CHAPTER 11

Emergency Preparedness: Identification and Management of Biological Exposures

COLLEEN M. TERRIFF, JASON E. BROUILLARD, LISA T. COSTANIGRO, AND JESSICA S. GRUBER

KEY CONCEPTS

1. Bioterrorism agents are organisms or toxins that can cause disease and death in humans, animals, or plants and elicit terror.
2. Category A bioterrorism agents include anthrax (*Bacillus anthracis*), tularemia (*Francisella tularensis*), smallpox (*variola major*), plague (*Yersinia pestis*), botulinum toxin (*Clostridium botulinum*), and viral hemorrhagic fevers.
3. Many bioterrorism agents cause symptoms similar to other more common infectious diseases, like seasonal influenza, and may be difficult to differentiate without confirmatory laboratory testing.
4. Anthrax is a highly virulent, lethal infection; human-to-human transmission, however, has not been documented.
5. Individuals with signs and symptoms of botulism should be administered a test dose prior to receiving equine antitoxin therapy.
6. Prompt initiation of appropriate empiric therapy, after cultures are obtained, is vital to decreasing the mortality rate associated with plague.
7. Emergency preparedness for those at risk and response efforts for those exposed to smallpox involves mass vaccination campaigns.
8. Viral hemorrhagic fever, caused by one of a variety of viruses, can manifest as a febrile illness with a large range of sequela, including bleeding complications.

The fall of 2001 forever changed how many people through out the world felt about flying, airport security, and even opening their mail. Terrorism, especially bioterrorism, became a common term used by the media, military analysts, both governments and public health officials, and the public at large. Anxiety caused by the 2001 intentional anthrax release through the United States mail system, and the ensuing exposures and deaths, was further escalated by numerous false alarms surrounding the delivery of parcels containing unidentified white powder.[1] Recent devastating natural disasters, such as tsunamis and hurricanes, have reawakened our appreciation of the power and destruction associated with natural disasters. Isolated reports during the past decade have heightened concern about a global outbreak of severe acute respiratory syndrome (SARS) or avian influenza and as a result many levels of the community, including schools, businesses, health systems, first responders, and governments, have begun to address the need for planning for public health emergencies. Stockpiling of antibiotics for bioterrorism attacks and antivirals for pandemic influenza is becoming a crucial public health issue. Healthcare providers need to play an active role in awareness and preparedness for biological threats released by terrorists or nature, and the decision-making process regarding postexposure prophylaxis (PEP), mass vaccination, and treatment of biologic exposures to help protect the public.

1 Bioterrorism agents—organisms or toxins that can cause disease and death in humans, animals or plants for the purpose of eliciting terror—have been used against civilians and military personnel for centuries. Thousands of years ago crude, but effective methods were used for bioterrorism. Filth, human cadavers, and animal carcasses were flung over city walls, poisons were dropped in drinking wells, and contaminated clothing and blankets were offered as gifts to cause disease and, ultimately, death to enemies. More recently, sophisticated methods have been utilized, such as aerosolized technology for spraying plague and an umbrella-looking device used to shoot ricin toxin pellets for a targeted assassination.[2,3] Over the past 80 years a variety of methods to weaponize biologic agents—enhance the shelf-life or dissemination properties (i.e., aerosolize) and/or fill munitions—have been researched.[3] Approximately 12 countries throughout the world are believed to have active biological weapons programs, ranging from conducting research on the virulence of selected agents to actually weaponizing them.[4]

This chapter describes the natural history, symptomatology, diagnostic procedures, pharmacologic and nonpharmacologic treatment of biological agents of highest concern that could be used in a bioterrorism attack, such as anthrax, botulinum toxin, plague, smallpox, tularemia, viral hemorrhagic fevers and select Category B and C agents. The potential consequences of infectious disease outbreaks surrounding natural disasters, which rival bioterrorist events in their devastating potential, are also discussed. An evidence-based approach evaluating the various treatment options, including those for special populations, is presented, when the relevant data is available. Finally, information about the roles of healthcare providers in emergency preparedness and response is shared.

GENERAL APPROACH TO THE EVALUATION OF RISK AND DEVELOPMENT OF PREVENTION STRATEGIES

2 In 2000, the Centers for Disease Control and Prevention (CDC) classified biologic agents into categories A, B, and C based on their ability to be easily disseminated or transmitted person-to-person;

TABLE 11-1 Priority Categorization of Threat Agents

- Category A
  - High mortality rate
  - Greatest potential for major public health and medical impact
  - Easily disseminated or transmitted from person to person
  - Might cause public panic and social disruption
  - Require special action for public health preparedness
- Category B
  - Moderately easy to disseminate
  - Result in moderate morbidity rates and low mortality
  - Lower medical and public health impact
- Category C
  - Emerging Infections
  - Could be engineered for mass dissemination in future because of
    - Availability
    - Ease of production and dissemination
    - Potential for high morbidity and mortality rates and major health impact

Adapted from reference 11.

cause high mortality, with the potential for major public health impact; cause public panic and social disruption; and require special action of public health preparedness[10] (Table 11–1). For example, anthrax is a category A agent because untreated inhalation anthrax has a very high mortality rate and cases would cause great stress on any medical community. *Yersinia pestis* (plague) and variola major (smallpox) are also examples of category A agents. *Brucella* species (brucellosis), ricin toxin, and *S. typhimurium* are classified as category B agents. Emerging pathogens such as SARS, and well-established infections like influenza, are grouped into category C (Table 11–2).

Bioterrorism agents most likely will be released as a covert or hidden attack, and delayed detection has great public health implications. Unless a terrorist group announces their intent, the exposure may go unnoticed. Victims may not present to a point within our healthcare system until symptoms are fulminant, days or weeks after exposure, well past the incubation period. Prolonged incubation periods and delays in diagnosis and starting PEP may allow a contagious agent like smallpox, influenza, or plague, to spread easily throughout the local and even global community, before the infection is identified.

Preparedness and response, focusing on preexposure vaccination, PEP and treatment, are key infection control measures where healthcare providers can make a significant impact. Preexposure vaccination is the administration of a protective vaccine to the public, military troops, or high-risk individuals prior to the potential exposure to an infectious disease. Mandatory childhood vaccinations against diphtheria, measles, tetanus and poliomyelitis, for example, and optional vaccination against seasonal influenza, have proven effective in protecting children and the general public.[13] Although there are some vaccines available for category A agents, the segment of the public who would qualify for preexposure inoculation is exceedingly small. For example, the United States Department of Defense has authorized mandatory anthrax vaccinations for only those military troops who will be serving in the high-risk countries of Afghanistan, Iraq, and South Korea.[14] Laboratory researchers studying tularemia, for exam-

TABLE 11-2 Category of Bioterrorism Threat Agents

- Category A
  - Anthrax *(Bacillus anthracis)*
  - Botulism *(Clostridium botulinum)*
  - Plague *(Yersinia pestis)*
  - Smallpox (variola major) and other related pox viruses
  - Tularemia *(Francisella tularensis)*
  - Viral hemorrhagic fevers
    - Arenaviruses
      - Lassa Fever
      - LCM, Junin virus, Machupo virus, Guanarito virus
    - Bunyaviruses
      - Hantaviruses
      - Rift Valley Fever
    - Flaviviruses
      - Dengue
    - Filoviruses
      - Ebola
      - Marburg
- Category B
  - Brucellosis *(Brucella species)*
  - Glanders *(Burkholderia mallei)*
  - Melioidosis *(Burkholderia pseudomallei)*
  - Psittacosis *(Chlamydia psittaci)*
  - Epsilon toxin of *Clostridium perfringens*
  - Q fever *(Coxiella burnetii)*
  - Ricin toxin from *Ricinus communis* (castor beans)
  - Typhus fever *(Rickettsia prowazekii)*
  - Staphylococcal enterotoxin B
  - Food & waterborne pathogens
    - Bacteria
      - *Campylobacter jejuni*
      - Diarrheagenic *Escherichia coli*
      - *Listeria monocytogenes*
      - *Salmonella typhimurium*
      - *Shigella* species
      - Pathogenic *Vibrios*
      - *Vibrio cholerae*
      - *Yersinia enterocolitica*
    - Viruses
      - Caliciviruses
      - Hepatitis A
    - Protozoa
      - *Cryptosporidium parvum*
      - *Cyclospora cayetanensis*
      - *Entamoeba histolytica*
      - *Giardia lamblia*
      - *Microsporidia*
      - *Toxoplasma*
  - West Nile virus
  - LaCrosse
  - California encephalitis
  - Venezuelan equine encephalitis virus (VEE)
  - Eastern equine encephalitis virus (EEE)
  - Western equine encephalitis virus (WEE)
  - Japanese Encephalitis virus
  - Kyasanur Forest virus
- Category C
  - Emerging infectious disease threats such as Nipah virus and additional hantaviruses.
  - Tickborne hemorrhagic fever viruses
    - Crimean-Congo Hemorrhagic Fever virus
  - Tickborne encephalitis viruses
  - Yellow fever
  - Multidrug resistant tuberculosis
  - Influenza
  - Other *Rickettsia* bacteria
  - Rabies
  - Prions
  - Chikungunya virus
  - Severe acute respiratory syndrome-associated coronavirus (SARS-CoV)
  - Antimicrobial resistance, excluding research on sexually transmitted organisms
  - Antimicrobial research, as related to engineered threats
  - Innate immunity, defined as the study of nonadaptive immune mechanisms that recognize, and respond to, microorganisms, microbial products, and antigens

Adapted from reference 12.

ple, may be administered a vaccine that is not otherwise available to the general public.

Vaccinating large numbers of people or the population of an entire region or country is an important method to curtail the spread of highly contagious agents, such as smallpox and pandemic influenza. Smallpox was successfully eradicated in 1977, a decade after mass vaccination campaigns commenced.[15] Global eradication of a vaccine-preventable disease is extremely challenging in part because of the rapidity of international travel, the growing world population and overcrowding in many urban areas, and the significant expansion of the numbers of immunocompromised individuals who now reside throughout the world.

On December 13, 2002, President Bush announced a smallpox preexposure plan for the United States. This policy to vaccinate not only military personnel, but civilians, against an eradicated virus, was controversial. Military personnel were to be vaccinated in the first stage, followed by a voluntary campaign, including tiers of smallpox response teams, consisting of public health staff and healthcare workers involved in initial care of smallpox patients. Finally, other healthcare workers and first responders were to be immunized. Vaccinating the general public was not recommended within the plan. This smallpox preexposure vaccination campaign stalled as a consequence of 120 cases of pericarditis, other vaccine-related reactions, issues about liability and compensation, and overall fear of side effects.[16,17] The risks outweighed the benefits, especially with the lack of a credible smallpox threat. Ultimately, only 1,071,000 military forces and healthcare workers were vaccinated.[16]

PEP involves dispensing or administering a medication (including a vaccine) to start immediately after exposure to a disease or organism, so as to prevent the disease from developing or spreading. For instance, after an anthrax-containing letter was delivered to and opened in the United States Hart Senate Office building in the fall of 2001, ciprofloxacin and doxycycline were dispensed to hundreds of congressional staff who had offices on the fifth and sixth floors of the southeast wing where the letter was discovered.[9] Some of the challenges surrounding PEP include assessing who was truly exposed to an organism or toxin, who is at high risk of acquiring the infection if it is spread person-to-person, and who is at risk of developing the disease and its sequelae. In most cases, because of the potential lethality of category A agents like anthrax, more individuals will be given PEP than is probably necessary. An important therapeutic concept surrounding prophylaxis involves prompt initiation of the regimen with the appropriate empiric antimicrobial.

