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Biological Terrorism

Gregory J. Moran, MD, FACEP, FAAEM[a,b,c,*],
David A. Talan, MD, FACEP, FAAEM, FIDSA[a,b,c],
Fredrick M. Abrahamian, DO, FACEP[a,b]

[a]*David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, USA*
[b]*Department of Emergency Medicine, Olive View-University of California Los Angeles Medical Center, Sylmar, CA, USA*
[c]*Department of Medicine, Division of Infectious Diseases, Olive View-University of California Los Angeles Medical Center, Sylmar, CA, USA*

The realities of the current world situation dictate that people prepare for bioterrorism. If an attack were to occur, many people could become ill in a very short time, putting an enormous, if not overwhelming, strain on local health care facilities [1]. The emergency department will be among the first areas affected by a large influx of patients, including the truly sick and the worried well [2]. The expertise of emergency physicians and infectious disease specialists will be critical to effective planning and execution of an effective response to a bioterrorism event. Many principles used to prepare for an outbreak caused by terrorists would also be applicable to developing a response to a natural outbreak, such as an influenza pandemic (eg, Avian influenza) or severe acute respiratory syndrome epidemic [3].

Critical actions in the early stages of an event include identifying the causative agent and, if necessary, initiating infection control measures to decontaminate victims and prevent further spread of the disease [4]. Priority must be given to protecting health care workers so they can continue to care for those affected by the attack. Resources must be mobilized to increase surge capacity of emergency departments, hospitals, and clinics [5]. Large-scale vaccination programs may need to be initiated or prophylactic antibiotics distributed to a large number of individuals within a very short period.

* Corresponding author. Department of Emergency Medicine, Olive View-University of California Los Angeles Medical Center, 14445 Olive View Drive, North Annex, Sylmar, CA 91342.
E-mail address: gmoran@ucla.edu (G.J. Moran).

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Although many potential problems associated with a bioterrorist attack seem intimidating, certain preparations could improve the ability to deal with this event. Physicians should be familiar with their contacts in the local public health department so that any suspicious illness can be reported promptly. Specific plans for bioterrorism should be incorporated in disaster planning [6]. Important topics would include infection control measures, communication with key agencies such as public health and law enforcement, mobilization of laboratory and pharmacy resources, plans for processing large numbers of patients, and increased security.

A wide range of microorganisms could potentially be used as weapons of mass destruction. The ideal agent for bioterrorism would be capable of producing illness in a large percentage of those exposed, be disseminated easily to expose large numbers of people (eg, through aerosol), remain stable and infectious despite environmental exposure, and be available to terrorists for production in adequate amounts. Fortunately, very few agents have these characteristics.

As part of their preparations for a possible bioterrorism event, the Centers for Disease Control and Prevention (CDC) have identified several organisms that are believed to have the greatest potential for use in this capacity [7]. Those believed to be top priority for preparations because of their suitability for weaponization and lethality are classified as category A agents. Several other organisms (categories B and C) are believed to be lower priority for specific preparations, but are recognized as possible bioterrorism agents. Box 1 lists the agents classified by the CDC as having potential for use in bioterrorism.

The potential for these agents to be turned into weapons varies considerably. Some are highly lethal but designated as lower-priority agents because they are unstable in the environment or would be difficult to disseminate effectively. Many of these agents cause nonlethal illness. Although highly lethal infections would create the most terror in the population, agents causing nonlethal illness could certainly provide significant social disruption, which would satisfy terrorist goals.

This article addresses some general issues related to preparing an effective response to bioterrorism. It also reviews the characteristics of organisms and toxins that could be used for bioterrorism, including clinical features, management, diagnostic testing, and infection control (Table 1).

Why biological terrorism?

Biological agents have several features that might make them more attractive to terrorists compared with conventional explosives, chemical weapons, or nuclear weapons. One advantage of biological agents is that they can inflict devastating damage even when used in minuscule amounts. They are odorless and easily concealed and are therefore difficult to detect. Enough botulinum toxin could be carried in one's pocket to kill millions of

Box 1. Agents with potential for use in biological terrorism

Category A

Easy to disseminate; cause high morbidity and mortality; and require specific enhancements of CDC's diagnostic capacity and enhanced disease surveillance

- Anthrax
- Plague
- Smallpox
- Hemorrhagic Fevers
- Botulism
- Tularemia

Category B

Somewhat easy to disseminate; cause moderate morbidity and low mortality; and require specific enhancements of CDC's diagnostic capacity and enhanced disease surveillance

- *Coxiella burnetii* (Q fever)
- *Brucella* species (brucellosis)
- *Burkholderia mallei* (glanders)
- Alphaviruses
- Venezuelan encephalomyelitis
- Eastern and Western equine encephalomyelitis
- Ricin toxin from *Ricinus communis* (castor beans)
- Epsilon toxin of *Clostridium perfringens*
- Staphylococcus enterotoxin B
- Food or waterborne agents
- *Salmonella* species
- *Shigella dysenteriae*
- *Escherichia coli* O157:H7
- *Vibrio cholerae*
- *Cryptosporidium parvum*

Category C

Emerging pathogens that could be engineered for mass dissemination in the future because of availability; ease of production and dissemination; and potential for high morbidity and mortality and major health impact

- Nipah virus
- Hantaviruses
- Tickborne hemorrhagic fever viruses
- Tickborne encephalitis viruses
- Yellow fever
- Multidrug-resistant tuberculosis

Table 1
Agents of bioterrorism

Disease	Clinical presentation	Diagnostic tests	Person-to-person transmission	Treatment	Vaccine/prophylaxis
Anthrax	Inhalation: fever, malaise for 1–2 days followed by respiratory distress, shock May have meningitis. Highly fatal if untreated Cutaneous: red papule progressing to shallow ulcer or blister, then black eschar	CXR may show wide mediastinum Gram-positive bacilli in blood, CSF, or skin lesion CSF may be bloody Blood culture is highest yield for inhalation anthrax	No	Ciprofloxacin or Doxycycline plus one to two other drugs Other active drugs include penicillin, clindamycin, rifampin, vancomycin, imipenem Levofloxacin or moxifloxacin probably also effective	Prophylaxis: ciprofloxacin or doxycycline for 60 days (30 days if given with vaccine) Bioport vaccine 0.5 mL SC at 0, 2, 4 weeks, 6, 12, 18 months, then annual boosters
Botulism	Cranial nerve palsies (particularly involving eyes) progressing to descending paralysis Paralysis lasts for weeks to months.	Diagnosis mostly clinical Mouse bioassay using patient serum takes several days, not widely available	No	Primarily ventilator support Antitoxin can prevent further progression, but will not reverse paralysis	None
Brucellosis	Fever, chills, anorexia, malaise May last weeks to months	Blood culture (slow-growing; notify laboratory if suspected) or serology Leukocyte counts variable CXR nonspecific	No Culture specimens may pose risk to laboratory workers	doxycycline or fluoroquinolone plus rifampin	doxycycline or fluoroquinolone plus rifampin for 6 weeks No vaccine available

Cholera	Severe watery diarrhea	Stool culture with special media	Rare Use body fluid precautions	Fluids, ciprofloxacin or doxycycline	Prophylaxis: ciprofloxacin or doxycycline Two-dose vaccine, not highly effective
Glanders (*Burkholderia mallei*)	Tender skin nodules, septicemia, pneumonia	Serology (not widely available) Blood culture often negative	Low risk, but respiratory isolation recommended Culture specimens may pose risk to laboratory workers	Doxycycline, TMP/SMX, chloramphenicol, fluoroquinolones, or aminoglycosides	Doxycycline, TMP/SMX, macrolides, or fluoroquinolones can be used for prophylaxis No vaccine
Pneumonic plague	Fever, chills, malaise, cough, respiratory distress, hemoptysis, meningitis, sepsis Highly fatal if untreated	Gram-negative coccobacilli in blood, sputum, lymph node aspirate Safety-pin appearance with Wright or Giemsa stain ELISA antigen test and serology using ELISA or IFA also available	High risk Use respiratory droplet isolation	Streptomycin, gentamicin, doxycycline, or chloramphenicol	Doxycycline or quinolone for 6 days Killed vaccine for bubonic plague, not effective against aerosol exposure (no longer manufactured)
Q fever (*Coxiella burnetii*)	Fever, chills, headache, sometimes pneumonia Mortality is low	Serology Titers may not be elevated until 2–3 weeks into illness	No Culture or tissue specimens may pose risk to lab workers.	Tetracycline or doxycycline	Tetracycline or doxycycline for 5 days for prophylaxis. Single dose inactivated whole cell vaccine, not licensed in United States
Ricin	Fever, dyspnea, vomiting, diarrhea, shock	CXR may show pulmonary edema Serology (not widely available)	No	Supportive	No vaccine or prophylaxis available

