when *C botulinum* replicating within the canned substance release toxins that are later ingested. Wound botulism results from the infection of a wound with *C botulinum*. It has been associated with intravenous and subcutaneous injection of black tar heroin, mostly of Mexican origin. Infant botulism occurs sporadically in some western states, probably from spores in soil or raw honey, with subsequent toxin production in the gastrointestinal tract. Botulinum toxin may also be intentionally released during a bioterrorism event in a form designed for oral ingestion or as an aerosol.

a. Clinical Presentation

Clinical disease begins with the acute onset of bilateral cranial neuropathies with rapidly descending weakness. Of note, no fever is present and the patient maintains normal mentation. The cranial neuropathies are usually symmetrical and often begin with ocular motor dysfunction. However, asymmetrical cranial nerve dysfunction has been reported. Diplopia, dysphagia, ptosis, and facial weakness are the most common. In foodborne exposure, gastrointestinal symptoms including nausea and vomiting may also occur. In infant botulism, poor feeding and lethargy may be noted. In both wound and foodborne forms of botulism, symptoms typically appear 12 to 36 hours after exposure and rapidly progress over the next 12 hours. If botulism is not suspected and treatment does not occur rapidly, eventual weakness and paralysis of respiratory muscles ensues, requiring mechanical ventilatory support. Once the muscles of respiration are involved, mechanical

support is required for 1 to 3 months. Death from botulism occurs from respiratory failure, so cases that receive prompt recognition and treatment have a low mortality.

b. Diagnosis

Early and prompt diagnosis of botulism is essential because early treatment can alter the progression of disease. Clinical findings of cranial nerve palsies, particularly in the appropriate clinical setting (eg, in heroin use), should prompt consideration. Laboratory diagnosis is by toxin or organism isolation, in either the spore or the vegetative form. Isolation of toxin from blood or stool is most reliable, and in some cases environmental isolation may be necessary to make the diagnosis. The growth of *C botulinum* from a stool or wound sample with the corresponding clinical findings may also confirm the diagnosis. Electromyography will support the diagnosis if toxin and organism isolation is unsuccessful.

c. Treatment and Prophylaxis

Treatment must be started promptly and is directed at toxin neutralization. An equine trivalent antitoxin (A, B, E) available from most state public health departments and the CDC has been shown to decrease mortality in foodborne outbreaks and to lessen the likelihood of respiratory failure in wound botulism. Anaphylaxis and serum sickness have been reported. A human-derived antitoxin is used in infant cases. Antibiotic administration is favored for wound botulism, with penicillin or clindamycin being the drugs of choice. Because botulism is caused by exposure to the toxin, antibiotics are not recommended for foodborne and inhalational cases. In all cases of botulism without respiratory failure, routine monitoring of forced vital capacity is recommended, with early intubation if the vital capacity falls below 10 mL/kg (approximately 30% predicted). There is no direct prophylaxis for exposure, but in high-risk threats a vaccine directed against toxins A through E is available and has been largely used in the military.

d. Infection Control

Given that botulism is a toxin-based disease, infection control should follow universal precautions (**Table 5-3**). Decontamination should follow exposure to spores or toxin, although secondary disease in medical personnel has not been reported.

5. Tularemia

Tularemia, caused by the gram-negative bacterium *Francisella tularensis*, is a zoonotic disease with humans as accidental hosts. *Francisella tularensis* is found throughout the northern hemisphere in a wide variety of wild and domesticated species. The organism persists in nature because it is passed transovarially in ticks, with disease coming after bites from infected vectors (ticks, flies, mosquitos). Human infections occur from vector contact (ticks and flies), handling infected animals, ingesting improperly prepared animal meat, animal scratches and bites, drinking contaminated water, or aerosolization of the organism from the environment or in bioterrorism. However, human-to-human transmission does not occur, largely because the organism is intracellular during infection and thus harder to spread from person to person.

a. Clinical Presentation

> *Six distinct clinical syndromes occur with tularemia: ulceroglandular, glandular, typhoidal, pneumonic, oropharyngeal, and oculoglandular.*

Approximately 6 distinct clinical syndromes occur with tularemia: ulceroglandular, glandular, typhoidal, pneumonic, oropharyngeal, and oculoglandular. Ulceroglandular disease accounts for approximately 60% to 70% of disease. Abrupt onset of fevers, chills, headache, and malaise occurs after an incubation period of 2 to 10 days. Most patients will have a single papuloulcerative lesion with a central eschar and associated tender lymphadenopathy. In glandular disease, enlargement of lymph nodes occurs without the characteristic lesion (about 15% of cases). Pneumonic tularemia occurs with primary inhalation or hematogenous spread from typhoidal tularemia, which is felt to be the main clinical presentation in a bioterrorism event with tularemia. The incubation period tends to be shorter in these cases, with rapid onset of pneumonia. Radiographic studies show patchy infiltrates bilaterally, lobar disease, and hilar adenopathy. Pleural effusions and a military pattern may also occur, although they are less common. Respiratory failure and ARDS develop quickly.

