INTRODUCTION

It has been more than a decade since the fall of 2001, a tragic time which awakened the American public to concerns about terrorism, previously only considered a threat by the military. While anxiety surrounding intentional bioterrorism attacks and the multitude of false alarms may have lessened, recent devastating natural disasters, such as tsunamis and hurricanes, have enhanced our appreciation of the power and destruction associated with Mother Nature. In addition, infectious disease outbreaks, such as the 2009 H1N1 influenza pandemic that caused an estimated 43 to 89 million cases of the flu in the United States and the 2012 pertussis epidemic in Washington State, impacting thousands of infants and children, will continue to occur.1,2

Emergency managers, healthcare providers, first responders, public health officials, businesses, schools, and community organizations must continually update their disaster and emergency response plans. It is important to be aware of and anticipate which resources are or will be needed and which are available, locally, regionally, and nationally. In particular, healthcare providers need to play an active role in community preparedness for biological threats. They also should be involved in the decision-making process regarding small-scale or mass vaccination or post exposure prophylaxis (PEP), and treatment of biologic exposures to help protect the public and save lives. For example, in late April of 2009 the Centers for Disease Control and Prevention’s (CDC) Division of the Strategic National Stockpile (SNS) released antiviral drugs, respiratory protection devices, and personal protective equipment, to help bolster local stockpiles which were quickly being depleted during the early phase of an influenza pandemic.3 Vaccine development and distribution, as well as execution of immunization campaigns for recommended targeted groups, was tasked to health departments, many of which actively sought recommendations and assistance from local healthcare providers and organizations. In Spokane, Washington, in response to the H1N1 pandemic more than 3,500 vaccinations were administered “at clinics held at the local sporting arena, YMCAs, and area homeless shelters” staffed predominantly by pharmacy and nursing students and faculty.4

Bioterrorism agents—organisms or toxins that can cause disease and death in humans and animals and thus elicit terror—have been used against civilians and military personnel for centuries. Thousands of years ago effective, albeit crude, methods were used as acts of bioterrorism. Filth, human cadavers, and animal carcasses were flung over city walls, poisons were dropped in wells, and contaminated clothing and blankets were offered as gifts to cause disease and, ultimately, death to enemies.5 More recently, sophisticated methods have been used, such as aerosolized technology for spraying plague and an umbrella-looking device used to shoot ricin toxin pellets for a targeted assassination.5,6 Over the past century a variety of methods to weaponize biologic agents—enhance the shelf life and dissemination properties (i.e., aerosolize) and/or fill munitions—have been researched.7 Only a handful of countries, which include Syria, North Korea, and the United States, are believed to have active biological weapons programs, either conducting research on the virulence of selected agents (defensive), weaponizing them (offensive), or both.7

This chapter describes the natural history, symptomatology, diagnostic procedures, and 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, and viral hemorrhagic fevers. 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.

KEY CONCEPTS

1. Bioterrorism agents such as bacteria and viruses, or toxins can cause disease and death in humans and animals and elicit panic, social unrest or 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. Anthrax is a spore-forming, toxin-producing organism, which can cause serious sequela, especially after inhalation.
4. Rapid recognition of botulism based on clinical presentation, which mimics a variety of other conditions, is essential to prompt antitoxin therapy.
5. Pneumonic plague is associated with a rapid onset of symptoms like influenza and bacterial community-acquired pneumonia and is highly lethal if not rapidly treated.
6. While smallpox has been globally eradicated smallpox vaccine is stockpiled in response to a suspected or confirmed outbreak.
7. Pharmacological treatment of viral hemorrhagic fever is predominantly supportive care.
8. Infectious disease outbreaks following a natural disaster are not common, yet they should be anticipated and promptly treated.
EVALUATION OF RISK AND DEVELOPMENT OF PREVENTION STRATEGIES

In 2000 the CDC published their strategic plan for biological and chemical terrorism preparedness and response, advocating for a strong public health infrastructure and enhanced healthcare capacity to provide early detection and control for both overt and covert attacks. Both the CDC and National Institute of Allergy and Infectious Diseases classified critical biological agents into three different categories (A, B, and C) based on their ability to be easily disseminated or transmitted person-to-person; cause high mortality, with the potential for major public health impact; cause public panic and social disruption; and require special action of public health professionals. Preparatory steps, such as enhancing detection and diagnostic capacity, establishing communication programs delivering accurate and timely information, and providing education materials for public and education and training for healthcare professionals, are still crucial and relevant today.

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The bioterrorism agents most likely will be released as a covert or hidden attack, allowing exposures to go unnoticed. Patients may present to a healthcare provider days or weeks after exposure, allowing for further spread of a contagious agent. This delayed detection and commencement of PEP and treatment may have great local, and even global, public health implications.

Preparedness and response, focusing on pre-exposure vaccination, PEP and treatment, are key infection control measures where healthcare providers can make a significant impact. Pre-exposure 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 recommended vaccination against seasonal influenza, have proven effective in protecting children and the general public. Although there are some vaccines available for category A agents, the segment of the public who would qualify for pre-exposure inoculation is exceedingly small. For example, BioThrax, an inactivated anthrax vaccine, is recommended for adults up to age 65, who are at high exposure risk. This group may include those working directly with B. anthracis in the laboratory or military personnel deployed to high-risk areas as recommended by the U.S. Department of Defense.

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. Global eradication of a vaccine-preventable disease is extremely challenging in part because of the rapidity of international travel, the growing world population, poor nutrition, overcrowding, and the significant expansion of the numbers of immunocompromised individuals who now reside throughout the world. Other general challenges include increasing vaccine refusal rates; constant evolution of circulating pathogens, such as influenza; and newly recognized side effects. For example, there were 140 reported cases of myopericarditis, which developed during the first year of the controversial U.S. smallpox vaccination program, to protect both our military and civilian population against this theoretical bioterrorist threat. This rare but serious sequela contributed to the halting of the U.S. smallpox mass vaccination program. In the meantime, more than 1,200,000 military forces and healthcare workers were vaccinated, and most adverse events occurred at rates lower than historical rates during this campaign.

PEP involves dispensing or administering a medication (including a vaccine) immediately or very soon after exposure to an organism (either from primary exposure or secondary exposure, such as person-to-person transmission), so as to prevent the disease from developing or worsening or spreading to others. For example, after an anthrax-containing letter was delivered to and opened in the Hart Senate Office Building in Washington, D.C., in fall 2001, ciprofloxacin and doxycycline were dispensed to hundreds of congressional staff who had offices on the fifth and sixth floors of the southeast wing. 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 for 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 approach surrounding prophylaxis involves prompt initiation of the regimen with the appropriate empiric antimicrobial. These concepts are no different from if there was a meningococcal outbreak on a college campus.