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Table 1 (*continued*)

Disease	Clinical presentation	Diagnostic tests	Person-to-person transmission	Treatment	Vaccine/prophylaxis
Smallpox	Fever, malaise, headache for 1–2 days, followed by papular rash progressing to vesicles and pustules.	Scabs or pustular fluid can be forwarded to CDC through local public health dept Can test vesicular fluid locally to exclude varicella	High risk Use strict respiratory isolation Identify any possible contacts Specimens can pose risk to laboratory workers	Supportive Cidofovir may be useful, but not tested	Vaccinia vaccine can prevent illness in contacts up to several days after exposure
Staphylococcal enterotoxin B	Sudden onset of fever, headache, myalgias, vomiting, diarrhea, dry cough Usually resolves within a day	Urine antigen, ELISA of nasal swab (not widely available)	No	Supportive	No vaccine
Tularemia	Fever, malaise, prostration, headache, weight loss and non-productive cough	CXR may show infiltrate, hilar adenopathy, or effusion Culture and gram stain of blood or sputum may show small, faintly staining, slow growing gram-negative coccobacilli. Serology usually positive after 1–2 weeks	No Culture specimens may pose risk to laboratory workers	Streptomycin, gentamicin, doxycycline, chloramphenicol, or fluoroquinolones	Doxycycline or ciprofloxacin for 14 days Investigational live attenuated vaccine

Venezuelan, Eastern, or Western equine encephalitis	Most have mild syndrome of fever, headache, and myalgia Rarely progresses to encephalitis	Serology of CSF or serum	Only via vector. Isolation not necessary	Supportive	Inactive vaccines for VEE, EEE, WEE are poorly effective Live vaccine for VEE has high incidence of side effects
Viral hemorrhagic fevers (eg, Ebola)	Fever, prostration, myalgia, conjunctival injection, petechial rash, bleeding Most are highly fatal	Thrombocytopenia Identification of virus requires special testing at CDC	Moderate risk Primarily transmitted through body fluids, but strict respiratory isolation is recommended	Primarily supportive Ribavirin may be effective for some, including Congo-Crimean HF, Lassa fever	No prophylaxis or vaccine available

Abbreviations: CDC, Centers for Disease Control and Prevention; CSF, cerebrospinal fluid; CXR, chest x-ray; EEE, Eastern equine encephalomyelitis; ELISA, enzyme-linked immunosorbent assay; HF, hemorrhagic fever; IFA, indirect fluorescent antibody; SC, subcutaneous; TMP/SMX, trimethoprim-sulfamethoxazole; VEE, Venezuelan equine encephalomyelitis; WEE, Western equine encephalomyelitis.

people if properly dispersed. Because biological agents do not trigger metal detectors, a terrorist could board a commercial airplane and transport the agent to any city in the world, where civilian populations are largely unprotected from this kind of attack.

Although access to hazardous biological agents is now more restricted than in the past, many agents are easy to obtain, certainly much more so than materials such as plutonium that could be used for other weapons of mass destruction. A biological weapon may be more difficult to prepare than a simple pipe bomb, but could often be prepared with only basic microbiology skills. Biological agents are also more difficult to trace because there is a delay between release of the agent and the first development of symptoms. A terrorist could release a biological agent in a major metropolitan area and be on another continent before anyone knows an attack occurred.

Biological agents certainly have the capacity to produce terror. Even if only a few people actually become ill, an entire city (or even country) could be disrupted if people believe they have been exposed to a deadly organism, such as Ebola virus or plague. In addition to preparing for the medical emergency, preparing for the panic and chaos that a bioterrorism attack would cause is also important. Thousands of people, ill or healthy, could descend on emergency departments and clinics, convinced they are about to die.

Probable scenarios and likely problems

One possible scenario for a large-scale biological attack would be aerosolized dispersal of a biological agent, such as from an airplane flying over a populated area or a small device planted in a ventilation system or crowded location. Fortunately, very few biological agents remain infectious after prolonged exposure to air and sunlight, making a large-scale attack difficult.

Because most illnesses caused by biological agents involve incubation periods, several days are likely to elapse before people become sick. In addition, because the victims will probably seek medical care at different facilities, some time may pass before the medical community is even aware that anything unusual has occurred. The epidemiologic pattern could be an early sign that an attack has occurred, but with patients presenting at different locations, often with relatively nonspecific signs and symptoms, suspecting that an act of terrorism has occurred will be difficult until the number of victims becomes significant.

In addition to the challenge of treating illnesses, clinicians will be faced with serious logistical problems if they receive a multitude of victims. Personnel, medications, and other resources are likely to be insufficient [8]. Prophylactic therapies are effective against some biological agents. However, knowing that doxycycline or ciprofloxacin can prevent illness in people exposed to anthrax will not help when immediate demand exceeds available supply. The federal government has stockpiles of antibiotics, as do many large cities, but rapid distribution to large numbers of people will be

difficult. Shortages of medicine could exacerbate the panic and chaos caused by the attack, not only among the victims streaming into emergency departments and hospitals but also among health care personnel.

Because some of the diseases caused by biological agents can be spread person-to-person, isolation of victims may be necessary, which will be another formidable challenge, especially with thousands of victims [9]. Many facilities do not have enough isolation beds even for their current needs [10], so patients will probably have to be cohorted in designated wards. Use of portable high-efficiency particulate air (HEPA) filters may also be useful in an outbreak situation [11].

Emergency department surveillance for bioterrorism events

As the front line of clinical medicine, emergency departments are key to an effective surveillance program [12]. Emergency physicians (and infectious disease specialists) must continue to be on the lookout for unusual syndromes or clusters of illness that could represent a natural or intentional outbreak.

Surveillance systems have been greatly expanded in recent years in response to concerns about bioterrorism. Many emergency departments are now part of regional syndromic surveillance systems [13]. Computerized emergency department information systems that continuously collect information have facilitated inclusion of many facilities in these types of systems and facilitate surveillance with minimal resource commitment. Systems that require human involvement to actively collect data or enter it into a dedicated system are likely to be abandoned or become less effective after many years of data collection with no real events [14]. Systems that run continuously in the background are more efficient and allow generation of data on the background incidence and variability of different clinical syndromes. Additional benefits of these systems include improved recognition of naturally occurring outbreaks and facilitation of research with large emergency department databases. These systems are generally designed so that individual patient identifiers are not sent to the central database, but public health reporting is exempted from Health Insurance Portability and Accountability Act (HIPAA) requirements for patient consent to share information [15].

Although syndromic surveillance systems could be useful in detecting disease outbreaks, the usefulness of these systems is unproven. Syndromic surveillance has been found to correlate with activity of some common viruses, such as influenza and respiratory syncytial virus (RSV) [16], but the more difficult task of detecting the first cases of a new outbreak has not been seen. Even with these surveillance systems in place, the initial detection of a bioterrorism event may still result from laboratory identification of anthrax, smallpox, plague, or Ebola virus. It is unlikely that any syndromic surveillance system would have detected the United States mail-related anthrax cases of 2001 before the first case was identified through laboratory

testing of cerebrospinal fluid (CSF). Unfortunately, microbiologic identification in the laboratory usually takes a couple of days, during which the outbreak may spread beyond easy containment. Investing in rapid laboratory testing methods that could be performed during emergency department evaluation might improve early detection. The real test will be when the next outbreak or bioterrorism event occurs.

The presence of syndromic surveillance systems does not remove the obligation of individual physicians to be vigilant for unusual clinical presentations and notify the local public health department if an infectious disease is suspected that could pose a threat to public health.

Agents with potential use as biological weapons

Some biological agents can be fatal, such as anthrax, botulinum toxin, and the viruses that cause hemorrhagic fevers, but terrorists could also meet their goals simply through making many people ill. Diseases such as brucellosis and tularemia are rarely lethal but can wreak havoc in a community if enough people are afflicted.