Typhoidal tularemia is rare and may occur with or without pneumonia. These patients present with febrile illness followed by sepsis but without the glandular disease. Oropharyngeal tularemia, also rare, occurs when undercooked infected meat or water is ingested. It is associated with fever, pharyngitis, and cervical lymphadenopathy. Oculoglandular tularemia is acquired through direct inoculation from contaminated fingers or accidental exposure. Besides conjunctival swelling and erythema, regional lymphadenopathy may be present.

The overall mortality for tularemia is around 4%, but mortality is probably higher in aerosolized disease that causes pneumonia or typhoidal tularemia.

b. Diagnosis

Francisella tularensis is very difficult to grow on culture media, and because it is largely an intracellular organism, diagnosis is difficult. Clinical suspicion must be high, particularly if the risk factors of vector exposure, animal exposure, or multiple community cases suggesting aerosolization occur. Serology by ELISA or histologic examination showing gram-negative intracellular organisms is the most likely method of diagnosis. If serology is performed, a single elevated titer may not be specific and thus acute and convalescent titers are more predictive.

c. Treatment and Prophylaxis

The treatment of tularemia is similar to the treatment of plague. Aminoglycosides such as gentamicin are the first-line treatment, with doxycycline or ciprofloxacin used as second-line therapy. For meningitis chloramphenicol is preferred. In cases of exposure, doxycycline or ciprofloxacin is the preferred treatment, with trimethoprim-sulfamethoxazole or

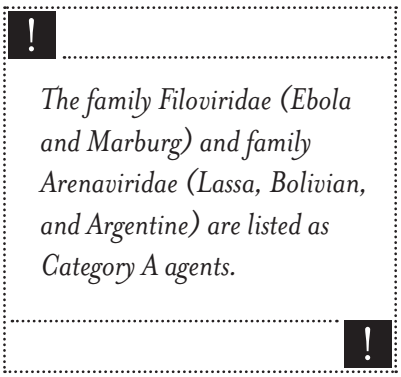
amoxicillin for children and pregnant patients. Particular ICU management of tularemia includes supportive care and appropriate ventilation strategies for ARDS.

d. Infection Control

Francisella tularensis is not transmitted from human to human, so once the diagnosis is confirmed, respiratory isolation can be lifted (**Table 5-3**). Guidelines for reporting tularemia to public health officials vary across North America, but pneumonic or typhoidal cases, particularly if felt to be secondary to a bioterrorism event, should be reported.

6. Viral Hemorrhagic Fevers

Viruses that cause hemorrhagic fever are numerous and distributed worldwide. Among them are the viruses that cause Ebola disease, Marburg disease, Rift Valley fever, Crimean-Congo hemorrhagic fever, Lassa fever, yellow fever, and dengue fever. Ebola and Marburg viruses are in the family Filoviridae; Lassa, Bolivian, and Argentine viruses are in the family Arenaviridae; and the Crimean-Congo and Rift Valley hemorrhagic fever viruses are in the family Bunyaviridae. Only the family Filoviridae (Ebola and Marburg) and family Arenaviridae are listed as Category A agents. Because the family Filoviridae serves as a classic template for viral hemorrhagic fevers (VHFs), the Ebola and Marburg viruses will be the main focus of discussion here.



Marburg virus has a single species, whereas Ebola has 4 different species that vary in virulence in humans. Transmission appears to occur through contact with nonhuman primates and infected individuals. Transmission has been observed among vaccine workers handling primate products, consumption of nonhuman primates for food (ie, eating monkeys in rural parts of Africa), laboratory workers, and nosocomially. The use of VHF in bioterrorism has also been postulated, largely based on its high contagiousness in aerosolized primate models. The exact reservoir for the virus was initially thought to be wild primates. However, bats have recently been identified as the reservoir, and they pass the infection on to nonhuman primates in the wild.

a. Clinical Presentation

Marburg disease and Ebola disease are similar in presentation and pathophysiology, with mortality being the only major difference between them. The incubation period after exposure to either virus is 5 to 7 days, and clinical disease begins with fever, chills, malaise, severe headache, nausea, vomiting, diarrhea, and abdominal pain. Disease onset is abrupt, and over the next few days, symptoms worsen to include prostration, stupor, and hypotension. Shortly thereafter, impaired coagulation occurs with increased conjunctival and soft-tissue bleeding. In some cases, more massive hemorrhage may occur in the gastrointestinal and urinary tracts, and in rare instances alveolar hemorrhage may occur. The onset of maculopapular rash on the arms and trunk also appears classic and may be a very distinctive sign. Bleeding, hypotension, and multiorgan failure eventually lead to death. Case fatality rates for Marburg have reached 80% to 90%, but Ebola case fatality rates appear lower at 50%.