3 Treatment for confirmed cases of a biologic agent exposure is challenging. People may not seek medical care until fulminant symptoms and signs are evident, which may thereby increase the likelihood of mortality. Based on limited case reports from zoonotic infections (non-bioterrorism related) in the latter half of the 20th century, if individuals with primary pneumonic plague did not receive treatment within 24 hours of exposure, the disease was rapidly and inevitably fatal.[18] Adults and children may present with nondescript symptoms that mimic common infections, such as community-acquired pneumonia or influenza. Treatment should not be delayed until the results of confirmatory laboratory tests become available days or weeks later. Suspected or confirmed cases require immediate treatment, including supportive care and empiric intravenous antimicrobial therapy, ideally within 24 hours, with conversion to oral regimens when appropriate.

Prior to the late 1990s only limited data and guidelines were available regarding the identification and management of bioterrorist exposures in civilians. Recommendations regarding special or vulnerable populations, such as women (pregnant or nursing), elderly, mentally ill, immunocompromised, neonates and children, were scarce. During 1999 to 2002, the Journal of the American Medical Association published a series of consensus papers on category A agents, which provided PEP and treatment recommendations for adults, children, and pregnant women.[18–23] However, there remains a lack of information regarding exposure management among other vulnerable groups.

BIOLOGIC AGENTS: CATEGORY A

ANTHRAX

The term *anthrax* is derived from the Greek word *anthrakis* meaning coal, because of the classic black eschar lesions caused by the cutaneous form of anthrax.[24] Anthrax was first described in the early biblical era of Moses and the fifth Egyptian plague in *Exodus* 9, and in the last three decades, numerous human cases have been reported. Poor veterinary vaccination programs in Zimbabwe lead to 6,500 human anthrax cases and 200 deaths in 1979 to 1980. An accidental exposure at a research center in what is now Ekateringburg, Russia, caused the death of 66 adults in 1979. In the fall of 2001, several envelopes containing anthrax were discovered in the United States, which led to 22 confirmed and suspected cases and 5 deaths.[24,25]

Etiology

B. anthracis is a gram-positive, spore-forming rod found endemically in the soil of many regions worldwide. Domesticated and wild herbivores (i.e., sheep, camels, elephants, horses, cattle, goats) commonly acquire anthrax; humans usually become infected through contact with infected animal tissue or, more recently, exposure as a result of an intentional release. One characteristic that separates anthrax from most other agents in category A is its ability to produce spores under adverse conditions. Endospores produced by the bacterium are resistant to most forms of sanitization and are thus capable of persisting for several years in contaminated environments; waiting for entry into the blood or tissue of an animal where they then germinate and cause disease.

Pathophysiology

4 Three clinical manifestations of anthrax exist: cutaneous (the most common, but least severe), inhalational (main bioterrorism concern), and gastrointestinal (very rare). Rare, but life-threatening neurologic complications, such as cerebral edema and hemorrhagic meningitis, are possible sequelae of all primary forms of anthrax infections.[26] Anthrax spores deposited into pulmonary alveoli may not germinate until taken up by alveoli macrophages and transported to regional lymph nodes. This may potentially take weeks or months, necessitating extended durations of antibiotic coverage. Replicating bacteria, once in a host, achieve their virulence via production of two main toxins, creatively named lethal toxin and edema toxin. Edema toxin, as its name implies, causes extensive systemic edema as the result of disruptions of electrolyte and water transport across cellular membranes, whereas lethal toxin is thought to be responsible for the tissue damage, shock, and high probability of death associated with infection.[26] Although anthrax is extremely virulent and pathogenic, there is no documented human-to-human transmission.

Clinical Presentation

Cutaneous Naturally occurring anthrax is nearly always attributable to cutaneous infection. Bacterium (acquired via handling of contaminated animal products) enters the body via abrasions on the skin and causes localized edema progressing to a small, pruritic papule 1 to 12 days after infection. Within 1 to 2 days, the papule enlarges to a round ulcer and then the characteristic painless, black eschar follows. One to 2 weeks after infection the eschar dries and sloughs away (Fig. 11–1). Subsequent lesions near the initial papule

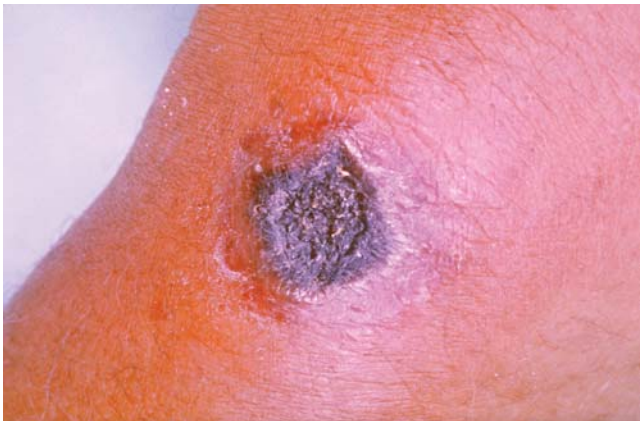

FIGURE 11-1. Lesion on forearm (eschar). *(Courtesy of the CDC and James H. Steele. "Anthrax lesion on the skin of the forearm caused by the bacterium Bacillus anthracis." CDC Public Health Image Library. http://phil.cdc.gov/phil/home.asp.)*

may occur. Once anthrax is suspected, a Gram stain of the vesicular fluid should yield gram-positive bacteria and, ideally, the stain is confirmed with culture.[11] Mortality rates from the cutaneous form are relatively low at approximately 5% to 20% in untreated cases and <1% in antibiotic-treated cases, with most deaths associated with disseminated disease or progression to sepsis.[26]

Gastrointestinal Acquiring the gastrointestinal form of anthrax is rare and usually occurs as a result of ingestion of contaminated meat. The incubation period is similar to the inhalation form and ranges from 1 to 7 days. Oropharyngeal ulcerations are common, along with sore throat and fever. Initially nausea, loss of appetite, and vomiting will predominate, transitioning into severe abdominal pain and bloody diarrhea after acute inflammation of the bowel. These typical symptoms often closely mimic other gastrointestinal maladies, making a definitive diagnosis difficult. Obtaining a thorough history and culturing ulcerations may be helpful. Mortality rates are higher, estimated at 25% to 60%, due to the difficulty in early diagnosis. Treatment protocols should involve antibiotics and surgical intervention of the affected intestine may be indicated.[13,26]

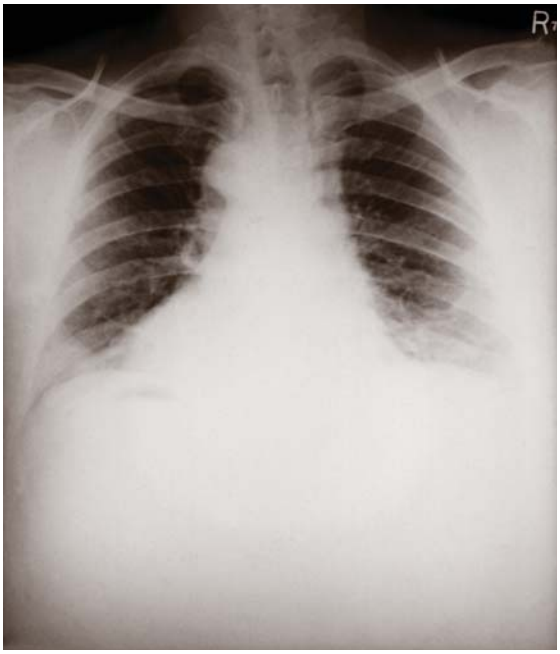

FIGURE 11-2. Anthrax chest radiograph. *(Courtesy of the CDC and Arthur E. Kaye. "This posteroanterior (PA) chest x-ray was taken 4 months after the onset of anthrax in a 46-year-old male, revealing bilateral pulmonary effusion, and a widened mediastinum, which are hallmarks of the disease process." CDC Public Health Image Library. http://phil.cdc.gov/phil/home.asp.)*

Inhalational Inhalational anthrax is the most likely form of infection encountered after intentional dispersal. The initial symptoms strongly resemble those of influenza infection; fever, nonproductive cough, myalgia, and fatigue after a short incubational period of 1 to 6 days (potentially extending out to 43 days because of endospores). One component of the prodrome not described before the bioterrorist attack in the United States in 2001 was the occurrence of profuse drenching sweat, which may prove beneficial in differentiating inhalation anthrax from viral illness. Chest radiographs often reveal mediastinal widening or pleural effusions, both hallmarks of anthrax exposure (Fig. 11–2). The CDC recommends obtaining the blood, pleural fluid, and cerebrospinal fluid, if available, for culture, Gram stain, and polymerase chain reaction (PCR). Sputum cultures are not recommended initially because of the lack of actual lung involvement. Without prompt antibiotic initiation, the mortality rate may be as high as 85% within 24 to 36 hours after symptom onset.[3] Prompt medical attention and initiation of antibiotic treatment is imperative; alarmingly, data from the outbreak in 2001 demonstrated that victims waited an average of 3.5 days to seek medical advice.[25] This lends high importance to the development of a strong clinical knowledge base regarding detection, diagnosis, and treatment.

PRESENTATION OF ANTHRAX

General

- Depending on route of exposure to anthrax, persons can present with some or all of the constellation of symptoms described below.

Signs and Symptoms

- Inhalational prodrome normally consists of fever, malaise, dry cough, and shortness of breath.
- Cutaneous forms produce the distinctive painless, black-crusted ulcer.
- Gastrointestinal anthrax is distinguished by abdominal pain, fever, and bloody diarrhea or emesis.
- Rhinorrhea is rarely reported with anthrax, thus assisting in differentiation from other influenza-like illnesses.
- Complaints of drenching sweats were reported in the 2001 anthrax outbreak in the United States.

Diagnostic Tests

- Standard, routine blood cultures before antibiotic administration
- Gram stain (from blood, cerebrospinal fluid, ulcer, pleural fluid)
- Confirmatory assays (PCR, enzyme-linked immunosorbent assay, or immunohistochemistry)
- Chest radiography will often demonstrate pleural effusions or mediastinal widening.
- Sputum cultures are rarely beneficial early in the course of inhalational cases.
- Leukocyte counts are normal or only mildly elevated.