Fortunately, most biological agents cannot be dispersed effectively through aerosol. Many are not stable enough to withstand temperature changes, exposure to sunlight, and drying. Anthrax is often cited as an agent likely to be used for bioterrorism because spores are stable for many years, even in extreme environments. The spores are also of an optimal size (1–2 μm), which allows them to be inhaled into the lungs and deposited in the alveolar spaces. Most viral agents, such as those that cause hemorrhagic fevers and encephalitis, are unstable and therefore would be difficult to disperse through aerosolized large-scale attacks, but smallpox virus can remain viable after many years of storage. Bacterial agents vary in their stability during storage and dispersal. Although toxins such as botulinum toxin and staphylococcal enterotoxin B can remain stable for many years in storage, they can be difficult to disperse effectively to cause illness in a large population.

The agents designated by the CDC as category A are believed to be the greatest threat because of ease of dissemination or transmission, high mortality rate, potential major impact on public health, ability to incite panic and social disruption, and the requirement for additional major public health preparedness measures (see Box 1).

Category B agents would be moderately easy to disseminate, would cause moderate morbidity and low mortality, and would require specific enhancements of the CDC's diagnostic capacity and disease surveillance capabilities. The agents classified by the CDC as category C are emerging pathogens that could someday be engineered for mass exposure because of availability, ease of production and dissemination, and potential for high morbidity and mortality. Preparedness for category C agents requires ongoing research to improve disease detection, diagnosis, treatment, and prevention. Which newly emergent pathogens terrorists might use is impossible to know in advance.

For detection and response to these agents, a strong public health infrastructure is essential. It is also important for physicians to notify the local health department if unusual patterns of illness are observed.

Category A agents

Anthrax

History and significance

Bacillus anthracis could be considered to be the perfect agent for bioterrorism. It occurs naturally as a zoonotic disease of persons who handle contaminated animal products, such as hair or hides. It forms spores that are stable over long periods and can withstand exposure to air, sunlight, and even some disinfectants. Anthrax was studied as a possible weapon by the United States when it had an active biological weapons program, and has been weaponized by other countries [17]. Anthrax bacteria are easy to cultivate in the microbiology laboratory and can be readily induced to produce spores. The Soviet Union produced weaponized anthrax in ton quantities during the cold war era. An outbreak of inhalational anthrax occurred near a Soviet bioweapons facility at Sverdlovsk in 1979, resulting in 77 infections and 66 deaths, with some victims becoming ill up to 6 weeks after exposure [18]. The Japanese cult group Aum Shinrikyo attempted several attacks with anthrax in the 1990s but were unsuccessful [19].

Anthrax became the most notorious bioterrorism agent after October 4, 2001, when a 63-year-old man died of inhalational anthrax that was traced to intentional exposure through the United States mail [20,21]. This instance represented the first inhalation anthrax case in the United States since 1976 [22]. Ultimately, 18 cases of anthrax (11 inhalational and 7 cutaneous) were confirmed. More than 30,000 people who were potentially exposed received postexposure prophylaxis, and none developed inhalational anthrax.

Clinical presentation

Anthrax can present as three distinct clinical syndromes in humans: cutaneous, inhalation, and gastrointestinal. Cutaneous anthrax, the most common naturally occurring form, is usually spread through contact with infected animals, particularly cows, sheep, and horses, or their products. Cutaneous anthrax (Fig. 1) typically produces large black eschars on the skin, but in early stages may appear as papules that progress to vesicles. Patients may also experience lymphadenopathy, fever, malaise, and nausea. Local cutaneous anthrax has a mortality rate of less than 1% if treated but can occasionally become systemic, with mortality rates approaching 20% [23].

Gastrointestinal anthrax is rare in humans. It is acquired by ingesting inadequately cooked meat from infected animals. As the ingested spores germinate, the infected person may develop ulcers in the mouth or esophagus, or may develop lesions lower in the intestinal tract that caused them to

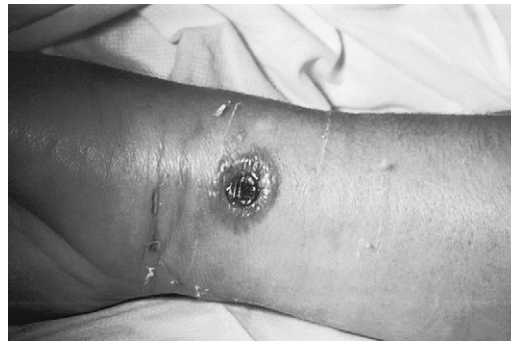

Fig. 1. Anthrax skin lesion. (*Courtesy of* Centers for Disease Control and Prevention/Dr. Philip S. Brachman.)

present with abdominal pain, fever, and diarrhea that progresses to a sepsis syndrome with high mortality.

A far greater threat is posed by the inhalational form of anthrax. This type of anthrax, also known as woolsorter's disease when it occurs naturally, is only rarely seen among wool or tannery workers, but is the form of anthrax most likely to be spread through a terrorist attack. Inhalational anthrax can be rapidly fatal once symptoms begin.

The victims of the 2001 anthrax attack presented with a fairly consistent clinical syndrome [24–26]. Symptoms began as a nonspecific prodrome resembling influenza, with malaise, dry cough, and mild fever. This progressed to chills, sweats, nausea, and vomiting, with development of chest pain and respiratory distress. Almost all patients had some abnormality on chest radiograph or CT scans, including infiltrates, pleural effusion, or mediastinal widening. Some patients developed meningitis. Inhalation anthrax can sometimes present without the usual symptoms of chest pain and shortness of breath [27]. The illness often progressed to septic shock and death approximately 24 to 36 hours after the appearance of respiratory distress.

Before the events of 2001 in the United States, almost all cases of inhalational anthrax were fatal when treatment was initiated after development of significant symptoms. The case fatality rate was 45% among the 11 confirmed inhalational cases resulting from bioterrorism in the fall of 2001, largely attributed to earlier and more aggressive supportive care and antibiotic therapy [22,28].

Diagnosis

Generally, diagnosis must be suspected on clinical grounds for treatment to be initiated in time to be beneficial. By the time the disease is confirmed through laboratory tests, many patients will be beyond help [29]. *B anthracis* is detectable through Gram stain of the blood and blood culture on routine media, but often not until the patient is seriously ill. An enzyme-linked immunosorbent assay (ELISA) for the anthrax toxin exists, but most hospital

laboratories do not have it readily available. The organism may also be identified in CSF, because approximately 50% of cases have hemorrhagic meningitis [30]. Chest films may show a widened mediastinum and pleural effusions [31], but those findings are not universal and are usually seen late in the disease.

Infection control precautions

Anthrax does not spread person-to-person, and standard precautions are recommended. However, persons who present shortly after exposure may still be contaminated with spores. Any persons coming into direct contact with a substance alleged to be anthrax spores should simply bathe with soap and water and store contaminated clothing in a plastic bag, but decontamination procedures for other persons in the area should not be necessary. Disinfectants such as bleach solutions can be used to decontaminate inanimate objects, but are not recommended for skin.

Treatment and prophylaxis

The mainstay of treatment is antibiotic therapy, but the regimen should be started as early as possible to be effective. Although penicillin is usually regarded as the preferred treatment for naturally occurring anthrax [32], penicillin-resistant strains are known to occur, and the belief is that terrorists would be likely to use a more resistant strain (although this was not the case in the 2001 attack). Penicillin is not recommended as empiric treatment until susceptibility of the organism is known. *B anthracis* is also susceptible to tetracyclines, erythromycin, chloramphenicol, gentamicin, and fluoroquinolones. Initial empiric treatment with ciprofloxacin or another fluoroquinolone is recommended until susceptibility is known [33]. Supportive therapy to maintain the airway, replenish fluids, and alleviate shock is also crucial. Because spores can be dormant for a long time, a 60-day course of antibiotics is recommended for treating anthrax.

In patients who were exposed to anthrax but are not yet sick, illness and death can be prevented with prophylactic antibiotics. The CDC recommends ciprofloxacin (500 mg orally twice daily) or doxycycline (100 mg orally twice daily) as first-line prophylaxis after inhalational exposure to anthrax, and for presumptive treatment of mild symptoms after anthrax exposure. If anthrax exposure is confirmed, antibiotics should be continued for at least 60 days in all exposed individuals, and patients should be followed up closely after antibiotics are discontinued.

A vaccine for anthrax, derived from an attenuated anthrax strain, has been licensed by the U.S. Food and Drug Administration since 1970 [34]. This vaccine has been used mostly for military personnel, and might not be generally available to the public in adequate amounts in the event of a large biological attack. The vaccine is given repeatedly in a series of six subcutaneous injections over 18 months and can cause several adverse effects [35]. It is not licensed for use against inhalational anthrax exposure, but some limited

animal data suggest protection [36]. Attempts to develop a better vaccine have met with technical problems and political interference [37].