b. Diagnosis

The rapid diagnosis of VHF is extremely important in order to initiate supportive care before the onset of shock, alert and involve the public health department, and institute infection-control measures. However, diagnosis is difficult outside of the endemic area. Viral hemorrhagic fever should be suspected in exposed laboratory workers, in acutely ill travelers from an endemic area (ie, central Africa), or when classic clinical findings and an increase of cases within the community suggest bioterrorism. In the absence of travel or laboratory exposure, a patient with high fever, malaise and joint pain, conjunctival bleeding and bruising, confusion, and progression to shock and multiorgan failure should raise suspicion of VHF, particularly if multiple cases are appearing in the community. Laboratory diagnosis includes antigen testing by ELISA or viral isolation by culture, but these tests are currently performed only by the CDC.

c. Treatment and Prophylaxis

Because no specific therapy is available, patient management consists of supportive care, including appropriate ventilation strategies if ARDS develops. For the arenavirus group (Lassa, Junin, Machupo) and Bunyaviridae (Crimean-Congo, Rift Valley fever), ribavirin is recommended. In a few cases during an outbreak of Ebola in Zaire in 1995, whole blood with immunoglobulin G antibodies against Ebola may have improved outcome, although analysis showed that those patients were likely to have survived anyhow. If a healthcare worker is exposed, there is no specific postexposure prophylaxis, and infection control and occupational health should be included with potential quarantine measures for exposed individuals.

d. Infection Control

Although VHF appears to be transmitted by droplet, airborne precautions are recommended, including respiratory protection with an N-95 respirator or PAPR and placement of the patient in a respiratory isolation room (**Table 5-3**). Equipment should be dedicated to that individual, and all higher-risk procedures should be done with adequate, full PPE. In any suspected case of VHF, public health officials and the infection-control department should become immediately involved because public health interventions and outbreak investigation will be paramount to reduce spread of disease within the community and to probe any potential bioterrorist attack.

B. Bioterrorism: CDC Category B Agents

Category B agents are moderately easy to disseminate and have lower mortality rates than Category A agents. The Category B agents are

- Brucellosis (*Brucella* species)
- Epsilon toxin of *Clostridium perfringens*
- Food safety threats (eg, *Salmonella* species, *Escherichia coli* O157:H7, *Shigella* species)
- Glanders (*Burkholderia mallei*)
- Melioidosis (*Burkholderia pseudomallei*)
- Psittacosis (*Chlamydia psittaci*)
- Q fever (*Coxiella burnetii*)
- Ricin toxin from *Ricinus communis* (castor beans)
- Staphylococcal enterotoxin B
- Typhus fever (*Rickettsia prowazekii*)
- Viral encephalitis (alphaviruses [eg, Venezuelan equine encephalitis, Eastern equine encephalitis, Western equine encephalitis])

Clinical features of these agents are summarized in **Table 5-4**.

Table 5-4. Features of CDC Category B Agents

	Agent	Species	Inoculation	Clinical Presentation	Diagnosis	Treatment
Brucellosis	Bacterial	*Brucella* species	Ingestion, inhalation	Fever, arthralgia	Blood culture	Doxycycline
Epsilon Toxin	Toxin	*Clostridium perfringens*	Ingestion, inhalation	Central nervous system dysfunction, pulmonary edema	Detection of toxin (ELISA)	Supportive
Glanders	Bacterial	*Burkholderia mallei*	Cutaneous, inhalation	Pneumonia, sepsis	Blood culture (may be misidentified)	Imipenem, 3rd-generation cephalosporin
Melioidosis	Bacterial	*Burkholderia pseudomallei*	Cutaneous, inhalation	Sepsis, metastatic foci, multiorgan failure	Blood culture	Imipenem, 3rd-generation cephalosporin
Psittacosis	Bacterial	*Chlamydia psittaci*	Inhalation	Atypical pneumonia	Serology	Doxycycline, macrolide, or fluoroquinolone

continued next page…

Table 5-4. Features of CDC Category B Agents (continued)

	Agent	Species	Inoculation	Clinical Presentation	Diagnosis	Treatment
Q Fever	Bacterial	*Coxiella burnetii*	Inhalation	Fevers, headache, myalgia, pneumonia	Serology	Doxycycline or fluoroquinolone
Ricin	Toxin	Toxin from castor beans	Ingestion, inhalation	Respiratory failure, metabolic acidosis, multiorgan failure	Environmental testing only	Supportive
Staphylococcal Enterotoxin B	Toxin	*Staphylococcus aureus*	Ingestion, inhalation	Vomiting and diarrhea, respiratory failure if inhaled	Urine for staphylococcal enterotoxin B	Supportive
Typhus Fever	Bacterial	*Rickettsia prowazekii*	Body louse, cutaneous, inhalation	Fever and headache, sepsis if untreated	Serology, PCR	Doxycycline, macrolide, or fluoroquinolone
Viral Encephalitis	Viral	VEEV, EEEV, WEEV	Mosquito, inhalation	Fever and headache, some progress to encephalitis	CSF PCR	Supportive

Abbreviations: VEEV, Venezuelan equine encephalitis virus; EEEV, Eastern equine encephalitis virus; WEEV, Western equine encephalitis virus; ELISA, enzyme-linked immunosorbent assay; PCR, polymerase chain reaction; CSF, cerebrospinal fluid.