TREATMENT

Anthrax

■ MANAGEMENT OF POTENTIAL EXPOSURE

Once a suspected or confirmed exposure case is known, identifying at-risk individuals becomes the highest priority. Persons with expo-

TABLE 11-3 Treatment and Prophylaxis for Anthrax *(Bacillus anthracis)*

Treatment (Symptomatic)	Postexposure Prophylaxis (Prevention)	Vaccination	Comments
Duration: 60 days **Life-threatening (inhalational, systemic or serious cutaneous)** **Adults**: Ciprofloxacin 400 mg IV q 12 h or Doxycycline 200 mg IV, then100 mg IV q 12 h or Levofloxacin 500–750 mg IV daily or Gatifloxacin 400 mg IV daily **Children**: Ciprofloxacin 10–15 mg/kg IV q 12 h (maximum 500 mg/dose) or Doxycycline IV (maximum 100 mg/dose): >8 years and >45 kg: 100 mg q 12 h >8 years and ≤45 kg: 2.2 mg/kg q 12 h ≤8 years: 2.2 mg/kg q 12 h plus 1–2 additional: ampicillin, chloramphenicol, clindamycin, imipenem, linezolid, meropenem, macrolide (erythro-/clarithro-/azithromycin), penicillin, rifampin, vancomycin **Supportive therapy**: (aggressive and early) for shock, fluid volume deficit, and adequacy of airway may be indicated.	**Duration**: minimum of 60 days after last exposure **Adults**: Ciprofloxacin 500 mg PO q 12 h or Doxycycline 100 mg PO q 12 h or Levofloxacin 500 mg PO daily or Gatifloxacin 400 mg PO daily **Children**: Ciprofloxacin 10–15 mg/kg PO q 12 h (maximum 500 mg/dose) or Doxycycline PO (maximum 100 mg/dose): >8 years and >45 kg: 100 mg q 12 h >8 years and ≤45 kg: 2.2 mg/kg q12h ≤8 years: 2.2 mg/kg q 12 h	**Preexposure prophylaxis**: BioThrax (Anthrax Vaccine Adsorbed) 0.5 mL SC at 0, 2, 4 weeks; 6, 12, 18 months with annual booster, as indicated **Postexposure prophylaxis**: BioThrax (Anthrax Vaccine Adsorbed) 0.5 mL SC at 0, 2, 4 weeks postexposure Vaccine is not readily available to general public and mass vaccination is not practical.	**Pregnancy and immunocompromised**: same recommendations **Cutaneous anthrax treatment (intentional release)**: Fluoroquinolone[a] or doxycycline for 60 days (10–14 days for contact with contaminated animal products) Modify antimicrobials (treatment and postexposure prophylaxis) as indicated by susceptibility testing Change from IV to PO when clinically appropriate Consultation with infectious disease specialist advised

[a]Fluoroquinolone: ciprofloxacin, levofloxacin, gatifloxacin.
From references 3, 19, and 28.

sure to an item or environment thought or known to be contaminated with *B. anthracis* should be offered antibiotic therapy, irrespective of laboratory test results. Nasal swabs can be used to help detect anthrax spores, but can not rule out exposure. Based on in vitro and animal data, the CDC has published treatment guidelines to assist healthcare professionals.[1,27] For PEP of inhalation anthrax (in adults, pregnant women, the immunocompromised, and children), oral doxycycline or ciprofloxacin is recommended as a first-line agent. Because spores may persist in lung tissue after aerosol exposure, antibiotic therapy must be continued for 60 days (Table 11–3).

CLINICAL CONTROVERSY

Some clinicians recommend fluoroquinolones as first-line agents in mass PEP after suspected or confirmed anthrax exposure. Others recommend doxycycline so as to prevent antimicrobial resistance development to fluoroquinolones.

Although no controlled studies using PEP after suspected cutaneous or gastrointestinal exposures exist, doxycycline, ciprofloxacin, penicillin, and amoxicillin all have reasonably predictable activity against *B. anthracis* and could be used for shorter durations (7 to 14 days).[13] Preexposure vaccination regimens are available, but are usually reserved for military personnel and select groups of people with potential exposure to anthrax. The vaccination schedule is laborious, requiring six injections over 18 months, in addition to annual boosters, and it is important to note that the vaccine itself is not without side effects. Data from various nonhuman studies show that vaccination alone is not protective postexposure and the Food and Drug Administration (FDA) has not approved a vaccination schedule for postexposure treatment, as of yet.[13]

TREATMENT OF CONFIRMED CASES

Intravenous doxycycline or ciprofloxacin are indicated for use in treatment of inhalation anthrax and gastrointestinal anthrax. In addition, one to two other antibiotics with documented activity against *B. anthracis* (see Table 11–3) should be added to the therapy. This combination should be continued for 60 days (conversion to oral antibiotics is recommended once the patient becomes clinically stable).[1] Treatment of cutaneous cases differs in that only one antibiotic (doxycycline or ciprofloxacin) is necessary and oral products may be used if cases do not include extensive edema or lesions of the head or neck. These clinically severe cases require intravenous antibiotics. Regardless of whether the cutaneous infection is deemed severe or not, the selected antibiotic should be continued for 60 days, just like treatment for inhalation or gastrointestinal anthrax. The extended duration is a result of the possibility of cutaneous infections being caused by intentional release and the potential inhalational exposure.[1] Those treated during the outbreak of 2001 all received combination therapy (at least 2 antibiotics with activity against *B. anthracis*) and their fatality rate of 45% was slightly lower than previous observations reported in the literature.[13,25] In addition to antibiotic therapy, aggressive supportive care should also be pursued. Drainage of pleural effusions, correction of electrolyte imbalances, and early mechanical ventilation all appear to positively affect survival rates.

SPECIAL POPULATIONS

Treatment options generally remain similar across population groups and scenarios. Conversion from ciprofloxacin or doxycycline to penicillin or amoxicillin is recommended when antibiotic susceptibilities are known because of potential adverse effects associated with tetracycline and fluoroquinolone use in children. Children 2 years old or younger should always be initially treated with intravenous antibiotics because of limited experience in this age group.[29] The risks and benefits of antibiotic administration need to be discussed with pregnant women exposed to anthrax as these medications are not normally recommended for these patients; rarely, however, do the risks of treatment exceed the risks associated with foregoing antibiotic treatment. Dosages do not necessarily need to be adjusted in the elderly population, but considerations with regard to renal function for all populations may be necessary (see Chap. 51).

BOTULINUM TOXIN

Botulinum toxin poses a major public health threat because of its ease of mass production and the potential for significant debilitation and destruction of human life. In 1995, Iraq admitted to producing 19,000 liters of concentrated toxin with the potential to kill more than the entire world's population by inhalation.[20] Missiles and bombs loaded with nearly 10,000 liters of the toxin were deployed; further details are unknown.[3] From local soils in Japan, the Aum Shinrikyo cult prepared botulinum toxin and aerosolized it at multiple sites in downtown Tokyo between 1990 and 1995. Mass dissemination can be carried out by aerosolization and from intentional contamination of food or water supplies. The estimated lethal inhalation dose is 0.70 to 0.90 mcg, whereas the lethal ingested dose is 70 mcg. Consequently, 1 g of crystalline toxin has the potential to kill more than 1 million people, making botulinum the most toxic substance known to humans.[3,20]

Etiology

Clostridium botulinum is an anaerobic, spore-forming, gram-positive bacillus. *Clostridium* spores are naturally found in soil, fresh water, and saltwater. The organism produces seven distinct botulinum neurotoxins, types A through G. Botulism is the syndrome that occurs after exposure to these toxins. Like *B. anthracis*, *Clostridium* spores are extremely hardy; yet, botulinum toxin itself is much less stable in the environment than the spores.[30] Foodborne botulism is the oldest recognized form acquired from ingesting ill-preserved foods such as canned goods. Likewise, infant botulism may be contracted from swallowing spores carried in dust particles or the soil. In addition to absorption through the gastrointestinal tract, botulinum toxin can be absorbed into the systemic circulation following cutaneous exposure from an open wound or as the result of an inhalation exposure. Botulinum is not contagious and human-to-human transmission has not been reported.[3,20]

Pathophysiology

C. botulinum toxins enter the bloodstream either through the mucosal surface, gastrointestinal tract and lung, or a wound. The neurotoxins are carried to nerve synapses and cause fatal neuroparalytic botulism by irreversibly inhibiting acetylcholine release across the neuromuscular junction causing progressive, flaccid paralysis often requiring mechanical ventilation.[3,20,31]

Clinical Presentation

Regardless of the transmission route, symptoms are similar. The incubation period depends on the size of the inoculum and the rate of absorption into systemic circulation. The onset of symptoms typically occurs within 12 to 36 hours, but may present after several weeks if the person was exposed to a small amount of the toxin.[3] A classic presentation begins with bilateral cranial nerve palsies, and progresses to paralysis, which can be prolonged, lasting weeks to months. The severity of the symptoms and rate of progression depend on the amount of toxin absorbed. Foodborne botulism is often preceded by gastrointestinal symptoms such as nausea, vomiting, diarrhea and abdominal cramps, but differs from gastroenteritis by the presence of autonomic and ocular findings. Inhalation botulinum, with few historical cases from which one can base a clinical picture, is anticipated to have a similar presentation as foodborne botulism.[30] The absences of fever and sensory changes with the presence of symmetrical neurologic findings are important characteristics to preclude other neuromuscular etiologies such as stroke, and paralytic shellfish poisoning. Diagnosis is made primarily on the basis of clinical presentation.[3,20,31]

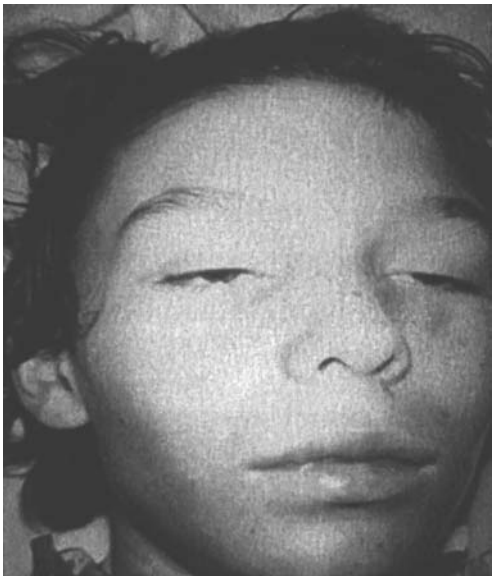

FIGURE 11-3. Botulinum facial weakness.

PRESENTATION OF BOTULISM

General

- Lethargy, acute respiratory distress, depending on the time between exposure and presentation.

Signs and Symptoms

- Weakness, blurred vision, dry mouth, diplopia, dyspnea, and dysphagia.
- Temperature will be normal or only mildly elevated.
- Symmetrical descending flaccid paralysis and bulbar palsies such as dysphagia, dysarthria, and facial nerve dysfunction are common (Fig. 11–3).
- Paralysis often continues to the limbs and thoracic muscles, resulting in respiratory failure.

Laboratory Tests

- Complete blood count is normal.
- Other laboratory tests, such as a cerebrospinal fluid sample and toxicology screening may be needed to rule out other neuromuscular etiologies.

Other Diagnostic Tests

- Confirmatory serum toxin identification is available through public health facilities but results typically require days to complete. Sample must be obtained prior to the administration of antitoxin.