Several anthrax hoaxes have been perpetrated in many United States cities, both before and after the 2001 attacks. Public health officials, working with law enforcement and first-response personnel, should determine the necessity for decontamination and prophylactic therapy after these alleged exposures. Until the substance can be identified, chemoprophylaxis is a reasonable precaution if the threat is credible. Good communication among public health, law enforcement, and clinicians caring for persons who may have been exposed is critical for appropriate management.

Plague

History and significance

Few illnesses carry as many terrifying connotations for the general public as plague, caused by the gram-negative bacillus *Yersinia pestis*. The ''Black Death'' killed millions of people throughout Europe in the fourteenth century. A more recent pandemic originated in China and spread worldwide at the turn of the twentieth century. Bubonic plague is the most common naturally occurring form. It is a zoonotic infection spread from the rodent reservoir to man through the bites of infected fleas. Plague, like anthrax, also has a pneumonic form, which can be transmitted through inhalation of droplets spread by cough or, in the event of a terrorist attack, through inhalation of an aerosol containing *Y pestis*. As with anthrax, the pneumonic form of the disease is far more dangerous. Left untreated, pneumonic plague is nearly always fatal within 2 days of onset of symptoms.

Plague is more difficult to use as a biological weapon than anthrax because *Y pestis* is susceptible to drying, heat, and ultraviolet light. However, unlike anthrax, secondary cases may result from person-to-person transmission. Attempts to use plague as a biological weapon date back to the ancient practice of flinging plague-infected corpses over the walls of cities under siege. The Japanese attempted to use plague as a biological weapon by releasing infected fleas over cities in Manchuria during World War II, but dissemination attempts met with limited success. The United States did not develop plague as a potential weapon because of its persistence in the environment and the possibility of noncombatant and friendly casualties after an attack. The Soviet Union reportedly developed dry, antibiotic-resistant, environmentally stable forms of *Y pestis* that could be disseminated as an aerosol [38].

Clinical presentation

Bubonic plague begins as painful adenopathy several days after the infecting flea bite. Without treatment, the illness progresses within several days to septicemia. Approximately 5% to 15% of patients will develop a secondary pneumonia that can spread plague through droplets from coughing.

Aerosol dispersal with resulting pneumonic plague would be more likely in a bioterrorism attack. After an incubation period of 2 to 3 days, patients who have pneumonic plague typically develop fulminant pneumonia, with malaise, high fever, cough, hemoptysis, and septicemia with ecchymoses and extremity necrosis. Findings on chest radiographs are generally typical of patients who have pneumonia. The disease progresses rapidly, leading to dyspnea, stridor, cyanosis, and septic shock. Death is normally the result of respiratory failure and circulatory collapse [39].

Diagnosis

A presumptive diagnosis can often be made by identifying *Y pestis* in Gram's, Wayson's, or Wright-Giemsa stain of blood, sputum, or lymph node aspirate samples. A definitive diagnosis is generally made with culture studies. An ELISA test for plague exists, but it is not widely available. Direct fluorescent antibody staining of the capsular antigen is also available. Buboes may be aspirated with a small-gauge needle, but incision and drainage should not be performed because of the risk for aerosolization of the organism. The organism has a characteristic bipolar "safety pin" appearance.

Hematologic studies will show leukocytosis with left shift. Bilirubin levels and serum aminotransferases are often elevated. Antibody studies are not useful for diagnosing disease during the acute phase. Blood, sputum, bubo aspirate, and CSF cultures on normal blood agar media are often negative at 24 hours but positive by 48 hours. The colonies of *Y pestis* are usually 1 to 3 mm in diameter and have been described as having a "beaten copper" or "hammered metal" appearance [36].

Infection control precautions

Unlike pulmonary anthrax, pneumonic plague is very contagious. Strict respiratory isolation is necessary until infected patients have undergone treatment for at least 3 days. Unfortunately, because the initial presentation resembles that of severe pneumonia caused by other agents, the actual diagnosis may not be known for several days. Therefore, patients who present with fulminant pneumonia after a suspected biological attack should be held in respiratory isolation until the cause has been determined.

Treatment and prophylaxis

Early treatment with antibiotics, within 24 hours of the appearance of symptoms, is crucial to the survival of patients who have pneumonic plague. Streptomycin is the traditional preferred agent but may not be readily available in some facilities. Doxycycline, gentamicin, ceftriaxone, chloramphenicol, and fluoroquinolones should also be effective. Treatment should be continued for a minimum of 10 days, or for 4 days after clinical recovery. Patients who have mild illness can be treated with oral doxycycline or fluoroquinolones.

Persons exposed to plague should receive postexposure prophylaxis with doxycycline (100 mg twice daily) or a fluoroquinolone for 6 days. Medical personnel who practice good infection control precautions should not require prophylaxis. A recombinant vaccine is under development and seems to protect against pneumonic plague.

Smallpox

History and significance

Smallpox (variola) is a DNA orthopoxvirus that has been a scourge to humans throughout recorded history. No nonhuman reservoirs or human carriers exist for smallpox; the disease survives through continual person-to-person transmission. The first documented epidemic of smallpox was during the Egyptian-Hittite war in 1350 BC. The mummy of Ramses V has lesions that suggest he died of smallpox at the age of 35 years in 1143 BC. Smallpox was used inadvertently as a biological weapon when Cortez introduced it to the new world in 1520, devastating much of the native population. The English used smallpox intentionally during the French and Indian war in 1754 when tainted blankets were distributed to Native Americans, with up to 50% mortality in many tribes. The last case of wild smallpox occurred in Somalia in 1977, although a few small outbreaks have occurred related to laboratory exposure. The disease was declared eradicated by the World Health Organization (WHO) in 1980 and routine vaccination was stopped soon after.

Because of its propensity for secondary human-to-human transmission, smallpox is one of the most feared agents that could be unleashed in a biological attack [40]. Because vaccination is no longer given, most persons today are susceptible to infection. Even those who were vaccinated as children are likely to be susceptible, because immunity wanes over time.

Stocks of variola virus are supposedly stored at only two WHO-approved storage facilities: the CDC in Atlanta and the NPO (Scientific and Production Association) in the Novosibirsk region of Russia. The Soviet Union may have developed stockpiles of weaponized smallpox and experimented with genetic manipulation of the virus [38]. Many believe that some virus samples may be in the hands of potential terrorists. Because the virus is difficult to obtain, an intentional smallpox exposure would require extensive resources that might be out of reach for small groups.

Clinical presentation

The incubation period associated with smallpox is approximately 12 days. Smallpox begins with a febrile prodrome a few days before the rash that may also be accompanied by chills, head and body aches, nausea, vomiting, and abdominal pain [41]. The characteristic rash develops on the extremities and spreads centrally. Skin lesions evolve slowly from macules to papules to vesicles to pustules, with each stage lasting 1 to 2 days. Unlike chickenpox, all smallpox lesions are at the same stage of development.

The first lesions are often on the oral mucosa or palate, face, or forearms. The vesicles or pustules tend to be distributed centrifugally, with the greatest concentration on the face and distal extremities, including the palms and soles. Vesicles and pustules are deep-seated, firm, or hard, round, well-circumscribed lesions; they are sharply raised and feel like small round objects embedded under the skin (Fig. 2). As they evolve, the lesions may become umbilicated or confluent and will scab over in 1 to 2 weeks, leaving hypopigmented scars.

If a biological attack is not known to have occurred, some early smallpox cases are likely to be mistaken for chickenpox or other diseases. Chickenpox differs from smallpox in that the prodrome is milder, the vesicles are superficial (ie, easily collapse on puncture) and predominate on the trunk as opposed to the distal extremities, and active and healing lesions occur simultaneously.

Mortality is reported as approximately 30% overall among unvaccinated persons, but this reflects historical data in populations without modern medical care. Mortality is higher in infants and elderly individuals, and would likely be much lower among healthy adults and older children. Death occurs late in the first week or during the second week of the illness and is caused by the toxemia induced by the overwhelming viremia. A rare hemorrhagic form occurs with extensive bleeding into the skin and gastrointestinal tract followed almost universally by death within a few days.

Diagnosis

The diagnosis of smallpox can be confirmed with electron microscopy or gel diffusion on vesicular scrapings, but these modalities are not available in most hospital laboratories. If smallpox is suspected, the laboratory must be notified to take proper precautions. Smallpox specimens should be handled under biosafety level 4 conditions. Because testing for varicella virus is usually available, a vesicular eruption in which varicella cannot be identified should alert clinicians to possible smallpox. Specimens could then be forwarded for testing at a specialized laboratory, such as at the CDC or U.S.