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 (nonbioterrorism 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. Adults and children may present with nondescript, albeit severe, 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

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eTable 11-1 Priority Categorization of Biological 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 | • Result in moderate morbidity rates and low mortality  
| • Lower medical and public health impact  
| • Moderately easy to disseminate  
| • Require specific enhancements of diagnostic capacity and disease surveillance |

| Category C | • Emerging infections that could be engineered for mass dissemination in the future because of:  
| • Availability  
| • Ease of production and dissemination  
| • Potential for high morbidity and mortality rates and major health impact |

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Data from references 9 and 10.
immediate treatment, including supportive care and empiric IV antimicrobial therapy, ideally within 24 hours, with conversion to oral regimens when appropriate.

Every few years and as recently as 2011 the United States Army Medical Research Institute of Infectious Diseases (USAMRIID) publishes medical information for biological agent exposure, for the U.S. military.2 Information and recommendations for the identification and management of bioterrorist exposures in civilians had been scant until the late 1990s when the Journal of the American Medical Association published a series of consensus papers on category A agents.15–20 These guidelines provided PEP and treatment recommendations for adults, children, and pregnant women. However, there still remains limited information regarding exposure management among other vulnerable groups, such as severely immunocompromised and patients with multiple comorbid disorders or disease states.

DESIRED OUTCOMES

There are multitudes of potential or theoretical individual and public health-related outcomes concerning the prophylaxis and/or treatment of suspected or confirmed cases of biological exposure. Much of what is available are case reports or in vitro and animal data. Global efficacy goals include prevention of disease progression, a reduction of serious sequela and mortality, decrease in transmission (for those agents which are contagious), and decrease in anxiety and panic, with a quick restoration of normalcy for the community and country. Maximizing safety issues and employing the most cost-effective modes of providing prophylaxis and treatment are important additional considerations.

For pre-exposure (i.e., vaccination) campaigns the main goal would be to immunize those who would be deemed at risk, while minimizing adverse events. The previous mentioned smallpox vaccination campaign is an example of a pre-exposure prophylaxis attempt, which was, overall, successful, but brought to light safety concerns. Post exposure prophylaxis data, beyond information from the anthrax exposure in Washington, D.C., is also scant. Without robust outcome data, one must turn to comparing pharmacologic actions, microbiological sensitivity, and cost for common antibiotics used for PEP. Some have considered doxycycline as the preferred agent for PEP management for many bioterrorism agents (including some category B agents), because of comparable microbiological effectiveness, low cost, and a low antibiotic resistance potential.21 Considering finances and effectiveness, researchers

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eTABLE 11-2  Bioterrorism Pathogen List

<table>
<thead>
<tr>
<th>Category A</th>
<th>Category B</th>
<th>Category C</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Anthrax (Bacillus anthracis)</td>
<td>• Brucellosis (Brucella species)</td>
<td>• Antimicrobial resistance, excluding research on sexually transmitted organisms</td>
</tr>
<tr>
<td>• Botulism (Clostridium botulinum toxin)</td>
<td>• Glanders (Burkholderia mallei)</td>
<td>• Research on mechanisms of antimicrobial resistance</td>
</tr>
<tr>
<td>• Plague (Yersinia pestis)</td>
<td>• Melioidosis (Burkholderia pseudomallei)</td>
<td>• Studies of the emergence and/or spread of antimicrobial resistance genes within pathogen populations</td>
</tr>
<tr>
<td>• Smallpox (variola major) and other related pox viruses</td>
<td>• Psittacosis (Chlamydia psittaci)</td>
<td>• Studies of the emergence and/or spread of antimicrobial-resistant pathogens in human populations</td>
</tr>
<tr>
<td>• Tularemia (Francisella tularensis)</td>
<td>• Epsilon toxin of Clostridium perfringens</td>
<td>• Research on therapeutic approaches that target resistance mechanisms</td>
</tr>
<tr>
<td>• Viral hemorrhagic fevers</td>
<td>• Q fever (Coxiella burnetii)</td>
<td>• Modification of existing antimicrobials to overcome emergent resistance</td>
</tr>
<tr>
<td>• Arenaviruses</td>
<td>• Ricin toxin from Ricinus communis (castor beans)</td>
<td>• Antimicrobial research, as related to engineered threats and naturally occurring drug-resistant pathogens, focused on development of broad-spectrum antimicrobials</td>
</tr>
<tr>
<td>– Lassa fever</td>
<td>• Typhus fever (Rickettsia prowazekii)</td>
<td>• Chikungunya virus</td>
</tr>
<tr>
<td>– LCM, Junin virus, Machupo virus, Guaranito virus</td>
<td>• Staphylococcal enterotoxin B</td>
<td>• Coccidioides immitis</td>
</tr>
<tr>
<td>• Bunyaviruses</td>
<td>• Tickborne encephalitis viruses</td>
<td>• Coccidioides posadasii</td>
</tr>
<tr>
<td>– Hantaviruses</td>
<td>• Tularaemia (Franciscella tularensis)</td>
<td>• Emerging infectious disease threats such as Nipah virus and additional hantaviruses</td>
</tr>
<tr>
<td>– Rift Valley fever</td>
<td>• Vesicular stomatitis</td>
<td>• Innate immunity, defined as the study of nonadaptive immune mechanisms that recognize, and respond to, microorganisms, microbial products, and antigens</td>
</tr>
<tr>
<td>• Filoviruses</td>
<td>• Pathogenic Vibrios</td>
<td>• Influenza</td>
</tr>
<tr>
<td>– Dengue</td>
<td>– Vibrio cholerae</td>
<td>• Other Rickettsia bacteria</td>
</tr>
<tr>
<td>– Ebola</td>
<td>– Yersinia enterocolitica</td>
<td>• Rabies</td>
</tr>
<tr>
<td>– Marburg</td>
<td>• Viruses</td>
<td>• Priions</td>
</tr>
<tr>
<td>• Bacteria</td>
<td>– Caliciviruses</td>
<td>• Severe acute respiratory syndrome-associated coronavirus (SARS-CoV)</td>
</tr>
<tr>
<td>– Campylobacter jejuni</td>
<td>– Hepatitis A</td>
<td>• Tickborne hemorrhagic fever viruses</td>
</tr>
<tr>
<td>– Diarrheagenic Escherichia coli</td>
<td>• Protozoa</td>
<td>• Crimean-Congo hemorrhagic fever virus</td>
</tr>
<tr>
<td>– Listeria monocytogenes</td>
<td>– Cryptosporidium parvum</td>
<td>• Tickborne encephalitis viruses</td>
</tr>
<tr>
<td>– Salmonella typhimurium</td>
<td>– Cyclospora cayetanensis</td>
<td>• Tuberculosis (TB), including drug-resistant TB</td>
</tr>
<tr>
<td>– Shigella species</td>
<td>– Entamoeba histolytica</td>
<td>• Yellow fever</td>
</tr>
</tbody>
</table>