TREATMENT

Botulism

The mainstays of therapy are supportive care, wound management, if applicable, and prompt administration of antitoxin. Respiratory function must be monitored closely, anticipating the need for mechanical ventilation. Timely administration of antitoxin, ideally within 24 hours after the onset of symptoms, may decrease disease severity and duration.[32] With the exception of BabyBIG, an intravenous human immune globulin, (indicated for the treatment of infant botulism), the majority of available antitoxins are derived from horse serum products. Consequently, the risk of serum

TABLE 11-4 Treatment and Prophylaxis for Botulism *(Clostridium botulinum)*

Treatment (Symptomatic)	Postexposure Prophylaxis (Prevention)	Vaccination	Comments
Type-specific antitoxin diluted and administered by slow IV infusion per product insert **Adults**: Equine antitoxins Dose: single 10-mL vial per patient Preparation: diluted 1:10 in 0.9% saline **Children ≥1 year**: refer to adults **Children <1 year**: Human-derived botulinum antitoxin (serotypes A, B), *BabyBIG* Dose: 50 mg/kg slow IV infusion. Preparation: dilute with 2 mL of sterile water for injection	None; antitoxin not recommended Observe and monitor Prompt treatment with antitoxin for first signs and symptoms	Pentavalent toxoid vaccine (A–E) for high-risk individuals; preexposure prophylaxis (investigational new drug)	Risk of anaphylaxis and serum sickness to equine antigens requires skin test Positive test requires desensitization before antitoxin administration Diphenhydramine and epinephrine should be readily available during administration for treatment of adverse reactions Information regarding skin testing, desensitization, preparation and administration available in product specific package insert

From references 3, 20, and 33.

sickness, anaphylaxis, and other infusion-related side effects are of concern. Antibiotics do not have a direct role for the treatment of botulism, but are indicated for the management of secondary bacterial infections. The use of aminoglycosides, clindamycin, tetracyclines, macrolides, and telithromycin are contraindicated because they may inhibit neuromuscular transmission and thereby exacerbate neuromuscular blockade. It is important to note that antitoxins are antigen toxin specific; for example, bivalent antitoxin (A and B) is not able to neutralize toxins C to G. Table 11–4 presents dosing information for antitoxins. Limited information is available for the treatment of special populations such as pediatric, pregnant, geriatric, and immunocompromised patients. Thus, standard treatment is recommended.[20] Isolation is not required as botulinum is not contagious.

Although antitoxins can provide passive immunity for PEP, this is not routinely recommended, because of the high risk of adverse reactions and a limited supply. For preexposure prophylaxis, a pentavalent toxoid vaccine (A, B, C, D, and E) is available as an investigational new drug (IND).[3,20,31] In addition to the toxoid vaccine, the CDC also can provide equine antitoxins (both IND monovalent antitoxins and an FDA-approved bivalent antitoxins) through their Vaccine and Antitoxin Program, which supplies product for regular foodborne outbreaks and large-scale disasters.[33] CDC also coordinates with the Pan-American Health Organization to provide antitoxins to other countries of the Western Hemisphere.[34] Canada maintains its own supply of antitoxin through the Botulism Reference Service for Canada and is available by contacting their Public Health Branch.[35] Other countries, such as Thailand, have received antitoxin from the World Health Organization in collaboration with the United Kingdom Department of Health.[36]

5 Use of antitoxins is associated with hypersensitivity reactions, including anaphylaxis and serum sickness. Prior to administration, skin testing is recommended with diphenhydramine and epinephrine readily available. Skin testing is performed by making two scratches or pricks on the patient's forearm. A drop of a 1:100 dilution of antitoxin in normal saline is applied to one scratch and normal saline is applied to the other scratch, which serves as a negative control. The application site is monitored for 20 minutes and is positive if a wheal at the site of antitoxin is more than 3 mm larger than the wheal on the negative control. Alternatively, a single dose of 0.02 mL of 1:1,000 dilution is administered intradermally to produce a raised wheal. If the test is negative, the intradermal application is repeated using a 1:100 dilution. Desensitization is required if antitoxin causes a positive skin test and is carried out by administering increasing serial dilutions of antitoxin intravenously every 15 minutes until 1 mL can be administered without a marked reaction.[37]

PLAGUE

The term *plague* evolved to describe the "Black Death" or pestilence that killed millions of people in Europe during the Middle Ages. The causative agent of Black Death was discovered to be *Yersinia pestis*, a zoonotic infection found in rodents and the fleas that infest them. This naturally occurring infection is transmitted to humans from bites of fleas harboring the bacteria, direct contact with infectious tissues or exudates, and, rarely, by respiratory droplets from an animal or human.[38] As a bioweapon plague may be aerosolized, a capability developed by both the United States and the former Soviet Union, effectively removing the flea as a vector. This agent is of particular concern, because if sprayed into a population or gathering of people, it could manifest as inhalation plague, a form of the disease that is highly lethal and contagious.

Etiology

Y. pestis is a gram-negative, non–spore-forming, coccobacilli in the Enterobacteriaceae family. Rat fleas maintain the zoonotic form of plague by infecting a variety of small mammals, including rats, ground squirrels, prairie dogs, and other rodents. Worldwide, excluding pandemics, there are 1,700 reported human cases a year. In the United States, plague is endemic in the Southwest and has caused approximately 400 cases during the period 1947 to 1996.[18] A few cases have been linked to domestic cats. Unlike anthrax, *Y. pestis* is less hardy and can be rendered nonviable when exposed to high temperatures, sunlight, and drying. Also, household disinfectants can kill this bacteria in a few minutes.[38]

Pathophysiology

Similar to anthrax and botulinum, plague can manifest in many different forms. Bubonic plague, the most common naturally occurring type, is a localized infection, named after the bubo or swollen, painful lymph node. Some patients bitten by fleas will not develop a bubo, but will suffer from primary septicemic plague, directly from overwhelming bacteremia. The resulting complications—sepsis, disseminated intravascular coagulopathy, multiorgan dysfunctions, secondary pneumonia and adult respiratory syndrome—are from an extensive immunologic cascade. The term *black death* describes gangrene of fingers, toes, and tips of the nose, which may occur during the advanced stages of sepsis (Fig. 11–4). Other bacteremia sequela include gastrointestinal plague, abscesses in liver or spleen, generalized lymphadenopathy, or plague meningitis.[38] Inhalation plague most likely leads to primary pneumonic plague, which has a high fatality rate, ranging from 57% (recent outbreaks) to 100% (untreated.)[3,18,38] A

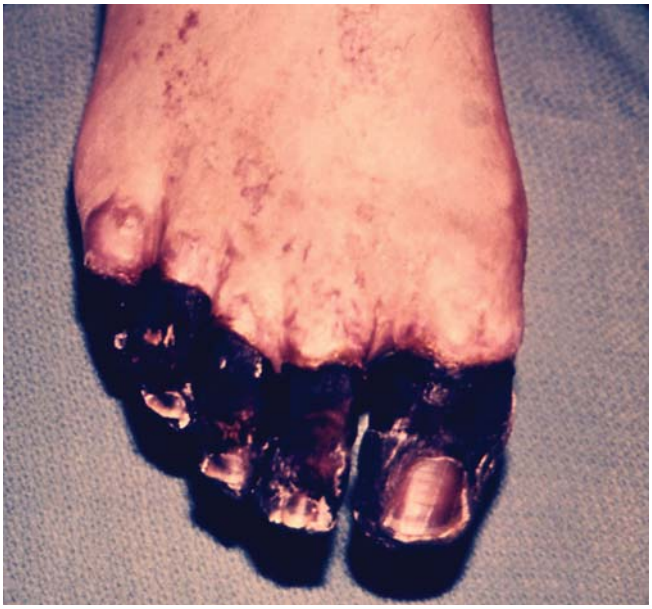

FIGURE 11-4. Necrotic toes from plague. *(Courtesy of the CDC and William Archibald. "This patient presented with symptoms of plague that included gangrene of the right foot causing necrosis of the toes. In this case, the presence of systemically disseminated plague bacteria* Y. pestis*, i.e., septicemia, predisposed this patient to abnormal coagulation within the blood vessels of his toes." CDC Public Health Image Library. http://phil.cdc.gov/phil/home.asp.)*

less-common manifestation of inhalation of *Y. pestis* is pharyngitis, as evidenced by swollen tonsils and inflamed lymph nodes.[38]

Clinical Presentation

After an incubation period of 1 to 6 days pneumonic plague causes a sudden onset of symptoms, similar to influenza or community-acquired bacterial pneumonia. Patient risk factors, such as travel history and exposure to rodents or fleas, should be assessed. Suspicion of a bioterrorist event should be raised when an outbreak of severe pneumonia occurs without a common source or prior rodent deaths in the area.[18,38] Death quickly follows, particularly if diagnosis and treatment are delayed.[18] Although limited data is available from epidemics occurring prior to the era of antibiotics, time from plague inhalation exposure to death is estimated at an average of 2 to 4 days, but can occur within 24 hours.[18,38,39]

PRESENTATION OF INHALATION PLAGUE

General

- Similar to severe community-acquired bacterial or influenza-like pneumonia.

Signs and Symptoms

- Sudden onset of fever, chills, headache, body aches, chest discomfort, and weakness.
- Productive cough, shortness of breath, hypoxia, and hemoptysis.
- Watery, frothy, blood-tinged, bloody, or purulent sputum.
- Gastrointestinal symptoms (nausea, vomiting, diarrhea, and abdominal pain) may be present.
- Chest radiograph may show segment or lobar infiltrates or consolidation, which may evolve bilaterally; cavitary lesions, pleurisy, or adult respiratory distress syndrome may be evident.

Laboratory Tests

- Gram stain and culture from affected tissue (i.e., lymph node, blood, cerebral spinal fluid, or sputum aspirate).
- Rapid and confirmatory diagnostic tests; limited availability.

TREATMENT

Plague

MANAGEMENT OF POTENTIAL EXPOSURE

PEP is crucial for plague, to not only prevent disease, but also to prevent its spread to others through coughing infectious droplets. Data elucidating which agent is best for prophylaxis is lacking in animals and limited to a few human case reports. Most of the oral antibiotics recommended for treatment are also reasonable for PEP (Table 11–5). Duration of prophylaxis is 7 days and should be started as soon as possible around the time of exposure.[3,18] If a person develops a fever and cough, treatment course for plague should commence.[3] Preexposure prophylaxis may be warranted for individuals traveling to endemic areas when exposure to vectors or pneumonic plague is unavoidable.[38]

In the past there were two types of vaccines available, but with variable activity against bubonic plague only, manufacturing was halted in 1999.[3,38] Currently, no vaccine is available to protect the public, but research is actively underway. There is no passive immunoglobulin for pre- or postexposure prophylaxis for plague.[3] While specimen cultures (i.e. blood or sputum) and sensitivity results are pending, treatment or PEP should be started promptly.

6 Most naturally occurring strains are susceptible to a variety of antibiotics, such as fluoroquinolones, aminoglycosides, and tetracyclines. However, a multidrug-resistant strain of *Y. pestis* was reported in a patient from Madagascar with bubonic plague.[40] Bioengineering of a resistant strain of *Y. pestis* by terrorists should not be ruled out.