1. Brucellosis (*Brucella* Species)

Brucellosis is caused by a number of species within the genus *Brucella*. The natural reservoir is domesticated animals. Symptoms develop a few weeks to months after exposure through ingestion of contaminated food or intentional aerosolization. Initially fevers persist irregularly over weeks to months, followed by arthralgias, gastrointestinal symptoms, and possibly endocarditis. Diagnosis is an epidemiologic link with isolation of the organism by blood culture. Growth in blood culture is slow, so all cultures should be kept for 4 weeks if the diagnosis is suspected. Treatment is doxycycline for up to 6 weeks, with trimethoprim-sulfamethoxazole for children.

2. Epsilon Toxin of *Clostridium perfringens*

The *Clostridium* species produce a wide variety of toxin. Epsilon toxin, produced by types B and D *Clostridium perfringens*, acts directly on the cell membrane, producing pores that cause nonselective permeability. In bioterrorism, ingestion or inhalation of the toxin without bacteria is most likely. Rapid ingestion or inhalation would cause diffuse tissue edema that would manifest as central nervous system dysfunction (weakness, ataxia, confusion), pulmonary edema (shortness of breath, cough, bronchospasm, respiratory failure), nausea, vomiting, tachycardia, and hypotension. Toxin can be detected by ELISA or enzyme immunoassay as well as by PCR. Treatment is supportive, with penicillin if *C perfringens* is released at the same time as the toxin.

3. Glanders (*Burkholderia mallei*)

The disease glanders is caused by the gram-negative bacterium *Burkholderia mallei*. Glanders is primarily a disease of horses, with humans becoming secondarily infected through broken skin or droplet inhalation. Naturally occurring human infection is rare, but occupational cases (eg, in horse veterinarians) do occur sporadically. In bioterrorism, aerosolization is the likely method of transmission. Glanders can occur as an acute or chronic skin infection, but with aerosolization, rapid pneumonia and/or sepsis will present. Diagnosis is by culture, but because *B mallei* is an uncommon organism, laboratories may misclassify it. Treatment includes supportive care as well as systemic antibiotics with imipenem or a third-generation cephalosporin. Ciprofloxacin is also an option. Given that glanders is a rare disease, human-to-human transmission has not been documented, but universal precautions with droplet isolation for respiratory cases is recommended. Any suspected case should involve immediate contact with the public health department.

4. Melioidosis (*Burkholderia pseudomallei*)

Melioidosis is caused by the gram-negative bacterium *Burkholderia pseudomallei*. This bacterium has a natural reservoir in the soil and contaminated water and is spread through direct contact or inhalation. Thus, melioidosis predominates during the rainy season. In bioterrorism, aerosolization of *B pseudomallei* would lead to a clinical picture of pneumonia or melioidosis sepsis. The incubation period of melioidosis can be highly variable, with some cases not presenting for extended periods and others remaining asymptomatic. Most symptomatic cases will develop sepsis with multiple metastatic foci and eventual multiorgan failure. Diagnosis is by culture, which occurs readily using routine methods. Treatment involves imipenem or a third-generation cephalosporin, followed by a 20-week treatment with doxycycline and trimethoprim-sulfamethoxazole for metastatic foci eradication.

5. Psittacosis (*Chlamydia psittaci*)

Psittacosis is caused by *Chlamydia psittaci*, an intracellular bacterium routinely associated with birds such as parrots, cockatiels, and canaries. It presents nonspecifically, and most cases go undiagnosed. Intentional aerosolization of *C psittaci* would lead to multiple cases of nonspecific atypical pneumonia with cough, fever, and headache. Diagnosis is not easy and relies on serology due to the difficulty of isolating the organism. Treatment is with doxycycline, a macrolide, or ciprofloxacin. Mortality is low at 1% in treated cases. Universal precautions are required for patient care, although an N-95 respirator with coveralls is recommended for environmental decontamination.

6. Q Fever (*Coxiella burnetii*)

Q fever is a zoonotic disease caused by *Coxiella burnetii*. Cattle, sheep, and goats are the primary reservoirs of *C burnetii*, and the disease is found worldwide. *Coxiella burnetii* usually does not cause clinical disease in animals, but organisms are found in milk, urine, feces, amniotic fluids, and placenta. The organisms are resistant to heat and drying and may cause infection when humans inhale environmental dust contaminated by dried placental material, birth fluids, and excrement. Incubation time is 1 to 2 weeks, after which only about one-half of all infected persons

develop a clinical illness. The clinical illness is characterized by high fevers (often greater than 40°C [104°F]), severe headache, myalgia, sore throat, nonproductive cough, nausea, vomiting, diarrhea, abdominal pain, and chest pain. Fever usually lasts for 1 to 2 weeks. Between 30% and 50% of patients with a symptomatic infection will develop pneumonia.