Data from reference 10.
from Toronto analyzed four strategies deployed after a hypothetical aerosolized *B. anthracis* incident: (a) no prophylaxis, (b) antibiotics, (c) vaccination, and (d) combination of antibiotics and vaccination.\(^2^5\) Their analysis indicated that when anthrax is released over an unvaccinated urban population starting both vaccination and antibiotic therapy would be the most effective and least expensive option. However, administering this combination would be a logistical challenge, because dispensed antibiotic quantities are large (long duration of prophylaxis) and the vaccine schedule is frequent.

**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.\(^3^1\) Anthrax was first described in the biblical era of Moses as the fifth Egyptian plague in Exodus 9. 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 and 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 five deaths.\(^2^4,2^5\)

**Etiology**

*B. anthracis* is a gram-positive, spore-forming rod found endemically in the soil of many regions worldwide. Domesticated and wild herbivores (e.g., sheep, camels, elephants, horses, cattle, goats) commonly acquire anthrax; humans usually become infected through contact with infected animal tissue, exposure due to an intentional release, or most recently, cutaneous infection from contaminated illicit injection drugs.\(^2^6\) 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.

**Pathophysiology**

Three clinical manifestations of anthrax exist: cutaneous (the most common, but least severe), inhalational (main bioterrorism concern), and gastrointestinal (very infrequent). Rare, but life-threatening neurologic complications, such as cerebral edema and hemorrhagic meningitis, are possible sequelae of all primary forms of anthrax infections.\(^2^7\) Anthrax spores deposited into pulmonary alveoli may not germinate until taken up by alveoli macrophages and transported to regional lymph nodes since this may take weeks or months, extended durations of antibiotic coverage may be required. Replicating bacteria, once in a host, achieve their virulence via production of two main toxins, 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.\(^2^7\) 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 two weeks after infection, the eschar dries and sloughs away (eFig. 11-1). Subsequent lesions near the initial papule 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.\(^2^8\) 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.\(^2^5\)

**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.

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 sweats, 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 (eFig. 11-2). The CDC recommends obtaining blood, pleural fluid, and cerebrospinal fluid, if available, for culture, Gram stain, and polymerase chain reaction (PCR). Sputum cultures may not be positive early on 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. 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. This lends high importance to the development of a strong clinical knowledge base regarding detection, diagnosis, and treatment.

Core Clinical Controversy... Anthrax

Some clinicians question the need for a full 60-day course of antibiotics for post exposure prophylaxis. Continuous therapy for long time periods poses multiple problems such as side effects, resistance emergence, poor adherence, and adverse events, for example, *Clostridium difficile* infection. Current data do not support shorter durations however.

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). Pre-exposure 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 five injections over 18 months, in addition to annual boosters. Data from various nonhuman studies show that vaccination alone is not protective post exposure, but the Food and Drug Administration (FDA) has approved the vaccination for post exposure treatment.
**Treatment of Confirmed Cases**

IV 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 eTable 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). Treatment of cutaneous cases differs in that only one antibiotic (doxycycline or ciprofloxacin) is necessary and oral products may be used initially. Clinically severe cases, such as those with extensive edema or lesions of the head or neck, require IV 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 anthrax. The extended duration is a result of the possibility of those treated during the outbreak of 2001 all received combination therapy (at least two antibiotics with activity against *B. anthracis*) and their fatality rate of 45% was slightly lower than previous observations reported in the literature. 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. One monoclonal antibody, raxibacumab, specifically directed at a component of the anthrax toxin demonstrates the impressive potential of these antibodies. When raxibacumab was administered to animals exposed to *B. anthracis* spores survival was improved and prolonged in both rabbits (at day 14) and monkeys (at day 28). In another study, when given in combination with levofloxacin, raxibacumab improved rabbit survival (at day 35) from 65% to 82%. Raxibacumab could potentially have a role in confirmed exposure cases or when initial antibiotic therapy response is perceived to be inadequate. Because of raxibacumab’s potential benefits for these patients, it has been added to the SNS. Additionally, a currently unlicensed anthrax immune globulin containing a polyclonal antibody preparation pooled from anthrax-vaccinated human donors has been added to the SNS.

### 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, although the FDA has approved ciprofloxacin’s use in children for post exposure prophylaxis. Children 2 years old or younger should always be initially treated with IV antibiotics because of limited experience in this age group. 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.

### Botulinum Toxin

Botulinum toxin poses a major public health threat because mass production is relatively easy, and it is exceptionally potent. Large quantities of toxin can be produced by industrial scale fermentation. The estimated lethal inhalation dose is 0.7 to 0.9 mcg, whereas the lethal ingested dose is 30 ng. 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. In 1995,
Iraq admitted to producing 19,000 L of concentrated toxin with the potential to kill more than the entire world’s population by inhalation. Missiles and bombs loaded with nearly 10,000 L of the toxin were deployed; further details are unknown. Mass dissemination can be carried out by airborne release and from intentional contamination of food or water supplies.

Etiology

*Clostridium botulinum*, an anaerobic, spore-forming, gram-positive bacillus, produces seven distinct botulinum neurotoxins, types A through G. *Clostridium* spores, naturally found in soil, fresh water, and saltwater, are extremely hardy. Yet the toxins are less stable and are inactivated by heating to 85°C (185°F) for 5 minutes. Botulism is the syndrome that occurs after exposure to these toxins. Foodborne botulism, the oldest recognized form, is acquired from ingesting ill-preserved foods. Likewise, infant botulism is caused by swallowing spores carried in honey, dust particles, or soil. The toxin is then absorbed through the gastrointestinal tract into systemic circulation. The third form of naturally occurring botulism can arise cutaneously through an open wound infected with the organism, which produces toxin. Intentional botulinum toxin exposure may result from mass dissemination via contamination of food or beverages, or aerolization. Botulinum is not contagious and human-to-human transmission has not been reported.