TREATMENT OF CONFIRMED CASES

Although streptomycin is recommended for treating inhalation plague, most data is with the bubonic form and this drug has limited availability. Gentamicin is considered an acceptable alternative to streptomycin. Clinicians should monitor renal function and aminoglycoside levels while patients are on therapy. Doxycycline and fluoroquinolones are also considered options. Although doxycycline has an indication for both treatment and prophylaxis of plague, there are concerns with resistance in some *Y. pestis* strains and theoretical lower efficacy (based on animal data) when compared to fluoroquinolones, especially if therapy is delayed.[28] Fluoroquinolones like ciprofloxacin or levofloxacin only have in vitro and animal data showing activity against plague.[28] Like doxycycline, fluoroquinolones are available in injectable and oral dosage forms and usually require limited patient monitoring. Chloramphenicol is an option for plague, especially if meningitis has developed, yet should be avoided in children who are younger than 2 years of age.[18]

SPECIAL POPULATIONS

Pregnant women should be immediately started on gentamicin, the drug of choice for this vulnerable patient population.[18,38] Because of the lethality of this infection, if gentamicin is not available, doxycycline or fluoroquinolones are reasonable alternatives. Although clinicians have multiple therapeutic options to treat children, aminoglycosides are the preferred agent.[16,38] For all patients, therapy should continue for at least 10 days or until the patient is afebrile for 2 to 3 days, whichever is longer.[38] Management includes starting empiric treat-

TABLE 11-5 Treatment and Prophylaxis for Plague *(Yersinia pestis)*

Treatment (Symptomatic)	Postexposure Prophylaxis (Prevention)	Vaccination	Comments
Duration: 10 days or until afebrile for 2–3 days, whichever is longer **Plague pneumonia**: **Adults**: Streptomycin 15 mg/kg (maximum 1 g) IM q 12 h or Gentamicin 2 mg/kg load, 1.7 mg/kg IV/IM q 8 h (or 5 mg/kg once daily) or Ciprofloxacin, levofloxacin, gatifloxacin, or doxycycline IV (see doses under anthrax section) or Chloramphenicol 25 mg/kg IV q 6 h **Children**: Streptomycin 25 mg/kg IM q 12 h (maximum dose 2 g) or Gentamicin 2.5 mg/kg IV/IM q 8 h or Ciprofloxacin or doxycycline IV (see pediatric doses in anthrax table) or Chloramphenicol 25 mg/kg IV q 6 h **Plague meningitis**: **Adults**: Chloramphenicol IV 25 mg/kg load, then 12.5 mg/kg q 6 h **Children**: Chloramphenicol 25 mg/kg IV load, then 15 mg/kg q 6 h	**Duration**: 7 days after last exposure **Adults**: Ciprofloxacin 500 mg PO q 12 h or Doxycycline 100 mg PO q 12 h or Levofloxacin 500 mg PO daily or Gatifloxacin 400 mg PO daily Alternatives: Chloramphenicol 25 mg/kg PO q 6 h or Tetracycline 500 mg PO q 6 h **Children**: Ciprofloxacin 15–20 mg/kg PO q 12 h (maximum 500 mg/dose) or Doxycycline 2.2 mg/kg/day PO q 12 h (maximum 100 mg/dose) or Tetracycline 20–50 mg/kg/day PO q 6 h or Chloramphenicol 25 mg/kg PO q 6 h	Former vaccine no longer available New vaccine under development	Treatment with doxycycline may need longer duration of therapy (10–14 days) Adjust aminoglycoside dose for renal function; optimal dosing should be determined based on measured serum concentrations Chloramphenicol requires monitoring of serum concentrations and CBC (bone marrow suppression); use cautiously in children <2 years old

CBC, complete blood count; IM, intramuscular.
From references 3, 18, 28, and 40.

ment immediately, initiating supportive care measures, and adjusting antibiotics as appropriate, based on renal function and susceptibility patterns. Serum concentrations should be monitored with the goal of achieving concentrations similar to those proposed for the management of other gram-negative pneumonias.[3]

SMALLPOX

7 Smallpox, or variola major, is an acute, contagious, viral disease that has played a deadly role in the shape of global history. As humans are the only reservoir of the disease, a global smallpox vaccination campaign led by the World Health Organization in 1967 aimed to eradicate naturally occurring smallpox from the planet. The campaign was successful: the last case of endemic smallpox was reported in 1977, and the World Health Organization confirmed and certified the eradication of the smallpox virus in 1980. Because of increased concern about the potential use of smallpox as a weapon of bioterrorism, the United States government has increased smallpox vaccine stockpiles in the 21st century to provide enough doses to immunize the American public in the event of an outbreak, and initiated the development of smallpox healthcare teams that would respond to a smallpox emergency.[19,41]

Etiology

Smallpox is caused by the variola virus, which belongs to the orthopoxvirus family along with three other types of virus (vaccinia, cowpox, and monkeypox). There are two distinct types of variola, known as major and minor; variola minor is a significantly milder form of the disease and has a mortality rate of ≤1%, whereas variola major, which is the agent of concern in a smallpox outbreak, has a mortality rate of approximately 30% in adults and ≥40% in children younger than age 1 year.[13,42]

There are four principal clinical classifications of the lesions that occur in variola major: ordinary, modified, flat or malignant, and hemorrhagic. Ordinary type is the most common, responsible for ≥90% of smallpox cases. Modified type smallpox occurs in previously vaccinated persons and usually is a mild form of disease. Both hemorrhagic and flat or malignant type are rare, severe, and highly fatal (≥90%).[13] Smallpox sine eruptione (smallpox without rash) is an uncommon form of smallpox that can occur among vaccinated patients; this type must be confirmed by laboratory tests because of the lack of lesion development.

Pathophysiology

The pathophysiology of ordinary type smallpox, the most common form, is well documented. Smallpox is transmitted from person to person via respiratory droplets or direct personal contact with an infected person, including scabs, or by exposure to fomites, such as contaminated clothing or bed linens. The infectious dose is believed to be only a few virions, though the exact dose is unknown.[21] Once the virus has implanted in the respiratory tract mucosa, it travels to the lymph nodes, spleen, and bone marrow where it multiplies. The incubation period of the virus ranges from 7 to 17 days, during which the patient is asymptomatic. Around the twelfth day the infected cells lyse and virus is detectable in the bloodstream.

Clinical Presentation

The viral incubation period is followed by a prodrome stage (Table 11–6), typically lasting 2 to 4 days, during which the patient is usually sufficiently compromised that the patient cannot perform normal daily activities. The end of the prodrome stage is followed by the abrupt development of an enanthem, in the mouth, which manifests as very small red spots on the tongue and oropharyngeal mucosa.

TABLE 11-6 Differentiating Smallpox from Chickenpox

Presentation	Smallpox	Chickenpox
Prodrome	Severe, lasting 1–4 days with fever ≥38.3°C (101°F), headache, prostration, and other symptoms	Short and mild or no prodrome
Lesion development	All lesions are at the same stage of development and maturation throughout body	Lesions are at different stages of development
Lesion location	Centrifugal distribution with highest concentration on distal extremities and face; also on palms and soles of hands and feet	Higher concentration on the trunk; rarely occurs on palms or soles of hands or feet.
Lesion presentation	Pustules occur deep in the dermis and have a hard, bead-like texture and a well-circumscribed border; vesicles may show umbilication or become confluent	Lesions are superficial and rarely show umbilication or become confluent; border of lesions is less circumscribed

From reference 11.

Upon development of the enanthem, the patient is now infectious, as a consequence of the rapid growth and ulceration of the lesions in the mouth, which release large amounts of virus into the saliva. The patient remains most contagious during the first week of illness because of the high viral titers in the saliva at this time. A unique characteristic is that the skin lesions are all at the same stage of development, although they may vary in size (Fig. 11–5).[13]

In addition to scarring and death, there are various complications that can develop as a result of smallpox infection. Blindness may occur as a result of corneal damage and ulceration. Secondary bacterial and viral infections are not common, but may manifest as respiratory complications. Encephalitis or arthritis may occur, but chronic infection does not normally occur with variola virus.[21]

FIGURE 11-5. Smallpox rash. *(Courtesy of the CDC and James Hicks. "This photograph depicting a Bangladesh boy with smallpox, reveals the usual distribution pattern of the maculopapular rash." CDC Public Health Image Library: http://phil.cdc.gov/phil/home.asp.)*

Testing and sample collection from any individual suspected to have smallpox should only be done by vaccinated and properly trained personnel. Smallpox diagnosis can be confirmed using an electron microscope assessment of collected specimens. The varicella zoster virus test can be used to rule out varicella, while the Tzanck smear rules out varicella as well as herpes simplex virus. The CDC recommends taking digital pictures of the clinical presentation and using strict droplet and contact precautions, including facemasks.[41] All suspected and confirmed cases of smallpox should be reported immediately to state and local health departments.

TREATMENT

Smallpox

There is no treatment currently available for smallpox infection other than supportive care (Table 11–7). Pre- and postexposure prophylaxis can only be achieved by using the smallpox vaccine, which is derived from live vaccinia virus. Smallpox vaccination is not currently available to the public but is reserved in national stockpiles in the event of an outbreak. The smallpox vaccine, administered through multiple skin pricks over the deltoid or triceps muscle with a bifurcated needle (Fig. 11–6), provides effective immunity for 5 to 10 years after vaccination, with decreasing immunity thereafter. If a patient is revaccinated, immunity will increase and last longer. Vaccination within 3 days of exposure to the virus will completely prevent or significantly modify smallpox infection in most persons, and vaccination within 4 to 7 days after viral exposure will likely offer some protection or modify the severity of the infection. Smallpox vaccine doses that have been diluted by up to a 1:10 ratio are equally effective at providing immunity as full-strength doses.[13]

An estimated 250 of every 1 million persons vaccinated may develop a severe cutaneous reaction to vaccination.[41] Other potential but very rare complications of smallpox vaccination include vaccinia keratitis, eczema vaccinatum, fetal vaccinia, myopericarditis, postvaccinial encephalitis, and death.[41] Serious adverse reactions are more common in immunocompromised patients and those receiving primary smallpox vaccination compared to those being revaccinated. Vaccinia immune globulin intravenous is considered first-line treatment for severe vaccination complications. Vaccinia immune globulin intravenous is not effective for treatment of postvaccinial encephalitis or smallpox infection. Like the smallpox vaccine, it is stored in the Strategic National Stockpile.

■ SPECIAL POPULATIONS

The smallpox vaccine is a live vaccine that should be administered cautiously to immunocompromised patients, only when the benefit outweighs the risk (of developing vaccinia reaction) as determined by the healthcare practitioner. Ribavirin may be a possible treatment option for vaccinia reaction in immunocompromised patients. There is a case report of ribavirin being used in combination with vaccinia immune globulin to effectively treat a patient with acquired immunodeficiency syndrome who developed progressive vaccinia as a result of a smallpox vaccination. Ribavirin is considered an IND for the treatment of vaccinia.[21] Cidofovir has IND status for treatment of vaccine reaction and is a possible treatment alternative for smallpox. Some in vitro studies suggest that cidofovir may show efficacy in preventing smallpox infection if administered within 48 hours after exposure.[13,21] However, both drugs have limited usefulness because of their sparse availability and potential for serious side effects (renal toxicity with cidofovir; anemia with ribavirin).[21]

TABLE 11-7 Treatment and Prophylaxis for Smallpox *(Variola major)*

Treatment (Symptomatic)	Postexposure Prophylaxis (Prevention)	Vaccination	Comments
Supportive care	Commence mass vaccination. Vaccinia vaccine effective in preventing or ameliorating infection if given within 96 hours of exposure. Vaccinia immune globulin (VIG) 100 mg/kg (2 mL/kg) IV (within 3 days of exposure; best within 24 hours). Limited information with VIG ± vaccine for post-exposure.	Review contraindications and precautions prior to smallpox vaccination (refer to most recent ACIP recommendations). VIG is indicated for certain vaccine complications and vaccinia exposures in immunocompromised persons. VIGIM–IND VIGIV–licensed; pediatrics and elderly–IND	VIGIV infusion: 1 mL/kg/h for 30 minutes then 2 mL/kg/h for 30 minutes then 3 mL/kg/h for remainder. **Potential treatment options**: Cidofovir (IND): in vitro data only for use as a second-line treatment for complications of smallpox vaccination.