Between 1% and 2% of people with acute Q fever die of the disease. A small percentage of those infected will develop chronic Q fever (infection that persists for more than 6 months). Complications of chronic Q fever include endocarditis. As many as 65% of persons with chronic Q fever die of the disease. The diagnosis of Q fever requires serologic testing, most commonly indirect immunofluorescence assay. The treatment of choice for acute Q fever is 100 mg doxycycline twice daily for 15 to 21 days. Quinolone antibiotics may be an effective alternative.

7. Ricin Toxin

Ricin is a potent biological toxin (toxic protein) derived from part of the waste when castor beans (*Ricinus communis*) are processed during the manufacture of castor oil. Ricin acts as a toxin by inhibiting protein synthesis. The lethal dose is thought to be 0.2 mg (1/5,000 g). Symptoms begin within 4 to 12 hours after exposure. Systemic effects of ricin poisoning will depend upon route of exposure and exposure dosage. Signs and symptoms from oral ingestions would include vomiting and profuse diarrhea; fever, myalgia and arthralgia, hallucinations, and seizures may occur. Hypovolemic shock and multisystem organ failure may occur and would be the likely cause of death.

After an inhalational exposure the symptoms could include cough, respiratory distress, and bronchoconstriction. Influenzalike symptoms (fever, myalgia, and arthralgia) may occur, as well as hypotension, respiratory failure, and multisystem organ failure. Few symptoms and signs separate ricin toxin from other causes of respiratory failure, though excessive diaphoresis has been reported and would be unusual in other causes. No validated biologic assays detect ricin toxin, though it may be detected through environmental testing. No specific treatment or antitoxin exists. Treatment consists of decontamination and supportive therapy.

8. Staphylococcal Enterotoxin B

Staphylococcal enterotoxin B, a toxin produced by *Staphylococcus aureus*, is commonly associated with food poisoning. Symptoms of food poisoning include vomiting and diarrhea several hours after ingesting food. Naturally occurring staphylococcal enterotoxin B is rarely lethal. The clinical presentation depends on the route of administration. Orally administered toxin (through contaminated food or water supplies) presents as vomiting and diarrhea. If the toxin is inhaled, respiratory failure with neurotoxic effects may be seen. Staphylococcal enterotoxin B is difficult to detect in the serum. However, because the toxin accumulates in the urine for the first several hours, urine samples should be obtained and tested.

9. Typhus Fever (*Rickettsia prowazekii*)

Typhus fever (also known as epidemic typhus) is caused by *Rickettsia prowazekii*. As in other rickettsial illnesses, clinical presentations of epidemic typhus vary, but common early symptoms are nonspecific and include fever, headache, and malaise. If the disease is untreated, sepsis and vascular collapse may follow. Epidemic typhus is typically transmitted by the human body louse.

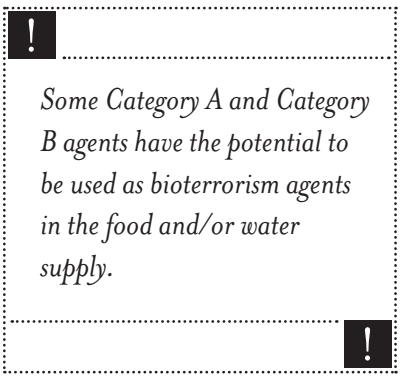
Natural infections are rare in most developed countries but occasionally occur in communities and populations in which body louse infestations are frequent (eg, the homeless). Infection may also be acquired naturally through inhalation or inoculation of the skin or conjunctiva (for example, if healthcare workers inhale louse feces). Those alternative pathways are likely to be targeted if typhus is used as a biological weapon. Widespread dissemination of infected lice is less likely. Human-to-human transmission does not occur.

Diagnosis is based on serology (immunofluorescence assays and ELISA), though PCR assays are being developed. Treatments for typhus fever are similar to those for most other rickettsial illnesses and include administration of appropriate antibiotics (eg, tetracyclines, fluoroquinolones, and macrolides, with chloramphenicol and rifampin as second-line agents) and supportive care.