Pathophysiology

*Clostridium botulinum* toxins enter the bloodstream either from a mucosal surface (gastrointestinal tract, lungs) or a wound. The neurotoxins irreversibly bind to cholinergic synapses, inhibiting acetylcholine release across the neuromuscular junction. The resulting neuromuscular etiologies such as stroke, and paralytic shellfish poisoning. Diagnosis is based primarily on clinical presentation, as confirmatory laboratory testing can take more than 24 hours, has low specificity, and is costly.

Clinical Presentation

Although symptoms are similar regardless of the transmission route, disease progression and severity of symptoms depend on the size of the inoculum. Symptoms typically occur within 12 to 36 hours, but may present after several weeks, if the person is exposed to a small amount of the toxin. Classic presentation begins with bilateral cranial nerve palsies, such as diplopia, dysphagia, dysarthria, and descending motor neuron paralysis, which can persists for weeks to months, resulting in death from respiratory muscle paralysis. Foodborne botulism is often preceded by gastrointestinal symptoms such as nausea, vomiting, diarrhea, and abdominal cramps, but differs from gastrointestinal by the presence of autonomic and ocular findings. Inhalation botulism is theorized to have a similar presentation, but few cases have been reported. Absence of fever, sensory changes, with positive symmetrical neuromuscular etiologies, such as stroke, and paralytic shellfish poisoning. Diagnosis is based primarily on clinical presentation, as confirmatory laboratory testing can take more than 24 hours, has low specificity, and is costly.
The mainstays of therapy are rapid diagnosis, prompt administration of antitoxin, and supportive care with mechanical ventilation. Extended periods of assisted ventilation may be necessary, increasing the risk of secondary bacterial infections. However, timely administration of antitoxin, ideally within 24 hours after the onset of symptoms, may decrease disease severity and duration. The antitoxins prevent disease progression, while reversal occurs with the regeneration of nerve terminals. The mortality rate is less than 5% if treated and approaches 60% without treatment. With the exception of BabyBIG®, an IV human immune globulin indicated for the treatment of infant botulism, the majority of available antitoxins are derived from horse serum products and may cause serum sickness, anaphylaxis, and other infusion-related side effects. 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, and other ribosomal antibiotics are contraindicated, as they may inhibit neuromuscular transmission and thereby exacerbate neuromuscular blockade. It is important to note that antitoxins are toxin specific; for example, bivalent antitoxin (A and B) is not able to neutralize toxins C to G. eTable 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. Isolation is not required as botulinum is not contagious.

A bioterrorist attack with botulinum toxins has the potential to involve a vast number of victims, who will need prompt administration of antitoxins and prolonged critical care, thereby testing the healthcare infrastructure. Rapid diagnosis is key; yet the majority of the population (including healthcare practitioners) has limited awareness of botulism. Streamlined intervention guidelines are essential. A botulism questionnaire and a management algorithm have been published for use by the lay public and clinicians. Data from references 5, 17, 37, 38.

### 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 *Y. 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. As a bioweapon plague may be aerosolized, a capability developed by 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

*Yersinia 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. In 2006 four states reported 13 cases, including two deaths. Thirty-eight percent of patients developed septicemia. A few of cases were linked to domestic dogs and 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 these bacteria in a few minutes.

## eTABLE 11-4 Treatment and Prophylaxis for Botulism (Clostridium botulinum)

<table>
<thead>
<tr>
<th>Treatment (Symptomatic)</th>
<th>Post exposure Prophylaxis (Prevention)</th>
<th>Vaccination</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type-specific antitoxin diluted and administered by slow IV infusion per product insert</td>
<td>None; antitoxin not recommended</td>
<td>Pentavalent toxoid vaccine (A–E) for high-risk individuals; pre-exposure prophylaxis (investigational new drug)</td>
<td>Risk of anaphylaxis and serum sickness to equine antigens requires skin test</td>
</tr>
<tr>
<td>Adults: HBAT (heptavalent equine antitoxin, serotypes A–G)</td>
<td>Observe and monitor Prompt treatment with antitoxin for first signs and symptoms</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>Dose: single 20 mL vial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children age ≥1 y: refer to adult dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children age &lt;1 y: Human-derived botulimum antitoxin (serotypes A, B), BabyBIG®</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose: 50 mg/kg slow IV infusion</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data from references 5, 17, 37, 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 abscessed lymph node. After inoculation of thousands of organisms from the flea bite, *Y. pestis* then migrates from skin through cutaneous to regional nodes. Some patients bitten by fleas will not develop a bubo, but will suffer from primary septicemic plague. *Y. pestis* carries a multitude of virulence factors that contribute to this extracellular proliferation, that can ultimately cause an ensuing high-grade bacteremia and inflammation in lymph nodes, liver, and spleen. The resulting complications—sepsis, disseminated intravascular coagulopathy, multiorgan dysfunction, secondary pneumonia, and adult respiratory distress syndrome—form an extensive immunologic cascade. Untreated septicemic plague is nearly 100% fatal. The term *black death* describes gangrene of fingers, toes, and tips of the nose, which may occur during the advanced stages of sepsis (eFig. 11-4). Other bacteremic sequela include gastrointestinal plague, abscesses in liver or spleen, generalized lymphadenopathy, and plague meningitis. Inhalation plague most likely leads to primary pneumonic plague, which has a high fatality rate, ranging from 57% (recent outbreaks) to 100% (untreated). A less-common manifestation of inhalation of *Y. pestis* is pharyngitis, as evidenced by swollen tonsils and inflamed lymph nodes.

Clinical Presentation

After a short incubation period of just a few 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. Death quickly follows, particularly if diagnosis and treatment are delayed. 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.

Management of Potential Exposure

PEP is crucial for plague, not only to prevent disease but also to prevent its spread to others through coughing infectious droplets.

TREATMENT

**CLINICAL PRESENTATION** 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—lymph node, blood, cerebral spinal fluid, or sputum aspirate.
- Rapid and confirmatory diagnostic tests, enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR); limited availability.