ACIP, Advisory Committee on Immunization Practices; IM, intramuscular; IND, investigational new drug.
From references 3 and 19.

CLINICAL CONTROVERSY

Preexposure smallpox vaccination is contraindicated in immunocompromised patients. However, because of the lethality and ease of spread of smallpox, clinicians may opt to commence vaccination of acquired immune deficiency syndrome (AIDS) patients, for example, during the start of a smallpox outbreak, well in advance of potential exposure.

TULAREMIA

Tularemia is caused by a small, gram-negative rod, named *Francisella tularensis* because it was first isolated in Tulare County, California, by Dr. Edward Francis who greatly contributed to the understanding of the bacteria through his research in the 1920s. This bacterium is nearly entirely confined to North America with only a single report from Europe.[43] Tularemia has long been investigated for use as a bioterrorism weapon. It was one of the many agents examined by Japanese germ warfare units in the 1930s and 1940s in Manchuria. The United States military developed weapons capable of disseminating *F. tularensis* aerosols in the 1950s and 1960s, and there are reports of intentional release during World War II.[22]

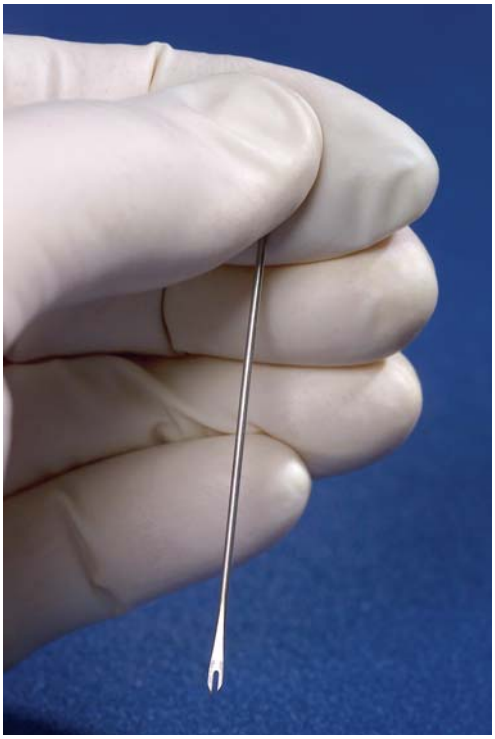

FIGURE 11-6. Bifurcated needle. *(Courtesy of the CDC and James Gathany. "The tip of a hand-held bifurcated needle used to vaccinate individuals with the smallpox vaccine. Vaccinia (smallpox) vaccine, derived from calf lymph, and currently licensed in the United States, is a lyophilized, live-virus preparation of infectious vaccinia virus. It does not contain smallpox (*variola*) virus." CDC Public Health Image Library: http://phil.cdc.gov/phil/home.asp.)*

Etiology

It is one of the most pathogenic bacteria known; as few as 10 organisms of bacteria are required to cause infection. Contact with small mammal hosts such as rabbits or exposure to contaminated environments is enough to contract infection.[22] Cases of tularemia are documented throughout the northern hemisphere, with at least one case reported in every state in the United States, except Hawaii.[43] Several pathways of transmission are possible, including direct contact with infected animals, inhalation or ingestion of contaminated water or dirt, or vector-borne infection via insects or ticks. A 1925 experiment famously described infection occurring by rubbing infected rabbit tissue on a person's arm.[44]

Pathophysiology

Clinical and pathogenic manifestations vary depending on the subspecies involved, but in general *F. tularensis* is an intracellular parasite and once inside its host will progress to regional lymph nodes. The major target organs after the lymph nodes include the lung, pleura, spleen, liver, and kidney.[22] Interestingly, it appears to intentionally avoid triggering an immune reaction while subverting the host's macrophages to help itself replicate.

Clinical Presentation

The incubation period varies widely from a few hours to as long as 2 to 3 weeks. After an average of 3 to 6 days, a sudden influenza-like, febrile illness develops, which can be similar to those observed after anthrax exposure. Fever, chills, muscle pains, headache, and dry cough are common, with various other manifestations occurring, depending on the pathway of infection. Ulcers at the site of cutaneous or mucous membrane contact, pharyngitis, ocular lesions, and pneumonia are also possible.[45] Early pulmonary radiologic findings may include infiltrates, pleural effusions and hilar lymphadenopathy. Although a study of volunteers showed incapacitation 1 to 2 days after aerosol exposure, untreated infections usually progress slowly, persisting for several weeks to months, with dissemination throughout the body and progression to sepsis possible.[46]

Because tularemia rarely affects humans in most areas, clinicians will likely possess a low index of suspicion when presented with this infection. *F. tularensis* is rarely cultured from blood samples, but cultures taken from sputum specimens or even pharyngeal washings remain the definitive means of confirming a suspected case. This

TABLE 11-8 Treatment and Prophylaxis for Tularemia *(Francisella tularensis)*

Treatment (Symptomatic)	Postexposure Prophylaxis (Prevention)	Vaccination
Duration: Streptomycin, gentamicin, or fluoroquinolone: 10–14 days Doxycycline or chloramphenicol: 14–21 days **Adults**: Streptomycin 1 g IM q 12 h or Gentamicin 5 mg/kg IV/IM daily or Ciprofloxacin, levofloxacin, or gatifloxacin IV daily (see doses in anthrax table); or doxycycline 100 mg IV q 12 h; or chloramphenicol 15 mg/kg IV q 6 h **Children**: Streptomycin 15 mg/kg IM q 12 h or Gentamicin 2.5 mg/kg IV/IM q 8 h or Ciprofloxacin or doxycycline IV (see doses in anthrax table) Chloramphenicol 15 mg/kg IV q 6 h	**Duration**: 14 days after last exposure **Adults**: Ciprofloxacin 500 mg PO q 12 h or Doxycycline 100 mg PO q 12 h or Levofloxacin 500 mg PO daily or Gatifloxacin 400 mg PO daily **Children**: Doxycycline 2.2 mg/kg PO q 12 h (maximum 100 mg/dose) or Ciprofloxacin 10–15 mg/kg PO q 12 h (maximum 500 mg/dose)	Vaccine no longer available New vaccine under development

IM, intramuscular; N/A, not applicable.
From references 3, 20, and 38.

bacterium grows best in cysteine-enriched broth, thioglycollate broth, buffered charcoal-yeast agar, or chocolate agar.[22] Direct fluorescent antibody examination or immunochemical stains of specimens should be performed promptly. *F. tularensis* can be differentiated from other microbes under light microscopy by its small size (0.2 micromolars × 0.2 to 0.7 micromolars), pleomorphic appearance, and its faint uptake of stain.[22] Mortality rates for tularemia in the pre-antibiotic era varied from 5% to 15% to upwards of 60% for those with untreated sepsis or severe pneumonia.[22] Mortality rates for *F. tularensis* infection are now less than 2%. As with most infectious processes, appropriate and prompt initiation of antibiotics are crucial. Supportive care measures (i.e., fluid resuscitation or mechanical ventilation) should also be addressed as necessary.

PRESENTATION OF TULAREMIA

General

- Sudden onset of an influenza-like illness.

Signs and Symptoms

- Fever chills, muscle pains, headache, and dry cough.
- Ulcers around mucous membranes.
- Untreated infections tend to progress slowly.

Diagnostic Tests

- Chest radiography may detect pulmonary infiltrates, pleural effusions, and hilar lymphadenopathy.
- Collect respiratory secretions and blood cultures before antibiotic administration.
- Differentiated on light microscopy by small size and pleomorphic appearance.
- Examination of secretions or exudates via direct fluorescent antibody or immunochemical stains.
- Growth in culture is the definitive confirmatory test (can be grown from sputum collections, pharyngeal washings, or even fasting gastric aspirate); normally visible after 24 to 48 hours
- Rarely cultured from blood samples.

TREATMENT

Tularemia

No vaccination is currently available to assist in treatment or prevention of tularemia infection. The CDC has published recommendations for treatment and for PEP. An aminoglycoside, streptomycin or gentamicin, is recommended as first-line agent for treatment of symptomatic infection, with doxycycline, ciprofloxacin, and chloramphenicol listed as alternative choices for adults, children, or pregnant women (Table 11–8 provides more detail). Aminoglycosides are generally favored in North America and tetracyclines are generally preferred in Europe as milder strains are encountered there. Tetracyclines possess bacteriostatic activity against *F. tularensis* and need to be given for at least 14 days to minimize the likelihood of a relapse.[22] In vitro data, animal data, and several case reports show that fluoroquinolones yield positive outcomes in children and adults.[28,47,48] Fluoroquinolones possess favorable pharmacodynamic properties since they achieve high concentrations in macrophages and exhibit bacteriocidal activity. Doxycycline or fluoroquinolones are easily transitioned to oral routes when appropriate. Randomized, controlled studies are not feasible in this setting, thus making it difficult to determine which antibiotic would be preferable in which situation. Although gentamicin, doxycycline, or ciprofloxacin all appear to be effective, third-generation cephalosporins, chloramphenicol, and potentially telithromycin also have demonstrated activity. Data is lacking for macrolides, clindamycin, and cotrimoxazole, and should, therefore, be avoided.[22,28,43] For PEP, the CDC and the literature support doxycycline or ciprofloxacin for 14 days (see Table 11–8 for more detail).

SPECIAL POPULATIONS

While the FDA has not approved fluoroquinolones for use in children, short courses are not associated with arthropathy.[22] Aminoglycosides given in short courses to pregnant women rarely pose risk to the unborn and benefits of treatment normally outweigh any potential risk. Using ciprofloxacin for PEP, however, is preferable to doxycycline in this group. Although adjustments for those persons with renal impairment should be made as appropriate, no specific recommendations exist for the elderly population.