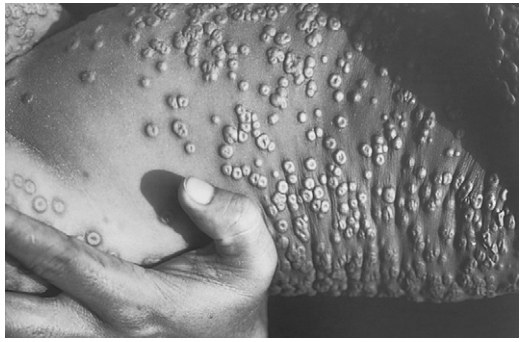

Fig. 2. Smallpox skin lesions on the trunk. (*Courtesy of* Centers for Disease Control and Prevention/James Hicks.)

Army Medical Research Institute of Infectious Diseases (USAMRIID). Electron microscopy cannot reliably differentiate between variola, vaccinia (cowpox), and monkeypox. New polymerase chain reaction (PCR) techniques that can rapidly diagnose smallpox may soon be available.

Infection control precautions

Identification of even a single case of smallpox would signal an infectious disease emergency of worldwide significance. Clinicians who suspect smallpox should immediately contact their local health department and their hospital infection control officer. The local health department will immediately contact the state public health department and the CDC. The most important issue concerning smallpox would be containment of any subsequent outbreak. If an initial outbreak cannot be contained within a single community, an arduous worldwide eradication effort may need to be begun anew.

Smallpox is readily transmitted person-to-person through respiratory droplets. Because delays in the initial diagnosis are likely, some secondary exposures may already have occurred by the time smallpox virus is identified as the cause of illness. Although people are generally not considered infectious until the rash begins, they can shed virus in early stages of the rash before it can be readily identified as smallpox.

Aggressive quarantine measures will be necessary to prevent further spread. Anyone who has had direct contact with an infected person should undergo strict quarantine with respiratory isolation for 17 days. In large-scale outbreaks, infected individuals may need to be kept at home.

Virions can also remain viable on fomites for up to 1 week. All laundry, including bedding of infected individuals, should be autoclaved or washed in hot water with bleach. Standard hospital antiviral surface cleaners are adequate for disinfecting surfaces (eg, counters, floors). Viable virus has been found in scabs that have been stored for up to 13 years, so meticulous decontamination is crucial. If possible, all bodies should be cremated to prevent subsequent exposure of individuals who have had contact with the deceased, such as funeral home workers.

Treatment and prophylaxis

No known effective treatment exists against smallpox. The drug cidofovir, used to treat cytomegalovirus infections, may be active against variola virus, but no data currently show the drug's efficacy in humans. Management of cases will be largely supportive care.

A vaccine based on the vaccinia virus is effective for immunizing against smallpox, and has been the mainstay of smallpox control. Unlike many other vaccines, smallpox vaccine can be effective in preventing disease even up to several days after exposure. Although stockpiles of the vaccine were low after routine vaccination ceased in the 1980s, concern about bioterrorism has prompted recent development of more modern vaccine manufacturing methods and creation of new stockpiles.

Smallpox vaccination is not without risk [42]. Risks are higher for those who have never been previously vaccinated. Complications from the use of the current smallpox (vaccinia) vaccine range from the relatively benign autoinoculation and generalized vaccinia through the more severe progressive vaccinia. The most serious complications include postvaccinial encephalopathy and encephalitis, but fortunately these are rare [43]. Because vaccinia is a live virus, potential exists for secondary transmission after vaccination [44]. In the era of routine smallpox eradication, the only contraindications to vaccination were pregnancy, certain immunocompromised conditions, and eczema. In the setting of a bioterrorism-related smallpox outbreak, those believed to have been exposed to the virus would have no absolute contraindications to vaccination.

In 2002, president Bush announced a program for the vaccination of health care workers against smallpox. The goal was to vaccinate 500,000 health care workers, but only a very small number actually received the vaccine. Many health care workers declined vaccination because of concerns about adverse reactions [45]. An advisory panel recommended against routine vaccination of emergency physicians because of concern that even a small risk for adverse reactions outweighed the minimal benefit that could be expected from smallpox vaccination in the absence of smallpox transmission anywhere in the world [46]. In the event of even a single smallpox case or a credible imminent threat, the benefits of smallpox vaccination would become clearer. Performing a rigorous scientific analysis of the risks and benefits for smallpox vaccination is impossible, because the true risk of a smallpox attack is unknown. The probability that any individual physician would be among those to see the first few cases of a smallpox outbreak is extremely low. Because smallpox vaccine can provide protection up to several days after exposure, a strategy to ensure timely vaccination of exposed health care workers and the general public if a smallpox case is identified would avoid the risk for unnecessary adverse reactions to smallpox vaccine while smallpox does not exist. Emergency and infectious disease physicians should work with public health authorities to ensure that these mechanisms are in place.

The Advisory Committee on Immunization Practices (ACIP) and the Health care Infection Control Practices Advisory Committee (HICPAC) recommend that each acute-care hospital identify health care workers who can be vaccinated and trained to provide direct medical care for the first smallpox patients requiring hospital admission and to evaluate and manage patients who are suspected as having smallpox [47]. When feasible, the first-stage vaccination program should include previously vaccinated health care personnel to decrease the potential for adverse events. Additionally, persons administering smallpox vaccine in this pre-event vaccination program should be vaccinated.

Smallpox vaccine is administered by using the multiple-puncture technique with a bifurcated needle packaged with the vaccine and diluent. According to the product labeling, 2 to 3 punctures are recommended for

primary vaccination and 15 for revaccination. A trace of blood should appear at the vaccination site after 15 to 20 seconds; if no trace of blood is visible, an additional 3 insertions should be made by using the same bifurcated needle without reinserting the needle into the vaccine vial. If no evidence of vaccine take is apparent after 7 days, the person can be vaccinated again. Optimal infection-control practices and appropriate site care should prevent transmission of vaccinia virus from vaccinated health care workers to patients. Health care personnel providing direct patient care should keep their vaccination sites covered with gauze in combination with a semipermeable membrane dressing to absorb exudates and provide a barrier for containment of vaccinia virus to minimize the risk of transmission. The dressing should also be covered by a layer of clothing [48].

Viral hemorrhagic fevers

History and significance

Like plague, the viral hemorrhagic fevers, which include Ebola and Marburg disease, Lassa fever, and Bolivian hemorrhagic fever, incite fear in the general public. Many of these viruses cause rapidly progressive illnesses that carry extremely high mortality rates. Viral hemorrhagic fevers can be spread in various ways. Lassa fever, for instance, is usually spread through the ingestion of food contaminated with rodent urine, although person-to-person transmission through contact with urine, feces, or saliva can also occur.

Yellow fever and dengue (Flaviviridae) are probably the archetypical diseases of this group but are not considered significant bioterrorism threat agents. Hantavirus (Bunyaviridae) is enzootic in rodents. West Africa's Lassa fever, and Argentine, Bolivian, Brazilian, and Venezuelan hemorrhagic fevers (Arenaviridae) are also enzootic in rodents within their respective areas. The most publicized viral hemorrhagic fevers are the Ebola and Marburg (Filoviridae) viruses. These viruses produce grotesquely lethal diseases, making them favorites with the popular media. The reservoir and natural transmission of Ebola and Marburg are unknown, but they are readily transmittable through infected blood and tissue. Aerosols may be formed naturally when infectious body fluids are expelled or, in the case of hantavirus, when rodent feces and urine are resuspended from movement in the area. Laboratory cultures can yield sufficient concentrations of organisms to provide a credible terrorist weapon if disseminated as an aerosol [36].

Clinical presentation

The clinical presentations of different viral hemorrhagic fevers vary, but all can involve diffuse hemorrhage and bleeding diatheses. The incubation periods of the hemorrhagic fevers range from 4 to 21 days. The more severe fevers, such as Ebola, generally have shorter incubation periods. Patients typically present with a nonspecific prodrome that includes fever, myalgia, and prostration. On physical examination, the only findings may be conjunctival injection, mild hypotension, flushing, and scattered petechiae.