**eFIGURE 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 systematically 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?pid=4139.)
eTABLE 11-5  

**Treatment and Prophylaxis for Plague (Yersinia pestis)**

<table>
<thead>
<tr>
<th>Treatment (Symptomatic)</th>
<th>Post exposure Prophylaxis (Prevention)</th>
<th>Vaccination</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plague pneumonia:</strong></td>
<td><strong>Duration:</strong> 7 days after last exposure</td>
<td><strong>Vaccination</strong></td>
<td><strong>Comments</strong></td>
</tr>
<tr>
<td>Adults:</td>
<td><strong>Duration:</strong> 10 days or until afebrile for 2–3 days, whichever is longer</td>
<td>New vaccine under development</td>
<td>Treatment should be initiated immediately (within 18–24 hours of symptoms onset). Treatment with doxycycline may need longer duration of therapy (10–14 days)</td>
</tr>
<tr>
<td>Streptomycin 1 gm IM q 12 h</td>
<td>Adults: Ciprofloxacin 500 mg PO q 12 h or Doxycycline 100 mg PO q 12 h or Levofloxacin 500–750 mg PO daily</td>
<td>Alternatives: Chloramphenicol 25 mg/kg PO q 6 h or Tetracycline 500 mg PO q 6 h</td>
<td>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 age &lt;2 y; not recommended for pregnant women.</td>
</tr>
<tr>
<td>Gentamicin 2 mg/kg IV q 8 h (or 5 mg/kg once daily) or Ciprofloxacin, levofloxacin, or doxycycline IV (see doses under anthrax section) or Chloramphenicol 25 mg/kg IV q 6 h</td>
<td>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</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Plague meningitis:</strong></td>
<td><strong>Duration:</strong> 7 days after last exposure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults:</td>
<td><strong>Duration:</strong> 10 days or until afebrile for 2–3 days, whichever is longer</td>
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</tr>
</tbody>
</table>

CBC, complete blood count; IM, intramuscular; PO, by mouth.

Data from references 5, 15, and 46.

and tetracyclines. However, a multidrug-resistant strain of *Y. pestis* was reported in a patient from Madagascar with bubonic plague. Bioengineering of a resistant strain of *Y. pestis* by terrorists should not be ruled out. Animal data confirm a critical window to start antibiotics post inhalation to prevent inhalation plague. Duration of prophylaxis is 7 days (or duration of risk exposure plus 7 days) and should be started as soon as possible around the time of exposure. If a person develops a fever and cough, treatment course for plague should commence. Pre-exposure prophylaxis may be warranted for individuals traveling to endemic areas when exposure to vectors or pneumonic plague is unavoidable.

In the past there were two types of vaccines available, but with variable activity against bubonic plague only, manufacturing was halted in 1999. Currently, while no vaccine is available to protect the general public, a live plague vaccine has been used for protection of plague researchers and people living within endemic territories, such as countries within the former Soviet Union. Research is actively underway, focusing on vaccines with protection against inhalation plague. Promising subunit candidates, such as an F1-V (virulence factors) fusion protein vaccine, are emerging.

### Treatment of Confirmed Cases

While specimen cultures (e.g., blood or sputum) and sensitivity results are pending, empiric treatment should be started immediately. 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 with fluoroquinolones, especially if therapy is delayed. Fluoroquinolones like ciprofloxacin or levofloxacin only have in vitro and animal data showing activity against plague. 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.

### Special Populations

Pregnant women should be immediately started on gentamicin, the drug of choice for this vulnerable patient population. 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 agents. 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. Management includes starting empiric treatment 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.

### Smallpox

Smallpox, or variola major, is an acute, contagious, viral disease that has played a deadly and important role in the shape of global history. In 1796, the concept of vaccination was introduced when Edward Jenner discovered that inoculating patients with pus from milkmaids’ cowpox lesions resulted in cross-protection against the smallpox virus. As humans are the only reservoir of the disease, a global smallpox vaccination campaign initiated by the World Health Organization in the 1960s was able to successfully eradicate naturally occurring smallpox from the planet by 1980. At this time, national vaccination programs ended, and remaining virus samples and vaccine were maintained by laboratory research facilities in Russia and the United States. 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.54

Etiology
Smallpox is caused by the variola virus, which belongs to the Orthopoxvirus family along with cowpox (vaccinia) and monkeypox. There are two distinct types of variola, known as major and minor.5 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 the unvaccinated.5,18

There are four principal clinical classifications of the lesions that occur in variola major: ordinary, flat or malignant, hemorrhagic, and modified. Ordinary type is the most common, responsible for ≥90% of smallpox cases. Both hemorrhagic and flat or malignant type are rare, severe, and often fatal (≥90%). Modified type smallpox occurs in previously vaccinated persons and usually is a mild form of disease.55

Pathophysiology
The pathophysiology of ordinary type smallpox, the most common form, is well documented. Smallpox is transmitted from person to person via respiratory droplets, direct personal contact with an infected person (including scabs or corpses), 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.18 Once the virus has implanted in the respiratory tract mucosa, it travels to the lymph nodes, spleen, and bone marrow where it multiplies. The patient is asymptomatic during the incubation period, which ranges from 7 to 17 days (average, 12 to 14 days).18,55 After this time the infected cells lyse and virus is detectable in the bloodstream.

Clinical Presentation
The viral incubation period is followed by a prodrome stage (eTable 11-6) typically lasting 2 to 4 days, during which the patient is typically prostrate with a high fever, severe body aches, and vomiting. The end of the prodrome stage is followed by the abrupt development of an enanthem in the mouth. These oral lesions grow and ulcerate rapidly, releasing large quantities of virus into the saliva. The patient is most contagious during the first week of illness once these oral lesions occur. At the same time, red spots erupt first on the face and forearms, and later spread to the trunk and legs. Lesions may erupt on the palms and soles as well. The spots progress to vesicles by day 4 or 5, and hard, deeply embedded pustules by day 7. Scab lesions typically appear around day 14. A unique characteristic of smallpox is that the skin lesions, though different sizes, are all at the same stage of development throughout the illness (eFig. 11-5).18,55

In addition to significant scarring and death, 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. Chronic infection does not normally occur with variola virus.18

Testing and sample collection from any individual suspected to have smallpox should only be done by vaccinated and properly trained personnel. Smallpox diagnosis should be confirmed at a variola testing laboratory, which can use PCR technology, such as the CDC.5,56 A presumptive diagnosis may be made based on examination of vesicular scraping under an electron microscope.5

<table>
<thead>
<tr>
<th>eTABLE 11-6 Differentiating Smallpox from Chickenpox</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presentation</td>
</tr>
<tr>
<td>Prodrome</td>
</tr>
<tr>
<td>Lesion development</td>
</tr>
<tr>
<td>Lesion location</td>
</tr>
<tr>
<td>Lesion presentation</td>
</tr>
</tbody>
</table>

Data from reference 78.

eFIGURE 11-5 Smallpox rash. (Courtesy of the CDC and Jean Roy. “This 1974 image depicted a young male Bangladesh villager who'd contracted smallpox and was displaying the classic maculopapular rash covering his entire body with pustules.” CDC Public Health Image Library. http://phil.cdc.gov/phil/home.asp.)
### Treatment and Prophylaxis for Smallpox (Variola major)