VIRAL HEMORRHAGIC FEVERS

Viral hemorrhagic fever (VHF) encompasses illness caused by a diverse group of viruses that can be dispersed and transmitted by aerosolization, resulting in severe disease associated with a high mortality rate. Hemorrhagic fever viruses were mass produced by the former Soviet Union and reportedly have been weaponized by the United States, the former Soviet Union, and possibly North Korea.[23] Exposure to only a few aerosolized virions is required to cause infection, and depending on the virus, can lead to severe complications and death.[3,23]

Etiology

Hemorrhagic fever viruses comprise one of four distinct families of RNA viruses: Filoviridae, Arenaviridae, Bunyaviridae, and Flaviviridae. The Filoviridae family includes Ebola and Marburg viruses. Lassa and New World Arenaviridae viruses are associated with Argentine, Bolivian, and Venezuelan hemorrhagic fevers. The Bunyaviridae family includes Rift Valley fever and select viruses of the hantavirus genus. The Flaviviridae family consists of Yellow fever, Omsk hemorrhagic fever, and Kyasanur Forest disease.[3,49] These viruses primarily reside in animal reservoirs or arthropod vectors such as rodents, mosquitoes, and ticks. With the exception of Rift Valley fever and diseases from the Flaviviridae family, these viruses can be spread by human-to-human contact. Many human cases of infection resulted from contact with blood, bodily secretions, and direct physical contact with an infected patient.[3]

Pathophysiology

Transmission to humans has occurred through a variety of ways: bites from infected arthropods, direct contact with or aerosolized droplets from infected animals, and inhalation of dust particles tainted with rodent excreta. Infections result from direct contact, either close and personal or percutaneously with virus-laden blood and bodily fluids.[3,23] The use of improperly sterilized needles, syringes and exposure to infected blood and bodily fluids contributed to an epidemic of Ebola virus in healthcare settings.[50] Infections are characterized by fever and bleeding diathesis. The pathogenesis for infection is not completely understood. These viruses are theorized to inhibit platelet function, destroy platelets and endothelial cells, and indirectly reduce coagulation factors. Mortality rates range from 0.2% to 90%, depending on the etiologic virus.[3,23]

Clinical Presentation

8 Classical symptoms of VHF are fever and hemorrhagic diathesis; resulting in microvascular damage and increased permeability. The incubation period ranges from 2 to 21 days. Prodromal symptoms such as fever, headache, and fatigue lasting less than 1 week have been reported, followed by nonspecific symptoms including fever, hypotension, and bradycardia. Progressive hemorrhaging ensues, resulting in petechiae, conjunctival hemorrhage, and potentially disseminated intravascular coagulation (see Fig. 11–7). Symptoms are often accompanied by renal insufficiency, neurologic changes, pulmonary compromise, and hematopoietic dysfunction. Hepatic impairment, consumptive coagulopathy, and damage to megakaryocytes may also contribute to other coagulopathies. Not all patients develop classic VHF symptoms, which may depend on specific host factors and viral strain.[3] Laboratory abnormalities include leukopenia, anemia, thrombocytopenia, and elevated aminotransferases. VHF should be suspected based on risk factors including travel history, sick contacts, and exposure to vectors. Multiple cases lacking these characteristics could potentially indicate a bioterrorism event. Diagnosis is confirmed by antigen detection or real-time PCR performed at specialized laboratories.[3,23]

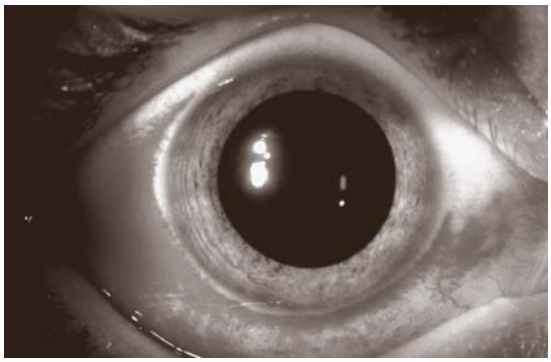

FIGURE 11-7. Viral hemorrhagic fever hemorrhagic conjunctiva.

PRESENTATION OF VIRAL HEMORRHAGIC FEVER

General

- Acute distress with various bleeding manifestations.

Signs and Symptoms

- Fever, often accompanied by myalgia, malaise, and abdominal pain.
- Signs of bleeding from a variety of sites such as mucous membranes and bloody diarrhea (Fig. 11–7).
- Maculopapular rash and jaundice may be found depending on the etiologic virus.

Laboratory Tests

- Thrombocytopenia is common, and may be profound (<10,000 cells/mm^3).
- Leukopenia or leukocytosis may occur.
- As infection progresses, evidence of disseminated intravascular coagulation may be found (i.e. prolonged bleeding time, elevated fibrin degradation products, decreased fibrinogen).
- Hepatic enzymes, amylase may be increased in infections caused by Marburg, Lassa, and Rift Valley viruses. Bilirubin also increases in Rift Valley virus.

Other Diagnostic Tests

- Real-time PCR to identify the causative virus can be performed at specialized laboratories.

TREATMENT

Viral Hemorrhagic Fever

Regardless of specific etiologic virus, the mainstay of treatment is supportive care. Aggressive fluid resuscitation and vasopressor support is often required because of capillary leak syndrome. Bleeding diathesis should be managed as a coagulopathy. Intramuscular injections and the use of aspirin, nonsteroidal antiinflammatory agents, and anticoagulants are contraindicated.[23] Antivirals specific for these viruses are not approved by the FDA, but a limited supply of intravenous ribavirin is available for compassionate use under an IND.[3] In the case of a massive biologic attack, oral ribavirin may be administered. Ribavirin displays in vitro and in vivo activity against Arenaviridae and Bunyaviridae family viruses, but has poor cerebrospinal fluid penetration and is inactive against Filoviridae or Flaviviridae family viruses.[3,23] Treatment should begin within the first 4 days of symptom onset. Small trials using ribavirin within 4 days of symptoms demonstrate a reduction in mortality for patients with Lassa fever and New World hemorrhagic fever (Table 11–9).[23] Healthcare providers should use strict barrier precautions when caring for patients as transmission is possible through contact with blood or bodily fluids, including vomitus, urine and stool.[23,51]

SPECIAL POPULATIONS

Limited data is available for the treatment of VHF in special populations. Ribavirin is pregnancy category X and therefore its use in humans is contraindicated because of teratogenic effects observed in animals at approximately 0.01 times the maximum recommended dose in humans. However, an increased risk of mortality is associated in this patient population and the benefits of treating VHF likely

TABLE 11-9 Treatment and Prophylaxis for Viral Hemorrhagic Fevers

Treatment (Symptomatic)	Postexposure Prophylaxis (Prevention)	Vaccination	Comments
Duration and route of therapy: IV: treatment of contained casualties, for 6 days Orally: treatment of mass casualties,[a] for 10 days **Arena-[b] or Bunyaviruses[c]:** **Adults** Ribavirin IV (IND): 30 mg/kg (maximum 2 g) load, then 16 mg/kg IV (maximum 1 g/dose) q 6 h × 4 days, then 8 mg/kg (max. 500 mg/dose) q 8 h × 6 days Ribavirin po: 2,000 mg load, then if >75 kg: 600 mg twice daily if ≤75 kg: 1,000 mg daily (400 mg in AM and 600 mg in PM) **Children** Ribavirin IV: same weight-based dosing as adults Ribavirin po: 30 mg/kg load, then 7.5 mg/kg twice daily **Filo-[d] and Flaviviruses[e]:** Supportive care	**High risk contacts (Arena-[a] or Bunyavirus[b]):** Observe/monitor for signs and symptoms of illness for 21 days after exposure; if fever >38.8°C (101°F) treat with ribavirin	Yellow fever vaccine only VHF vaccine available. Not recommended for infants <6 months, and if possible, wait until infant is ≥9 months. Not recommended for pregnant and immunocompromised patients.	Ribavirin does not have activity against Filo-[d] and Flaviviruses[e]; empiric treatment may be appropriate before identification of virus Ribavirin: pregnancy category X Ribavirin may have activity against West Nile virus **Supportive care:** fluids (monitor for pulmonary edema), vasopressors, APAP (for fever) **Supportive care:** IM injections, NSAIDs/ASA, and anticoagulants

APAP, acetaminophen; ASA, aspirin; IM, intramuscular; IND, investigational new drug; NSAIDs, nonsteroidal antiinflammatory drugs; VHF, viral hemorrhagic fever.
[a]Mass casualty defined as threshold number of cases that exhaust supply of ribavirin IV and IV treatment would not be possible.
[b]Arenaviruses: Lassa fever, Machupo, Junin, Guanarito, Sabia.
[c]Bunyaviruses: Rift Valley fever, Congo-Crimean hemorrhagic fever, hantaviruses.
[d]Filoviruses: Ebola, Marburg.
[e]Flaviviruses: Yellow fever, Dengue, Omsk hemorrhagic fever, Kyasansur Forest disease, West Nile virus.
From references 3 and 23.

outweigh the risks to the fetus. The recommended dose is the same as for adults. For pediatric patients, only the inhaled dosage form of ribavirin is approved for the treatment of respiratory syncytial viral infections. Although oral and intravenous ribavirin is not approved, treatment of VHF with either of these dosage forms is recommended. A pediatric syrup formulation is available under an IND.[3,23]

PEP is limited by the absence of clinical data and pharmacologic agents with activity against these viruses. With the exception of yellow fever, licensed vaccines are not available. Persons who have had close personal contact, mucous membrane or percutaneous exposure to bodily fluids of an infected individual should be under medical surveillance for 21 days after the potential exposure. If a temperature of 38.3°C (101°F) or greater develops, and a Filoviridae or Flaviviridae virus is not the causative pathogen, prompt initiation of ribavirin for presumptive VHF is indicated. Because the clinical usefulness of ribavirin in asymptomatic patient is unknown, preexposure therapy is not recommended.[23]

CATEGORY B AGENTS

This category serves as a catch-all for those agents not virulent or researched enough to meet Category A standards; but they still warrant more attention than those listed in Category C. Key agents in this category are briefly discussed to familiarize clinicians with their presentation, transmission, and treatment. Therapeutic recommendations refer to adults because of limited or no data in special populations. However, it is reasonable to extrapolate pediatric and pregnancy guidelines from category A agents to those mentioned hereafter because of the high morbidity that may occur in exposed individuals.

BRUCELLA

Among the most common zoonotic infections encountered, *Brucella*, a gram-negative coccobacillus has begun to emerge in prominence as global trade and travel increases. While it possesses attractive transmission characteristics via inhalational routes, its low mortality and broad antibiotic susceptibility patterns limit its overall effectiveness as a biologic weapon. Several species exist, the two most notable being *Brucella melitensis*, which is associated with most human disease, and *Brucella suis* which was reportedly weaponized more than 50 years ago by various governments.[52] A significant disease in animal populations, brucellosis primarily affects the reproductive system, causing infertility or abortion of existing animal pregnancies. Transmission occurs when animals or humans come in contact with contaminated tissues or fluids, such as consumption of raw milk or other animal products, as well as inhalation of contaminated soil particles.[3] Normally presenting as a nonspecific febrile illness, it becomes very difficult to accurately diagnose when incubation periods range from 3 days to several months. General malaise, chills, and backaches normally accompany the underlying intermittent fever and gastrointestinal distress (i.e., abdominal pain, constipation, vomiting, etc.) which occur in nearly 70% of adult cases.[3] Treatment normally includes doxycycline 100 mg orally twice daily with rifampin 600 to 1,200 mg orally daily for 6 weeks or doxycycline 100 mg orally twice daily for 6 weeks with streptomycin 15 mg/kg IV daily for 2 to 3 weeks.[53] The latter regimen is thought to be superior, but streptomycin requires parenteral administration and has limited availability.[54] Fluoroquinolones also exhibit in vitro activity and are generally considered adequate for treatment.[55] Monotherapy with fluoroquinolones yields unacceptable relapse rates and therefore should only be used in combination with one of the other agents discussed earlier.[56]

Q FEVER

Coxiella burnetti, the causative agent for Q fever, is an obligate intracellular gram-negative bacterium. It is an occupational hazard of those who work with animals that commonly acquire the bacterium (cattle, sheep, and to a lesser extent, goats). It can be aerosolized in large quantities, but possess an extremely low mortality rate, lessening

its significance as a bioterrorism threat. Clinical manifestations occur 10 to 21 days after exposure and usually mimic those of flu-like illness or atypical pneumonias. Complications are rare and normally self-limiting, but a chronic fatigue like syndrome has been documented.[52]

CLINICAL CONTROVERSY

Persons exposed to *C. burnetti* do not necessarily require antibiotic therapy because of the self-limiting nature of the disease and low mortality rate. However, some clinicians advocate always treating exposures to prevent potential sequelae of hepatitis, endocarditis, and granulomatous.