Laboratory testing may show thrombocytopenia or other signs of disseminated intravascular coagulation or elevated levels of liver enzymes or creatinine. Within hours or days after the initial presentation, patients will experience a quick deterioration of their status, followed by mucous membrane hemorrhage and shock, often with signs of neurologic, pulmonary, and hepatic involvement [49].

Diagnosis

Specific tests for some hemorrhagic fevers exist but are not available at most hospital laboratories. Specific identification requires ELISA detection of antiviral IgM antibodies or direct culture of the viral agent from blood or tissue samples. These tests can only be performed at specialized laboratories, such as those available at CDC or USAMRIID. If the agent remains unknown, it may be visualized through electron microscopy (Fig. 3) followed by immunohistochemical techniques. The laboratory should be notified if Ebola or Marburg viruses are suspected because specimens should be handled under biosafety level 4 precautions.

Infection control precautions

Contact precautions are necessary for all health care personnel managing persons who have hemorrhagic fever [50]. All body fluids should be considered infectious. In several outbreaks in Africa, hospital personnel were able to prevent transmission to themselves and other patients simply through wearing gowns, gloves, and masks. Respiratory isolation, however, may be necessary for patients who experience massive hemorrhage into the lungs. Aerosol transmission of hemorrhagic fever has been shown in animal studies but does not appear to be a significant mode among humans. Under ideal conditions, each patient should be cared for in a private room. The room should be entered through an adjoining anteroom that is used for decontamination and hand washing.

Treatment and prophylaxis

Good supportive care is the mainstay of therapy for patients who have any viral hemorrhagic fever. Special care must be taken during fluid

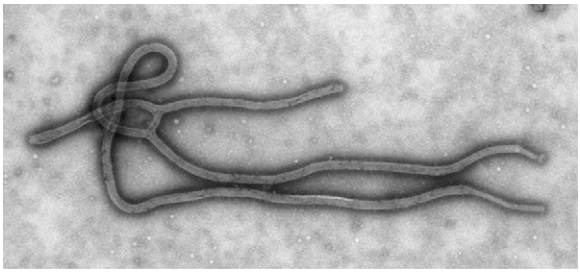

Fig. 3. Electron micrograph of Ebola virus. (*Courtesy of* Centers for Disease Control and Prevention/Cynthia Goldsmith.)

resuscitation, because fluid transudation into the lungs will occur in some patients. In addition, because the risk for hemorrhage is high among these patients, caution is also necessary when placing intravenous and other lines. For patients who have Lassa fever, Bolivian hemorrhagic fever, Congo-Crimean hemorrhagic fever, or Rift Valley fever, the antiviral agent ribavirin may offer some benefit [49].

Botulism

History and significance

Botulism is a syndrome caused by exposure to one or more of the seven neurotoxins produced by the bacillus *Clostridium botulinum*. The botulinum toxins are among the most potent toxins in existence. They are 100,000 times more toxic per microgram than the nerve agent sarin, which was used by the cult Aum Shinri Kyo in their terrorist attack in the Tokyo subway system in 1995. Theoretically, enough toxin is present in a single gram of crystallized botulinum toxin to kill more than 1 million people.

Most cases of naturally occurring botulism result from the ingestion of improperly prepared or canned foods; the disease is also associated, although rarely, with infected wounds or abscesses related to injection drug use. Terrorists could conceivably contaminate food supplies with the botulinum toxins or initiate a large-scale attack by dispersing the toxins through aerosol over a vast area [51]. Despite efforts to produce an effective botulinum toxin weapon, botulism is unlikely to ever be effectively deployed as a weapon of mass destruction. Aerosol delivery would require large quantities of toxin at the optimal time, because botulinum toxin quickly degrades in the environment and is rendered nonlethal within minutes after release. Municipal water reservoirs are most likely safe from contamination by terrorists, because ton quantities of toxin would be necessary due to the effects of dilution. Botulinum toxin is not stable for extended periods in water, and chlorination provides an effective means of destruction.

Clinical presentation

Unlike most other bioterrorism-related illness, botulism has a fairly characteristic presentation and therefore can usually be diagnosed from the clinical signs and symptoms alone. The clinical syndrome is similar regardless of whether the botulinum toxins are ingested or inhaled. Once absorbed, the toxins block the cholinergic synapses and thereby interfere with neurotransmission. After an incubation period of 1 to 5 days, patients generally present with neurologic manifestations. Bulbar palsies are extremely common, with ocular signs such as diplopia and mydriasis. Other bulbar effects may include dysarthria and dysphagia. Eventually, patients will experience progressive weakness, followed by skeletal muscle paralysis. The cause of death is usually respiratory failure. On physical examination, infected patients are generally afebrile, alert, and oriented. They may have postural hypotension, and some complain of dry mouth.

Diagnosis

Laboratory testing is generally not helpful. The diagnosis usually must be made on clinical and epidemiologic grounds. Botulinum toxins are generally difficult to detect, and most patients do not have antibody responses because the amount of toxin required to produce clinical symptoms is so small. Some bioassay tests are available, such as a mouse bioassay, in which the specimen is injected into mice that are then observed for changes. These assays are labor-intensive and take several days, and are only available in a few laboratories.

Infection control precautions

Standard universal procedures should be taken whenever a patient presents with botulism. Patients who may have the toxin on their skin as a result of aerosol exposure should bathe thoroughly with soap and water and discard their clothes.

Treatment and prophylaxis

The mainstay of treatment is hemodynamic and ventilatory support. Most patients who have botulism will survive if they are given proper ventilatory assistance. Full recovery, however, generally takes several weeks or months, during which the patient is required to remain on a ventilator, because new synapses must grow to replace the ones damaged by the botulinum toxin. Unfortunately, this strategy would present insurmountable logistical problems in the event of a terrorist attack, when hundreds or thousands of people may be afflicted with respiratory failure. Mechanical ventilators will be in short supply, and bag-ventilation would be impractical for weeks to months. The sudden demand for limited resources could make proper care for the many victims nearly impossible.

A trivalent equine botulinum antitoxin is available from the CDC and some state health departments [52]. Unfortunately, it is effective only in preventing further deterioration; it will not reverse muscle weakness that has already developed. It would not be available in adequate amounts to treat the number of people resulting from a large-scale exposure. Because the antitoxin is a horse serum product, skin testing for horse serum sensitivity is recommended before the drug is administered. A newer human botulism immunoglobulin has been shown to be effective for infant botulism [53], and would probably also be effective for preventing progression of botulism related to bioterrorism events.

Tularemia

History and significance

Otherwise known as *rabbit* or *deer fly fever*, tularemia is usually contracted after contact with infected animals or from the bites of infected deerflies, mosquitoes, or ticks. It can also be caused by the ingestion of contaminated food and water and the inhalation of contaminated air. The

causative organism, *Francisella tularensis*, is a small, intracellular gram-negative coccobacillus. *F tularensis* remains viable for weeks in water, soil, carcasses, and hides, and for years in frozen meat. It is easily killed by heat and disinfectants but can survive for months in temperatures of freezing and below.

F tularensis was weaponized by the United States in the 1950s and 1960s during the offensive biowarfare program, and other countries are also suspected to have weaponized the organism. *F tularensis* could potentially be stabilized for weaponization and produced in either a wet or dried form for delivery in a terrorist attack [54]. As few as 10 to 50 organisms may cause disease if inhaled or injected intradermally; however, approximately 10^8 organisms are required to cause infection after oral ingestion.

Clinical presentation

Tularemia can manifest in several ways, depending on the route of infection. Ulceroglandular tularemia resulting from contact with infected animals is the most common form, accounting for up to 85% of cases. This form manifests as fever, chills, headache, malaise, an ulcerated skin lesion, and painful regional lymphadenopathy. Skin ulcers typically begin in the area of exposure to the organism, most commonly on the hands.

Typhoidal tularemia, which is caused by infectious aerosols, is the form most likely to appear after a terrorist attack. After an incubation period of 2 to 10 days, most victims present with fever, headache, chills, myalgia, nausea, vomiting, and diarrhea. They may also have cough and other respiratory symptoms. Initial laboratory evaluations are generally nonspecific. Approximately 80% of patients will have pneumonia. These nonspecific signs and symptoms would make a specific diagnosis of tularemia difficult in the event of a terrorist attack, leading to increased mortality. Case fatality rates of untreated naturally acquired typhoidal cases is approximately 35%, compared with 1% to 3% for appropriately treated cases.