10. Viral Encephalitis

Venezuelan equine encephalitis, Eastern equine encephalitis, and Western equine encephalitis are mosquito-borne RNA alphaviruses. These viruses primarily cause equine disease, though humans are occasionally accidental hosts. Venezuelan equine encephalitis is the most common. It is seen primarily in Latin America and occasionally spreads to the southern United States. Eastern equine encephalitis is found primarily in the United States east of the Mississippi River, while Western equine encephalitis occurs in the western United States and western Canada; both cause occasional disease in Latin America. Human disease, which is rare, usually takes the form of a self-remitting flulike syndrome. Venezuelan equine encephalitis and Eastern equine encephalitis progress to encephalitis in 1% of adults and 3% to 5% of children, with 20% to 50% mortality. Western equine encephalitis has a lower mortality rate (3%-5%). Severe disease in Western equine encephalitis is rare for adults (over 1:1,000) but as high as 50% for the young pediatric population. The attractiveness of Western equine encephalitis and Eastern equine encephalitis as biological weapons is based on their potential for widespread infection through aerosolization or release of infected mosquitoes and their low infective dose for humans. The characteristics of Western equine encephalitis make it an unlikely biological weapon if the intent is to affect adults, but by using it to target a pediatric population, terrorists could try to produce panic and social paralysis. Human-to-human transmission does not occur for any of the agents. Diagnosis is based on PCR detection of the viruses in cerebrospinal fluid samples. There is no known definitive treatment.

C. Threats to Food and Water Safety



Foodborne and waterborne pathogens are potentially strong agents of bioterrorism because they are easy to spread and could affect massive numbers of people. Some Category A and Category B agents have the potential to be used as bioterrorism agents in the food and/or water supply. Other bacterial, viral, and protozoan agents can also cause disease. Many of these foodborne and waterborne agents cause natural epidemics that affect millions of people around the world, often due to inadvertent contamination. Therefore, it is difficult to identify a food- or waterborne epidemic as an act of bioterrorism, and suspicion will depend on the particular agent and whether it

is associated with natural outbreaks, the breadth of the outbreak, and the intent, if known. In addition, the characteristics of food- and waterborne agents vary. For example, some pathogens have the potential to spread more broadly through secondary human-to-human transmission.

Enteropathogenic gram-negative bacteria, such as *Escherichia coli, Salmonella*, and *Shigella*, constitute a large group of agents that may threaten the food supply. Every year these bacteria are implicated in numerous episodes of food contamination that result in localized outbreaks and large-scale product recalls. In an intentional release, these agents will produce widespread gastrointestinal symptoms leading to significant morbidity but with low mortality. After an incubation period of 3 to 7 days, exposed individuals will experience abdominal cramping, nausea, vomiting, and diarrhea that may be voluminous and bloody. Diagnosis is by stool culture of the agents. Aggressive public health investigations usually yield the initial agent, and bioterrorism outbreaks will resemble a point source outbreak. Treatment is intravenous hydration as needed and for some agents (*Salmonella, Shigella*), antibacterial therapy with ciprofloxacin.

Other bacterial threats include *Campylobacter jejuni, Vibrios cholerae, Listeria monocytogenes*, and *Yersinia enterocolitica*. Viral agents include noroviruses and hepatitis A. Protozoan agents include *Cryptosporidium parvum, Cyclospora cayetanensis, Entamoeba histolytica, Giardia lamblia, Microsporidia* species, *Enterocytozoon bieneusi*, and *Toxoplasma gondii*. A thorough discussion of each agent's presentation, diagnosis, and treatment exceeds the scope of this chapter. For sources of further information, see the Suggested Readings.

IV. NATURALLY OCCURRING EMERGING INFECTIOUS THREATS

A. Pandemic Influenza

Sporadic human cases of H5N1 have occurred over the last several years, as have outbreaks of H7N3, H7N7, H9N2, and H10N7. (Antigenic variants of influenza A are classified on the basis of their surface antigens [hemagglutinin and neuraminidase] using the pattern H*x*N*x*, with *x* corresponding to the number of the specific type of antigen.) Gene reassortment of these viruses with other animal or human influenza viruses could produce more virulent and transmissible viruses.

1. Clinical Presentation

The incubation period is 1 to 4 days followed by clinical symptoms including fever, myalgia, sore throat, and nonproductive cough. The clinical presentations of episodic zoonotic infections vary by the infecting strain. The most common strain to date is H5N1. Most patients with H5N1 virus infections present with fever, cough, and difficulty breathing. A primary viral pneumonia develops quickly, with pulmonary infiltrates on chest radiographs. Respiratory distress progressing to failure is frequent. H7N7 virus has caused outbreaks of conjunctivitis and infrequent viral pneumonia, H9N2 virus has caused an illness indistinguishable from seasonal influenza, and H7N3 virus has caused conjunctivitis and mild respiratory-tract illness. Presumably a pandemic influenza would cause respiratory disease.

2. Diagnosis

There are several modalities to document influenza infection. These include direct viral detection (antigen tests, PCR, and culture) or serologies. Rapid antigen testing is available for seasonal influenza. Generally, these tests are very specific (95%-100%), but their sensitivity is modest, especially in adults (50%-70%). Nucleic acid testing (PCR) is gaining widespread use due to its versatility while maintaining high sensitivity and specificity (approaching 100%). Culture is performed by inoculation of cell cultures that support viral replication. A minimum of 48 hours is needed to demonstrate viral growth, with additional time for specific viral identification. The presence of influenza does not preclude the concurrence of another pathogen, especially pneumococcus or staphylococcus.