Treatment, if necessary, involves abbreviated courses of doxycycline 100 mg IV twice daily (7 to 10 days, transitioning to oral regimens when appropriate) or alternative agents like ciprofloxacin, erythromycin, cotrimoxazole, or rifampin.[52,58]

RICIN

Ricin toxin, a derivative of the castor bean plant *Ricinus communis*, exhibits its deleterious effects via inhibition of protein synthesis, leading to cellular death. Diagnosis of those poisoned is difficult because of the lack of blood or other fluid detection techniques. Ricin possesses many of the qualities suitable for a bioterrorism weapon, namely: stable aerosolized form, relative ease of production and procurement, and no known antitoxins presently available. Animal data from mice and monkeys indicate that aerosol exposure leads rapidly to death as the result of alveolar flooding and other respiratory complications.[52] Isolated case reports taken from the literature show various symptoms, including allergic-type reactions and gastrointestinal sequela. Fever, chest tightness, arthralgia, and cough present within 4 to 8 hours of inhalational exposure; pulmonary edema from alveolar flooding, and severe respiratory distress, may ensue and hypoxemia and death often occur within 18 to 72 hours.[3] Treatment centers on supportive care for pulmonary edema and respiratory distress, although activated charcoal may be beneficial in gastrointestinal ingestion cases. Doxycycline 100 mg IV or orally twice daily (7 to 15 days) is the standard antibiotic treatment in persons thought to be afflicted.[59] Chloramphenicol 2 g IV divided four times daily is also an acceptable alternative.[59] Numerous antitoxins are currently in development, but none are available.[60]

CATEGORY C AGENTS

Category C Agents do not require the same degree of public health preparedness as category A and B agents, yet have the potential to cause similar degrees of morbidity and mortality. Category C agents are emerging pathogens that could be engineered for bioterrorism, but are currently more difficult to disseminate.[11] Examples include the Nipah virus, selected hantaviruses, tickborne hemorrhagic virus, tickborne encephalitis virus, multidrug-resistant tuberculosis, influenza, and severe acute respiratory syndrome.[12] Epidemics in humans occur periodically, as evidenced by the recent emergence of SARS and avian influenza in the 21st century. The following section discusses SARS.

SEVERE ACUTE RESPIRATORY SYNDROME

SARS is a viral respiratory illness caused by a previously unrecognized human coronavirus known as SARS-associated coronavirus. SARS-associated coronavirus first appeared in southern China in November 2002, and developed into a global threat in March 2003. The virus jumped from animals to humans and spread from China to 29 countries within 90 days.[3] The disease has a case-fatality rate of approximately 10%, which may increase to more than 50% in patients older than 60 years of age. By the time the threat was contained in July 2003, more than 8,000 cases had been reported, numerous countries had been affected, and 774 deaths had occurred as a consequence of SARS infection.[61] SARS-associated coronavirus is a potential agent for bioterrorism because of the ease and quickness of spread and short incubation period.

Etiology and Pathogenesis

Limited information is available about this newly discovered virus, possible human or animal reservoirs, and how this lethal virus causes disease in humans.

Clinical Presentation

SARS is transmitted person-to-person by respiratory droplets or close personal contact. The median incubation period is 4 to 6 days; symptoms have been reported as early as 2 and as late as 13 days after exposure. Early signs and symptoms are nonspecific, flu-like in nature, and cannot be distinguished from the early clinical presentation of other viral illnesses. Atypical pneumonia develops in most patients by day 7 to 10. Rhinorrhea, sore throat, and other upper respiratory symptoms may occur but are not as common in SARS infection.[61] Clinicians should obtain a complete travel history from patients in whom they suspect a potential SARS infection.

PRESENTATION OF SEVERE ACUTE RESPIRATORY SYNDROME

General

- Nonspecific, flu-like symptoms initially, then progressing to an atypical pneumonia.

Signs and Symptoms

- Headache, myalgia, fever >38°C (100.4°F)
- GI symptoms (i.e., diarrhea) occur in 10% to 20% of patients.
- Patients experience nonproductive cough and dyspnea (by days 2 to 7).
- Lymphopenia may develop (70% to 90% of cases).

Laboratory and Diagnostic Tests

- Chest radiography shows an atypical pneumonia.
- A variety of respiratory specimens (i.e., nasopharyngeal swab or wash, tracheal aspirate, sputum) should be collected.
- Consult with health department for appropriate testing information.
- Research is ongoing for a rapid-screening SARS test.

TREATMENT

Severe Acute Respiratory Syndrome

SARS vaccines are currently being developed and tested in the United States and China.[62,63] Social distancing, vigilant hand hygiene, and N95 masks were used by healthcare workers and the public during the global outbreak in 2003 to reduce exposure to infection. There is no current effective treatment for SARS. Supportive treatment such as mechanical ventilation may be beneficial. Results have been inconclusive for all treatments tried and studied to date, including ribavirin, lopinavir/ritonavir, corticosteroids, interferon-α, intravenous immunoglobulin, and convalescent plasma. Ribavirin studies have shown

possible harm. Lack of consistent treatment regimens and control groups are confounding factors in evaluating treatment results.[64]

In 2004, an outbreak of SARS occurred in a Chinese virology lab among four lab workers who were handling inactivated SARS virus that appears to not have been fully inactivated. Although the outbreak was successfully contained and limited to the laboratory workers, this event raised global concern about laboratory biosafety and outbreak control measures.[65] Vigilant hand and respiratory hygiene, droplet precautions, and proper disposal of contaminated materials should be performed with any patient who is suspected of SARS infection. Healthcare providers should report to the state or local health department any suspected case of SARS.[61]

SPECIAL POPULATIONS

Elderly patients infected with SARS may lack respiratory signs on clinical examination and their mortality rate increases significantly from 10% to 50%. During the 2003 SARS outbreak, children and infants accounted for only a small percentage of SARS cases, developed milder disease, and had better outcomes than adults; consequently, the role of children in transmission is considered to be less significant than the role of adults.[61]

INFECTIOUS DISEASE RELATED TO NATURAL DISASTERS

Mother Nature could be considered our most menacing bioterrorist.[66] Natural disasters have unleashed formidable foes throughout the centuries including: pathogenic viruses, smallpox and pandemic influenza; lethal bacteria, such as *Y. pestis*, multidrug-resistant tuberculosis, staphylococcus, *Escherichia coli*, and a variety of disease-causing parasites, yeast, and molds. Many of these microbes were discussed in previous sections of this chapter. Infectious disease outbreaks following natural disasters, like bioterror agent exposures, can cause panic, social unrest and tax any country's medical and public health system.

Natural disasters, such as earthquakes, hurricanes, tsunamis, and drought, are catastrophic events. Mortality associated with these events is usually caused by drowning, crush-related injury, and blunt trauma. Morbidity may include, but is not limited to, anxiety and stress-related conditions, and population displacement. Communicable disease, related directly to outbreaks from large number of deceased, is not common, and may be limited to a few situations. Table 11–10 gives examples of communicable diseases associated with displaced populations that should be an integral part of postdisaster patient assessment.[67] Healthcare providers responding to a disaster should focus on preventing illness and injury, ensuring food and water safety, and recreating medical records. In addition, care should be directed toward patients with special needs, such as children, pregnant women, people with disabilities, mental illness, chronic medical conditions (especially the provision of continuing maintenance medications).[68] A prime example of illness prevention is the administration of immunizations, both to the displaced population and the healthcare providers traveling to the affected area(s). The CDC has vaccination recommendations appropriate for disaster response.[68]

HEALTHCARE PROVIDERS IN EMERGENCY PREPAREDNESS

The CDC has described five main areas of preparedness and response to acts of biologic terrorism: preparedness and prevention; detection and surveillance; diagnosis and characterization of agents; response; and communication.[10] Healthcare providers play an integral role in many of these general categories. Diagnosis and characterization of agents involved and securing therapeutic options for some of the main bioterrorist threats are critical. The leadership and administrative role and responsibilities of healthcare professionals during a biologic emergency are also paramount.

A variety of providers may be asked to assist with triage/screening, obtaining medical resources, administration of vaccinations, dispensing postexposure prophylaxis, acute treatment and maintaining chronic medications, and monitoring for side effects of medications and vaccinations during a disaster response. Healthcare providers are key to accurate and timely communication, notifying appropriate authorities of potential bioterrorism case or cases, sending samples and receiving diagnostic test results, and educating the public. Table 11–11 elaborates on the specific areas of planning, education, response, and volunteer opportunities.

TABLE 11-10 Natural Disaster Epidemics

Categories of Disease	Organism(s)/Condition	Comments
Water related	*Vibrio cholerae* *Escherichia coli* Norovirus Salmonella Cryptosporidium Hepatitis A and E Leptospirosis	Contaminated drinking water or a lack of access to safe water and sanitation
Associated with crowding	Measles *Neisseria meningitidis* Acute respiratory infections	Facilitated transmission
Vector borne	Malaria Dengue	Affected breeding sites and disease transmission
Power outages	Diarrhea	Disruption of refrigeration
Others	Tetanus (*Clostridium tetani*) Coccidioidomycosis	Disturbed earth/soil

From Watson et al.[67]

CONCLUSIONS

Although healthcare providers care for millions of patients with diabetes, heart disease, and a variety of common infectious diseases every year, they need to understand and prepare for scenarios that are sometimes unthinkable, unpredictable, and daunting. Biologic

TABLE 11-11 Role of Healthcare Providers for Emergency Preparedness and Response

Planning
- Join health systems or community disaster/emergency response planning committees
- Help write disaster plans
- Research availability of antitoxins, vaccines, and antimicrobials
- Develop treatment and prophylaxis algorithms for first responders and healthcare providers
- Assist with local and regional stockpiling decisions

Education
- Understand emergency management and role of healthcare providers
- Enhance knowledge of healthcare providers and public about potential acts of terrorism and disasters

Response
- Supervise technicians, students, interns, residents
- Select appropriate preexposure, postexposure, and treatment regimens
- Encourage adherence to regimens
- Advocate for diagnostic tests, cultures, and sensitivities, when appropriate
- Assist with screening, triage, drug information, administration of vaccines, dispensing medications, patient education, monitoring side effects
- Join community assistance and emergency response teams

exposures from bioterrorism attack or natural disasters may occur with devastating consequences. However, through education and recognition, treatment and infection control, healthcare providers will be an integral member of response capabilities and could lessen the impact from biologic exposures on national or global public health.

ABBREVIATIONS

CDC: Centers for Disease Control and Prevention

FDA: Food and Drug Administration

IM: intramuscular

IND: investigational new drug

IV: intravenous

PCR: polymerase chain reaction

PEP: post exposure prophylaxis

SARS: severe acute respiratory syndrome

VHF: viral hemorrhagic fever

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