<table>
<thead>
<tr>
<th>Treatment (Symptomatic)</th>
<th>Post exposure Prophylaxis (Prevention)</th>
<th>Vaccination</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supportive care</td>
<td>Commence mass vaccination Limited information with vaccinia immune globulin (VIG) ± vaccine for post exposure</td>
<td>Review contraindications and precautions prior to smallpox vaccination (refer to most recent ACIP or CDC recommendations)</td>
<td>VIGV for severe complications of vaccinia vaccination: 6,000 units/kg (9,000 units/kg may be considered if patient does not respond to initial dose)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VIG is indicated for certain vaccine complications and vaccinia exposures in immunocompromised persons</td>
<td>VIGIV infusion: 2 mL/min (max: 4 mL/min)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VIGIV—licensed; pediatrics and &gt;65 y of age—IND</td>
<td>&lt;50 kg: max. rate—0.04 mL/kg/min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VIGIM 0.6 mL/kg; third line</td>
<td>Cidofovir (IND): second line</td>
</tr>
</tbody>
</table>

ACIP, Advisory Committee on Immunization Practices; CDC, Centers for Disease Control and Prevention; IND, investigational new drug; VIG, vaccinia immune globulin; VIGIM, vaccinia immune globulin intramuscular; VIGIV, vaccinia immune globulin intravenous.

Data from references 5, 18, and 59.

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**TREATMENT**

6. There is no treatment currently available for smallpox infection other than supportive care (eTable 11-7). Pre- and post exposure prophylaxis can only be achieved by using the smallpox vaccine, which is derived from live vaccinia virus.

**Vaccination**

Smallpox vaccination is not currently available to the public, but is reserved in national stockpiles in the event of an outbreak. The original, first-generation smallpox vaccines were derived from the New York City Board of Health (NYCBH) strain of vaccinia, prepared from lymph fluid of calf skin, and stored as a lyophilized product. Until 2007, the first-generation Dryvax was the only commercially approved smallpox vaccine available for limited use in the United States, until being replaced by ACAM2000. 53,57

ACAM2000, a live vaccinia virus derived from plaque purification cloning of a Dryvax isolate that was manufactured using tissue culture system, has replaced all stores of Dryvax vaccine as of February, 2008. 53 Third- and fourth-generation vaccines are being developed and studied as well. 53 ACAM2000 has a similar efficacy and safety profile in comparison to Dryvax, and is also acceptable as a booster for previously vaccinated patients. 58

The ACAM2000 smallpox vaccinia vaccine, like the first-generation vaccine, is administered through multiple percutaneous skin pricks (intradermal) delivered with a bifurcated needle into the upper arm over the insertion of the deltoid muscle. When performed correctly, a drop of blood will form at the vaccination site. The patient will develop a major cutaneous reaction over the following 10 days characterized by a pustule at the site of inoculation, which dries and forms a scab by days 14 to 21. The scab separates and leaves a pitted scar. The upper arm is the only site approved for vaccination, allowing for easy site care and management as well as easy evaluation of a proper vaccine “take” 6 to 8 days after vaccination (eFig. 11-6). 58

An FDA–approved, current, ACAM2000 medication guide must be dispensed to every vaccine recipient; and recipients should be thoroughly educated about proper care of the vaccine site to prevent accidental vaccinia transmission to other sites or other people. Vaccine recipients should not handle infants, breast-feed, swim or use hot tubs, donate blood, receive tuberculin testing, or get pregnant until at least 4 weeks after the vaccination and not before the vaccination site has healed. Inadvertent inoculation of other sites such as the face, nose, mouth, lips, and genitalia is the most frequent complication of the vaccinia vaccination. Frequent hand washing, proper care of the vaccination site, and careful disposal of bandages can reduce the risk of these events. Malaise, fever, myalgia, and headache are also common adverse events following vaccination, though they are less common in revaccination than first-time vaccination. 58

Smallpox vaccination provides effective immunity for at least 3 years after vaccination, with decreasing immunity thereafter. 5,58 If a patient is revaccinated, immunity will increase and last longer. Vaccination within 3 to 4 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. 5,58

---

Serious, but uncommon complications, following either primary or revaccination with live vaccinia smallpox vaccine include: myocarditis, pericarditis, encephalitis, encephalomyelitis, encephalopathy, eczema vaccinatum, progressive vaccinia, generalized vaccinia, erythema multiforme (eFig. 11-7), including Stevens-Johnson’s syndrome, and death. Serious and severe adverse reactions are more common in immunocompromised patients and those receiving primary smallpox vaccination compared with those who are revaccinated. Close contacts of vaccinees are also at risk for the same complications if the live vaccinia virus is inadvertently transmitted to them. Vaccinia immune globulin IV (VIGIV) and cidofovir are treatment options for serious smallpox vaccine reactions. Limitations of VIGIV include its lack of effectiveness for treatment of postvaccinial encephalitis or smallpox infection and complex administration schedule. Cidofovir is considered a second-line option in part because there is limited human data, the potential for renal toxicity, and use restrictions under an investigational new drug (IND) protocol. Like the smallpox vaccine, both VIGIV and cidofovir are stored in the SNS.

Special Populations
The ACAM2000 vaccine contains trace amounts of the antibiotics neomycin and polymyxin B and therefore should not be given to anyone with a history of anaphylaxis to these antibiotics. Although there are few absolute contraindications, the smallpox vaccine is a live vaccine that should be not be administered to patients with a history of eczema, immunodeficient patients (including cancer and HIV patients), infants younger than 12 months of age, and pregnant women, unless the benefit outweighs the risk (of developing vaccinia reaction) as determined by the healthcare practitioner. 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. However, the risk of serious side effects with cidofovir, including renal toxicity, must be weighed against the potential benefits of treatment.

Clinical Controversy...

Smallpox
Once smallpox was globally eradicated, smallpox vaccination programs halted. However, with bioterrorism concerns, mass vaccination and revaccination programs may need to commence after a suspected or confirmed smallpox case or threat.

Tularemia
Tularemia is caused by a small, gram-negative rod, named Francisella tularensis. 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. 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 U.S. 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.

Etiology
Francisella tularensis 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. Two main variants of F. tularensis exist, type A and type B. Type A, predominately found in North America, is a more virulent form and type B is found in Europe and Asia. Cases of tularemia are documented throughout the Northern Hemisphere, with at least one case reported in every state in the United States, except Hawaii. 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.