3. Treatment and Prophylaxis

Treatment of pandemic influenza needs to be guided by the sensitivities of the circulating strain. Amantadine and rimantadine should no longer be used for the treatment of influenza due to the high incidence of resistance (exceeding 90% of H3N2 in 2005-2006 and intrinsic in several types of avian influenza) and therefore would not be first-line therapy for pandemic influenza. Recommended treatment of sporadic cases of avian influenza in humans is to use oseltamivir at currently licensed doses. Zanamivir is efficacious in animal models, but there is no experience with this agent in the treatment of humans with avian influenza.

4. Infection Control

Patients with influenza should be isolated with droplet precautions. There is no demonstrated added value to placing patients with influenza in rooms for airborne infection isolation (ie, negative-pressure rooms) or to using N-95 or powered air-purifying respirators. If a highly virulent form of influenza were to circulate widely, however, such added precautions might well be prudent.

B. Tick-borne Hemorrhagic Fever Viruses (Crimean-Congo Hemorrhagic Fever)

Crimean-Congo hemorrhagic fever (CCHF) is caused by infection with a tick-borne virus (*Nairovirus*). The disease was first characterized in Crimea in 1944 and then recognized as the cause of illness in the Congo in 1969, thus resulting in its current name. Crimean-Congo hemorrhagic fever is found in eastern Europe, particularly in the former Soviet Union. It is also distributed throughout the Mediterranean, in northwestern China, central Asia, southern Europe, Africa, the Middle East, and the Indian subcontinent.

Ixodid (hard) ticks, especially those of the genus *Hyalomma*, are both a reservoir and a vector for the CCHF virus. Numerous wild and domestic animals, such as cattle, goats, sheep, and hares, serve as amplifying hosts for the virus. Transmission to humans occurs through contact with infected animal blood or ticks. Crimean-Congo hemorrhagic fever can be transmitted from one infected human to another by contact with infectious blood or body fluids.

1. Clinical Presentation

The onset of CCHF is sudden, with initial signs and symptoms including headache, high fever, back pain, joint pain, stomach pain, and vomiting. Red eyes, a flushed face, a red throat, and petechiae (red spots) on the palate are common. Symptoms may also include jaundice, and in severe cases, changes in mood and sensory perception. As the illness progresses, large areas of severe bruising, severe nosebleeds, and uncontrolled bleeding at injection sites can be seen, beginning on about the fourth day of illness and lasting for about two weeks. In documented outbreaks of CCHF, fatality rates in hospitalized patients have ranged from 9% to as high as 50%.

2. Diagnosis

Laboratory tests that are used to diagnose CCHF include antigen-capture ELISA, real-time polymerase chain reaction (RT-PCR), virus isolation attempts, and detection of antibody by ELISA (IgG and IgM). Laboratory diagnosis of a patient with a clinical history compatible with CCHF can be made during the acute phase of the disease by using the combination of detection of the viral antigen (ELISA antigen capture), viral RNA sequence (RT-PCR) in the blood or in tissues collected from a fatal case and virus isolation. Immunohistochemical staining can also show evidence of viral antigen in formalin-fixed tissues. Later in the course of the disease, in people surviving, antibodies can be found in the blood. But the antigen, viral RNA, and the virus are no more present and detectable.

3. Treatment and Prophylaxis

Treatment for CCHF is primarily supportive. Care should include careful attention to fluid balance and correction of electrolyte abnormalities, oxygenation and hemodynamic support, and appropriate treatment of secondary infections. The virus is sensitive in vitro to the antiviral drug ribavirin. It has been used in the treatment of CCHF patients reportedly with some benefit.

4. Infection Control

There is a risk of nosocomial spread of infection when patients with CCHF are admitted to the hospital. Paitents with suspected or confirmed CCHF should be isolated and full barrier preautions implemented. Healthcare workers are at risk of acquiring infection from sharp injuries during surgical procedures and from contact with blood and body waste.

C. Severe Acute Respiratory Syndrome

In mid-February 2003, the government of China reported to the WHO 305 cases of atypical pneumonia, including 5 deaths that had occurred in Guangdong province, since the fall of 2002. The CDC subsequently referred to this syndrome as severe acute respiratory syndrome (SARS). Before identification of the causative organism, SARS had spread through travel to 26 countries, including the United States. It was subsequently shown that SARS was caused by a novel, hitherto unknown coronavirus.