Diagnosis

Tularemia can be diagnosed through culturing the organism from blood, ulcers, conjunctival exudates, sputum, gastric washings, and pharyngeal exudates, although culture is difficult and the yield is low. The organism grows poorly on standard media but can be grown on media containing cysteine or other sulfhydryl compounds (eg, glucose cysteine blood agar, thioglycollate broth). The laboratory should be notified if tularemia is suspected, because the organism represents a hazard to laboratory personnel. Culture should only be attempted using biosafety level 3 precautions.

Tularemia is usually diagnosed serologically using bacterial agglutination or ELISA. Antibodies to *F tularensis* appear within the first week of infection, but levels adequate to allow confidence in the specificity of the serologic diagnosis (titer $>1{:}160$) do not appear until more than 2 weeks after infection [55]. Cross-reactions can occur with other organisms, such as

Brucella, *Proteus*, and *Yersinia*. Because antibodies may persist for years after infection, serologic diagnosis depends on a fourfold or greater increase in the tularemia tube agglutination or microagglutination titer during the course of the illness. Titers are usually negative during the first week of infection, become positive during the second week in 50% to 70% of cases, and achieve a maximum level in 4 to 8 weeks [56].

Infection control precautions

Although person-to-person transmission of tularemia is rare, health care personnel should follow standard universal precautions whenever managing patients who have the disease.

Treatment and prophylaxis

The traditional treatment for patients who have tularemia is a 10- to 14-day course of streptomycin, but this agent may not be readily available in the event of an attack. Other agents that have proven effective against the disease include gentamicin, tetracycline, chloramphenicol, and fluoroquinolones [57]. Ciprofloxacin or doxycycline could be used for postexposure protection against tularemia, based on in vitro susceptibilities. A 2-week course should be effective as postexposure prophylaxis when given within 24 hours of aerosol exposure.

Category B agents

Coxiella burnetii *(Q fever)*

History and significance

Not all potential agents of bioterrorism cause fulminant, life-threatening illnesses; some produce milder, longer-lasting illnesses. Q fever is a good example of the latter. The disease has a long incubation period, after which it tends to produce nonspecific, fairly mild symptoms. Only very rarely is it fatal. However, a terrorist group could still disrupt and terrify a community by causing nonfatal illness.

Q fever is an acute or chronic zoonotic illness caused by the rickettsial organism *Coxiella burnetii*. The illness was described during a 1935 outbreak in Queensland, Australia, and was called Q (query) fever because the origin was not currently identified.

Q fever occurs worldwide and usually results from exposure to infected livestock such as sheep, cattle, or goats. Infected animals are usually asymptomatic; parturient animals may have large numbers of organisms present in the placenta, resulting in environmental contamination. Humans typically become infected through inhaling aerosols containing *C burnetii*. The organism proliferates in the lung and then spreads through the bloodstream.

C burnetii has a spore-like form that can survive for weeks or months in the environment. The organism can survive heat and drying and can be

disseminated through airborne spread. *C burnetii* is highly infectious to humans; a single viable organism is adequate to cause infection. Because of these characteristics, it is considered suitable for use as a bioweapon.

Clinical presentation

The presenting symptoms of Q fever are nonspecific. In fact, many infections appear to be asymptomatic. In those who become ill, the most common findings are fever, chills, and headache. Onset may be sudden or gradual, and the incubation period can vary considerably from approximately 10 days up to several weeks. Most patients have a self-limited febrile illness that resolves within 1 or 2 weeks. Overall mortality is low: 2.4% in one large series of hospitalized patients [58]. However, many patients report malaise and fatigue that persist for months.

Q fever may manifest as pneumonia. Many patients who have Q fever have radiographic evidence of pneumonia but no cough. If cough is present, it is usually nonproductive. Severe headache is frequently associated with Q fever pneumonia. Hepatic transaminase levels are frequently elevated, but the peripheral white blood cell count is usually normal. Some patients have a rapidly progressing pneumonia syndrome similar to Legionnaire's disease. Although Q fever pneumonia may have various radiographic appearances, multiple rounded opacities (often pleural-based) are a suggestive pattern. Pleural effusion (usually small) is found in approximately one third of cases [59].

Q fever can also have various chronic manifestations, including endocarditis, intravascular infection, hepatitis, and osteomyelitis. Endocarditis typically involves abnormal or prosthetic valves but can sometimes develop in normal valves. *C burnetii* will not grow in routine blood cultures, so culture-negative endocarditis is a typical clinical picture. Liver involvement may manifest as acute hepatitis or as a fever of unknown origin, with granulomas found on liver biopsy.

Diagnosis

Most laboratories do not have the facilities to isolate *C burnetii*. Serologic testing through complement fixation, indirect fluorescent antibody (IFA) or ELISA is the mainstay of diagnosis for Q fever. However, titers may not be elevated until 2 to 3 weeks into the illness. Convalescent titers characteristically show a fourfold increase 2 or 3 months after onset of illness.

Infection control precautions

Human-to-human spread of Q fever does not seem to occur, and therefore isolation is not required. However, tissues from patients who have Q fever may pose a threat to laboratory workers and should be processed under biosafety level 3 conditions.

Treatment and prophylaxis

Several antibiotics have activity against *C burnetii* and seem to shorten the duration of illness. Antibiotics also seem to prevent illness when given

during the incubation period [60]. Tetracyclines are most commonly used for treatment. Other drugs that have been used include macrolides, quinolones, chloramphenicol, rifampin, and trimethoprim-sulfamethoxazole. The optimal duration of therapy is unclear. Treatment for uncomplicated infections or prophylaxis is generally given for 5 to 7 days. Prolonged combination treatment (eg, doxycycline plus a quinolone or rifampin) is usually given for chronic infection such as endocarditis. A vaccine against Q fever is being used in Australia but is not licensed in the United States [61].

Brucella *species (brucellosis)*

History and significance

Brucellosis is a zoonotic infection that can have various manifestations in humans. *Brucella* species are small, aerobic, slow-growing gram-negative coccobacilli. The genus *Brucella* is divided into several species on the basis of preferred animal hosts and other features. The main manifestations in animals are abortion and sterility. Humans can become infected from (1) direct contact with animal secretions through breaks in the skin, (2) infected aerosols, or (3) ingestion of unpasteurized dairy products. Brucellae are facultative intracellular pathogens, and replication and spread seem to occur through lymphatics and hematogenous dissemination. *Brucella* species can survive for many weeks in soil or water. *B suis* was weaponized by the United States in the 1940s and 1950s; other countries are also suspected to have weaponized brucellae. Brucella organisms are highly infectious when aerosolized; consequently, inhalation will be the most likely route of infection during a terrorist attack. The organism could be spread as a slurry in bomblets or as a dry aerosol [61].

Clinical presentation

Clinical symptoms of brucellosis are varied and nonspecific. Like Q fever, brucellosis can begin insidiously, with an influenza-like illness. Symptoms generally begin 2 to 4 weeks after exposure, but the incubation period can be 8 weeks or more. The infection tends to localize in tissues with large numbers of macrophages, such as lung, spleen, liver, central nervous system (CNS), bone marrow, and synovium. Symptoms vary because of the widespread nature of infection. In most instances, the intermittent fever phase lasts for several weeks, followed by a period of remission, during which symptoms may wane or disappear altogether. The fever and other symptoms then recur. This pattern of periodic febrile waves and remission can last for months or even years. Although chronic cases of brucellosis can be very debilitating, the disease is rarely fatal. Fever, chills, sweats, anorexia, headache, and malaise are common manifestations. Although patients may complain of many symptoms, physical findings are often lacking.

Liver involvement is common, although transaminase levels are usually only mildly elevated. Hepatic granulomas are characteristic of some species,

such as *B abortus*. Several skeletal complications are also found, including arthritis, osteomyelitis, and tenosynovitis. Large weight-bearing joints (eg, sacroiliac, hips, knees, ankles) are most commonly involved. Hematologic findings include anemia, leukopenia, and thrombocytopenia. The rare serious complications of brucellosis include endocarditis and CNS infection. Although depression and difficulty concentrating are common complaints in patients who have brucellosis, direct invasion of the CNS (eg, meningitis, encephalitis) occurs in fewer than 5% of infected individuals [62]. Endocarditis occurs in fewer than 2% of cases but is responsible for most deaths.

Diagnosis

Brucellosis can be diagnosed through isolation of the organism in cultures or by serology. Because brucellae are slow-growing, the laboratory should be alerted to hold culture specimens for at least 4 weeks if brucellosis is suspected. Cultures of bone marrow have a higher yield than blood. Rapid bacterial identification systems used by many laboratories may reduce the time to isolation, but misidentification of brucellae with these systems has been reported [63]. A presumptive diagnosis can be made on the basis of high or rising antibody titers. Most patients who have infection have titers higher than 1:160. Febrile agglutinin tests are not adequately sensitive. PCR techniques may soon yield a rapid method of diagnosing brucellosis.