Pathophysiology
Clinical and pathogenic manifestations vary depending on the subspecies involved (e.g., F. tularensistularensis is more virulent than F. tularensispalearctic). In general F. tularensis is an intracellular parasite that, once inside its host, will progress to regional lymph nodes. The major target organs include the lung, pleura, spleen, liver, and kidney. Interestingly, the bacteria 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. 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.

Because tularemia rarely affects humans in most areas, clinicians will likely possess a low index of suspicion when presented with this infection. While *F. tularensis* is rarely cultured from blood samples, cultures taken from sputum specimens or even pharyngeal washings remain the definitive means of confirming a suspected case. This bacterium grows best in cysteine-enriched broth, thiglycollate broth, buffered charcoal-yeast agar, or chocolate agar. Direct fluorescent antibody examination or immunochemical stains of specimens should be performed promptly. *Francisella tularensis* can be differentiated from other microbes under light microscopy by its small size (0.2 micron × 0.2 to 0.7 micron), pleomorphic appearance, and its faint uptake of stain. Mortality rates for tularemia in the preantibiotic era varied from 5% to 15% to upwards of 60% for those with untreated sepsis or severe pneumonia. Mortality rates for *F. tularensis* infection are now less than 2%. As with most infectious processes, appropriate and prompt antibiotic initiation is crucial. Supportive care measures (e.g., fluid resuscitation or mechanical ventilation) should also be addressed as necessary.

**TREATMENT**

A live-attenuated vaccine derived from the type B variant of *F. tularensis* was available as an investigational drug. This vaccine is now under review by the FDA for official approval. 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 (eTable 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. In vitro data, animal data, and several case reports show that fluoroquinolones yield positive outcomes.

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

<table>
<thead>
<tr>
<th>Treatment (Symptomatic)</th>
<th>Post exposure Prophylaxis (Prevention)</th>
<th>Vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration:</strong></td>
<td><strong>Duration:</strong></td>
<td>Live-attenuated vaccine under review by FDA</td>
</tr>
<tr>
<td>Streptomycin, gentamicin, or fluoroquinolone:</td>
<td>14 days after last exposure</td>
<td></td>
</tr>
<tr>
<td>10–14 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxycycline or chloramphenicol:</td>
<td>10–14 days</td>
<td></td>
</tr>
<tr>
<td>14–21 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adults:</strong></td>
<td><strong>Adults:</strong></td>
<td></td>
</tr>
<tr>
<td>Streptomycin 1 g IM q 12 h</td>
<td>Ciprofloxacin 500 mg PO q 12 h or</td>
<td></td>
</tr>
<tr>
<td>Gentamicin 5 mg/kg IV/IM daily or</td>
<td>Doxycycline 100 mg PO q 12 h or</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin or levofloxacin 4 daily (see doses in anthrax table):</td>
<td>Levofloxacin 500–750 mg PO daily</td>
<td></td>
</tr>
<tr>
<td>or doxycycline 100 mg IV q 12 h or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>chloramphenicol 15 mg/kg IV q 6 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Children:</strong></td>
<td><strong>Children:</strong></td>
<td></td>
</tr>
<tr>
<td>Streptomycin 15 mg/kg IM q 12 h</td>
<td>Doxycycline 2.2 mg/kg PO q 12 h (max. 100 mg/dose) or</td>
<td></td>
</tr>
<tr>
<td>Gentamicin 2.5 mg/kg IV/IM q 8 h or</td>
<td>Ciprofloxacin 10–15 mg/kg PO q 12 h (max. 500 mg/dose)</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin or doxycycline IV (see doses in anthrax table)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloramphenicol 15 mg/kg IV q 6 h</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FDA, Food and Drug Administration; IM, intramuscular; PO, by mouth.

Data from references 5, 19, and 21.
in children and adults. Fluoroquinolones possess favorable pharmacodynamic properties because 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 are lacking for macrolides, clindamycin, and cotrimoxazole, and should, therefore, be avoided. For PEP, the CDC and the literature support doxycycline or ciprofloxacin for 14 days (see eTable 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. 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 Fever
Viral hemorrhagic fever (VHF) encompasses illness caused by a diverse group of viruses that can be dispersed and transmitted by aerosol release, 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. Exposure to only a few aerosolized virions is required to cause infection, and depending on the virus, can lead to severe complications and death.

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, Crimean-Congo hemorrhagic fever, and select viruses of the Hantavirus genus. The Flaviviridae family consists of yellow fever, Omsk hemorrhagic fever, and Kyasanur forest disease. 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 person.

Pathophysiology
Transmission to humans has occurred through a variety of ways: bites from infected arthropods, direct contact with or aerosolized droplets from infected animals, inhalation of dust particles tainted with rodent excreta, and direct contact with virus-laden blood and bodily fluids. The use of improperly sterilized needles and syringes contaminated with infected bodily fluids contributed to an epidemic of Ebola virus in healthcare settings. Infections are characterized by fever and bleeding diathesis, but 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.

Clinical Presentation
Classical symptoms of VHF are fever and hemorrhagic diathesis with capillary leak; resulting in microvascular damage and hemodynamic shock. 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 (eFig. 11-8), and hematuria. Disseminated intravascular coagulation and circulatory shock can occur in severe cases. Symptoms are often accompanied by renal insufficiency, neurologic changes, compromised pulmonary function, 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 host-specific factors and the viral strain. Laboratory abnormalities include leukopenia, anemia, thrombocytopenia, whereas elevated aminotransferases and disseminated intravascular coagulopathy are seen in severe infections. VHF should be suspected based on risk factors including...
travel history, sick contacts, and exposure to vectors. Lacking these characteristics, multiple incidences potentially indicate a bioterrorism event. Diagnosis is confirmed by antigen detection or real-time PCR performed at specialized laboratories.5,20

**TREATMENT**

**Management of Potential Exposure**

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. Treatment with ribavirin is an option when Filoviridae or Flaviviridae virus can be excluded as causative pathogens, but recommended only under select circumstances. In cases of contact with infected persons, suspected patients should be under medical surveillance for 21 days after the potential exposure. During surveillance, if a temperature of 38.3°C (101°F) or greater and signs and symptoms of infection develop, prompt initiation of ribavirin for presumptive VHF is indicated.20 High risk exposure from contact with acutely febrile individuals may warrant immediate use of oral ribavirin. Examples include penetration of the skin by contaminated sharp objects (e.g., needlestick); contact of mucous membranes with infected blood or bodily secretions; nonuse of personal protective equipment while assisting in emergency procedures (e.g., bronchoscopy), or sharing an enclosed space for prolonged extended period of time (e.g., within 6 feet for hours).69 Because the clinical usefulness of ribavirin in asymptomatic patient is unknown, pre-exposure therapy is not recommended.20

**Treatment of Confirmed Cases**

7 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.20 Antivirals specific for these viruses are not approved by the FDA, but a limited supply of IV ribavirin is available for compassionate use under an IND.1 In the case of a massive biologic attack, oral ribavirin is an alternative. 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.3,20 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 (eTable 11-9).20 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.20,70

**Special Populations**

Limited data are available for the treatment of VHF in special populations and the benefits of treatment likely outweigh the risk.