1. Clinical Presentation

Severe acute respiratory syndrome has an incubation period of 2 to 11 days before the development of symptoms. Fevers appear nearly always. Shortly after the fever, a cough begins in most cases and is often described as nonproductive. Dyspnea often begins 3 to 5 days after the onset of fevers. Rigors, malaise, and headaches occur frequently, and pleurisy occurs occasionally. Rhinorrhea and sore throat are not commonly seen in this disease.

2. Diagnosis

The diagnosis of SARS is primarily with serologies (acute and convalescent), though PCR assays are available. Given the limited spread of SARS, the sensitivity and specificity of these assays are unknown.

3. Treatment and Prophylaxis

Treatment of SARS is largely supportive, with supplementary oxygen and ventilatory support as needed. Patients often receive broad-spectrum empirical antibiotics. There have been a few anecdotal reports of treatment with hyperimmune serum. With the recognition of a viral etiology, ribavirin was used frequently; however, this agent lacks antiviral activity against SARS coronavirus and should be avoided.

4. Infection Control

SARS has been transmitted nosocomially to healthcare workers and other patients. Infected patients should be placed in negative pressure isolation. Healthcare workers should use contact and airborne precautions when caring for infected patients.

D. Chikungunya Virus

Chikungunya fever is a viral disease transmitted to humans by the bite of infected mosquitoes. The virus circulates throughout much of Africa, with transmission thought to occur mainly between mosquitoes and monkeys.

1. Clinical Presentation

The incubation period for chikungunya is usually 3 to 7 days. Acute chikungunya fever is characterized by fever, headache, fatigue, nausea, vomiting, muscle pain, rash, and joint pain. Some patients have reported incapacitating joint pain or arthritis that may last for weeks or months.

2. Diagnosis

The definitive diagnosis of Chikungunya virus is made by acute and convalescent serologies.

3. Treatment and Prophylaxis

No vaccine or specific antiviral treatment for chikungunya fever is available. Treatment is symptomatic—rest, fluids, and ibuprofen, naproxen, acetaminophen, or paracetamol may relieve symptoms of fever and aching.

4. Infection Control

Chikungunya is transmitted by the bite of infected mosquitoes and is not transmitted human to human. Standard precautions should be implemented for care of affected individuals.

Key Points

INTENTIONAL AND NATURAL OUTBREAKS OF INFECTIOUS DISEASE

- Emerging infectious diseases and bioterrorism, though uncommon, will strongly affect the medical and public health infrastructure.
- Most CDC Category A agents, along with some emerging natural infections such as influenza, begin with nonspecific symptoms such as fever, malaise, and shortness of breath. However, specific clinical features or epidemiological links will alert the clinician to one of these uncommon agents.
- If bioterrorism or an emerging infectious disease is suspected, airborne and contact isolation of the patient should begin immediately, and public health and institutional infection-control officials should be notified.
- Because Category A agents carry high mortality and morbidity and are easily transmissible, they are of the highest public health priority. Diagnosis, treatment, and infection-control measures vary by agent, and all agents must be immediately reported to the local health department.
- The CDC Category B agents are moderately easy to disseminate but carry a much lower mortality and more moderate morbidity than Category A agents. This category consists of viruses, bacteria, and some biological toxins with a broad range of clinical presentations and treatments.
- Emerging and naturally occurring infectious diseases often have a common epidemiologic link, such as travel, contact with sick animals, or a cluster of cases.
- Emerging infections may involve a novel agent, as do pandemic influenza or SARS, or a new change to an older agent, as in methicillin-resistant *Staphylococcus aureus* or multidrug-resistant tuberculosis. Novel agents can be more difficult to detect, and diagnosis often relies on case definitions and patient contact tracing.
- If a patient presents with a febrile illness and an emerging pathogen is suspected, isolation should begin immediately. High-risk procedures should be avoided because they can increase the likelihood that the agent will be aerosolized.
- When there is doubt about the nature or source of an infection, public health and institutional infection control should be contacted.

Suggested Readings

Dembek ZF, Kortepeter MG, Pavlin JA. Discernment between deliberate and natural infectious disease outbreaks. *Epidemiol Infect*. 2007;135(3):353-371.

Kman NE, Nelson RN. Infectious agents of bioterrorism: a review for emergency physicians. *Emerg Med Clin North Am*. 2008;26(2):517-547.

Pappas G, Panagopoulou P, Christou L, Akritidis N. Category B potential bioterrorism agents: bacteria, viruses, toxins, and foodborne and waterborne pathogens. *Infect Dis Clin North Am*. 2006;20(2):395-421.

Rotz LD, Hughes JM. Advances in detecting and responding to threats from bioterrorism and emerging infectious disease. *Nat Med*. 2004;10(12)(suppl):S130-S136.

Web Sites

Centers for Disease Control and Prevention. Emergency Preparedness and Response: Bioterrorism. http://emergency.cdc.gov/bioterrorism/.

Centers for Disease Control and Prevention. Infection Control in Healthcare Settings. http://www.cdc.gov/ncidod/dhqp/.