### eTable 11-9 Treatment and Prophylaxis for Viral Hemorrhagic Fevers

<table>
<thead>
<tr>
<th>Treatment (Symptomatic)</th>
<th>Post exposure Prophylaxis (Prevention)</th>
<th>Vaccination</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definitive, high-risk contacts</strong> (Arenaviruses or Bunyaviruses):</td>
<td>Ribavirin PO: 35 mg/kg (maximum 2.5 g), then 15 mg/kg (maximum 1 g) three times a day for 10 days</td>
<td>Yellow fever vaccine only VHF vaccine available. Not recommended for infants &lt;6 mo, and if possible, wait until infant is ≥ 9 mo. Not recommended for pregnant and immuno-compromised patients</td>
<td>Ribavirin does not have activity against Filovirus and Flavivirus; empiric treatment may be appropriate before identification of virus</td>
</tr>
<tr>
<td><strong>High-risk contacts:</strong></td>
<td>Ribavirin PO: 35 mg/kg (maximum 2.5 g), then 15 mg/kg (maximum 1 g) three times a day for 10 days</td>
<td></td>
<td>Ribavirin: pregnancy category X</td>
</tr>
<tr>
<td><strong>Monitor for signs and symptoms of illness for 21 days after exposure; if fever ≥ 38.3°C (101°F) treat with ribavirin</strong></td>
<td></td>
<td></td>
<td>Ribavirin may have activity against West Nile virus</td>
</tr>
<tr>
<td><strong>Supportive care:</strong></td>
<td></td>
<td></td>
<td>Supportive care: Fluids (monitor for pulmonary edema), vasopressors; APAP (for fever)</td>
</tr>
<tr>
<td><strong>Contraindications:</strong> IM injections, NSAIDs/ASA, and anticoagulants</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

APAP, acetaminophen; ASA, aspirin; IM, intramuscular; IND, investigational new drug; NSAID, nonsteroidal antiinflammatory; PO, by mouth.

5Mass casualty defined as threshold number of cases that exhaust supply of ribavirin IV and IV treatment would not be possible.

5Arenaviruses: Lassa fever, Machuputo, Junin, Guanarito, Sabia.

5Bunyaviruses: Rift Valley fever, Congo-Crimean hemorrhagic fever, hantaviruses.

5Filoviruses: Ebola, Marburg.

5Flaviviruses: Yellow fever, dengue, Omsk hemorrhagic fever, Kyasanur forest disease, West Nile virus.

Data from references 5, 20, and 69.
Ribavirin is pregnancy category X because of teratogenic effects observed in animals. However, an increased risk of mortality is associated in this patient population and vertical transmission has been reported. A case report of a 36-week pregnant woman treated with oral ribavirin for Crimean-Congo hemorrhagic fever documented the first known baby born from an infected mother to survive. In addition, the mother was cured, and the virus was not transmitted to the baby. For pediatric patients, only the inhaled dosage form of ribavirin is approved for the treatment of respiratory syncytial viral infections. Although oral and IV ribavirin is not approved, treatment of VHF with either of these dosage forms is recommended. A pediatric syrup formulation is available under an IND.

### INFECTIOUS DISEASE RELATED TO NATURAL DISASTERS

Mother Nature could be considered our most menacing bioterrorist. 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. Some of these microbes were discussed in previous sections of this chapter and others in various chapters throughout this text. Infectious disease outbreaks following natural disasters, as with 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.

However, communicable disease, related directly to outbreaks from large number of deceased, is not common, and may be limited to a few situations. Haiti, for example, is still responding to waves of ill and dying citizens from multiple cholera outbreaks post-earthquake. Ironically, genetic sequencing of the diarrhea-inducing, fatal cholera strains found this bacterium was most likely introduced by human activity, particularly from aid workers from countries where cholera is endemic, and not by contaminated local water supply.

Multiple communicable diseases have been associated with displaced populations and should be considered as an integral part of postdisaster patient assessment (eTable 11-10). Healthcare providers responding to a disaster should focus on preventing illness and injury, ensuring food and water safety, and recreating medical records. Dissemination of accurate and up-to-date information on personal and public safety topics, such as types of disasters and weather emergencies, health and safety concerns such as cleanup and mold, and information for certain groups, such as evacuees and volunteers, is an important role for healthcare providers. Ideally, advanced planning for provision of continuing maintenance medications and medical supplies, particularly for patients with special needs, such as children, pregnant women, and people with disabilities, mental illness, or chronic medical conditions, has occurred. Finally, the administration of immunizations to both the displaced population and the healthcare providers traveling to the affected area(s) is an important mode of illness prevention.

### Healthcare Providers in Emergency Preparedness

The CDC has described five main areas of preparedness and response to acts of biologic terrorism: (a) preparedness and prevention; (b) detection and surveillance; (c) diagnosis and characterization of agents; (d) response; and (e) communication. 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 PEP and chronic medications and supplies, providing acute treatment, and monitoring for side effects of medications and vaccinations during and after 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. eTable 11-11 elaborates on the specific areas of planning, education, response, and volunteer opportunities.

### eTable 11-10 Natural Disaster Epidemics

<table>
<thead>
<tr>
<th>Categories of Disease</th>
<th>Organism(s)/Condition</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water related</td>
<td>Vibrio cholerae, Escherichia coli, Norovirus, Salmonella</td>
<td>Contaminated drinking water or a lack of access to safe water and sanitation</td>
</tr>
<tr>
<td>Associated with crowding</td>
<td>Measles, Neisseria meningitidis</td>
<td>Facilitated transmission</td>
</tr>
<tr>
<td>Vector borne</td>
<td>Malaria, Dengue</td>
<td>Affected breeding sites and disease transmission</td>
</tr>
<tr>
<td>Power outages</td>
<td>Diarrhea</td>
<td>Disruption of refrigeration</td>
</tr>
<tr>
<td>Others</td>
<td>Tetanus (Clostridium tetani), Coccidioidomycosis</td>
<td>Disturbed earth/soil</td>
</tr>
</tbody>
</table>

Data from reference 74.
REFERENCES