Infection control precautions

Because human-to-human transmission seems to be rare, isolation is not necessary. However, the organisms are highly infectious through aerosol, and culture specimens may pose a threat to laboratory workers. The laboratory should be notified if brucellosis is suspected; laboratory biosafety level 2 or 3 precautions are recommended. Contact isolation should be used for patients who have open draining lesions.

Treatment and prophylaxis

Although most patients will recover without treatment, antibiotics reduce the severity and duration of illness. Many antibiotics have in vitro activity, but those with good intracellular penetration are most effective clinically. Combination treatment is most effective. Doxycycline plus rifampin for 6 weeks is the most commonly used regimen. Gentamicin or streptomycin is sometimes included in the regimen for more severe infections such as endocarditis. No effective human vaccine is available for brucellosis.

Antibiotics will unlikely prevent disease if given before the onset of symptoms, although the optimal regimen is unknown. Because of the long incubation period, the opportunity for prophylaxis is greater with brucellosis than for some other agents with shorter incubation periods, such as anthrax or tularemia. An economic model estimated that the economic impact of a bioterrorist attack with brucellosis on a population of 100,000 people would be approximately $478 million. Timely intervention with antibiotic prophylaxis could reduce the economic impact through preventing illness [64].

Burkholderia mallei *(glanders)*

History and significance

Glanders is a disease of horses, mules, and donkeys caused by the bacterium *Burkholderia mallei* (previously known as *Pseudomonas mallei*). The infection can also occur in humans and other animals. Human infection is rare but can be severe. *B mallei* is a nonmotile, gram-negative bacillus. The route of naturally occurring infection is unclear, but infection is believed to occur through broken skin or nasal mucosa contaminated with infected material. Infection also seems to occur through an aerosol route, as evidenced by infections in laboratory workers from routine handling of cultures [65,66]. Its ability to cause serious illness and infect through aerosol indicate that *B mallei* may have potential use in bioterrorism. In fact, this organism has been used as a bioweapon; animals were deliberately infected with glanders during World War I [67].

Melioidosis is a human illness caused by *B pseudomallei*, which is clinically similar to glanders but does not seem to be particularly infectious through aerosol.

Clinical presentation

Infection from inoculation through a break in the skin typically results in a tender nodule with local lymphangitis. Inoculation of the eyes, nose, and mouth can result in mucopurulent discharge with ulcerating granulomas. With systemic invasion, a generalized papular or pustular eruption is frequent. This septicemic form is often fatal within 7 to 10 days. The incubation period after infection through inhalation (most likely in a bioterrorism event) is approximately 10 to 14 days. The most common manifestations include fever, myalgias, headache, and pleuritic chest pain. Lymphadenopathy or splenomegaly may be present. The disease often manifests as pneumonia [65].

Diagnosis

The organism can be difficult to identify. Blood cultures are usually negative, except in the terminal stages of septicemia. Automated bacterial identification systems used in many laboratories may not correctly identify *B mallei*. Serologic tests will usually show a rise in titers by the second week, but agglutination titers are not very specific. Complement fixation titers are more specific but less sensitive. Serologic tests are not standardized or widely available. *B mallei* and *B pseudomallei* cannot be distinguished morphologically, but a PCR procedure has been developed that can differentiate the two [68].

Infection control precautions

Because person-to-person transmission can occur, isolation is indicated. Culture specimens pose a threat to laboratory personnel, and therefore

the laboratory should be notified if *B mallei* is suspected. Biosafety level 3 precautions are indicated.

Treatment and prophylaxis

The paucity of human cases has prevented any systematic study of treatment. Sulfadiazine has been effective in experimental animal infections and humans. Agents known to be effective for human melioidosis include tetracyclines, trimethoprim- sulfamethoxazole, amoxicillin-clavulanate, and chloramphenicol. In vitro, *B mallei* is susceptible to aminoglycosides, macrolides, quinolones, doxycycline, piperacillin, ceftazidime, and imipenem [69]. No vaccine is available.

Alphaviruses

History and significance

Venezuelan Equine Encephalomyelitis and Eastern and Western Equine Encephalomyelitis (VEE, EEE, and WEE, respectively) are mosquito-borne viral infections found in North and South America. EEE occurs primarily along the eastern and gulf coasts of the United States. Although human illness is rare, the case-fatality rate can be as high as 50% to 70%. WEE viruses are found primarily west of the Mississippi. During an epidemic, WEE infection rates are much higher than for EEE, but the case fatality rate is much lower (approximately 3%–4%). Outbreaks occur primarily in the summer, and equine cases greatly outnumber human cases. VEE occurs in many areas of South and Central America, and outbreaks have occurred in North America.

These alphaviruses are limited in their geographic distribution by the mosquito vector, and therefore finding these viruses outside the endemic areas should arouse suspicion of an intentional release. All of these viruses are highly infectious through aerosol. Because they are stable during storage and can be produced in large amounts with unsophisticated equipment, they are regarded as having potential for weaponization [61].

Clinical presentation

Most infections with these viruses result in nonspecific symptoms of fever, headache, and myalgia. Only a fraction of individuals infected will experience progression to frank encephalitis. Viral encephalitides should be included in the differential diagnosis of nonspecific viral syndromes after a possible bioterrorism event. Reports of ill horses in the vicinity would obviously suggest an equine encephalitis virus. Whether aerosol exposure, as in a bioterrorism event, would lead to a pattern of symptoms different from that of the mosquito-borne illness is unknown.

EEE is the most severe of these infections, with high mortality rates and high rates of neurologic sequelae [70]. WEE and VEE have lower rates of progression to neurologic symptoms. Infants and elderly individuals are

more prone to developing encephalitis. In people who develop encephalitis, the initial viral prodrome is followed by confusion and somnolence, which may progress to coma. Peripheral blood counts often show leukopenia in the early stages of illness, which can progress to leukocytosis. CSF protein is elevated, and lymphocytic pleocytosis is usually present.

Diagnosis

Virus can sometimes be isolated from blood during the early stages of illness, but viremia has usually resolved by the time symptoms of encephalitis develop. Virus can sometimes be isolated from CSF or postmortem brain tissue. The specific viral pathogen is generally identified through serologic testing of the CSF or serum (or both), but these results will not be available until later. Virus-specific IgM antibodies can be detected with ELISA [71]. Subsequent testing of convalescent serum may confirm the diagnosis but will not be helpful in initial management. Physicians should attempt to obtain enough CSF for specialized testing if encephalitis is a diagnostic possibility. Experimental PCR assays have been developed for several viral pathogens and will likely become more standardized and readily available in the future.

Infection control precautions

Isolation is not necessary since person-to-person transmission does not occur.

Treatment and prophylaxis

No specific treatment for these viral encephalitides. Treatment is supportive. Inactivated vaccines are available for EEE, WEE, and VEE, but none is widely used because of problems with poor immunogenicity and need for multiple doses. A live attenuated vaccine is available for VEE but has a high incidence of side effects, such as fever, headache, and malaise. Newer vaccines using recombinant technology are in development.

Ricin toxin from ricinus communis (castor beans)

History and significance

Ricin is a protein toxin derived from the castor bean plant. Castor beans are easily obtained worldwide, and it is relatively easy to extract the toxin. One million tons of castor beans are processed annually in the production of castor oil worldwide; the waste mash from this process is approximately 5% ricin by weight. Ricin was used in the assassination of Bulgarian exile Georgi Markov in London in 1978. Markov was attacked with a specially engineered weapon disguised as an umbrella, which implanted a ricin-containing pellet into his leg [72].

Ricin toxin is somewhat less toxic by weight compared with botulinum toxin or staphylococcal enterotoxin B, but can be produced in large

quantities easily. Ricin toxin is stable and can be disseminated as an aerosol. It is toxic through several routes of exposure, including respiratory and gastrointestinal.

Clinical presentation

Ricin toxin inhibits protein synthesis. When inhaled as an aerosol, the toxin can produce symptoms within 4 to 8 hours. Typical symptoms include fever, chest tightness, cough, dyspnea, nausea, arthralgias, and profuse sweating. With a sublethal dose of toxin, the symptoms should improve within several hours. In animal studies, lethal doses produced necrosis of the respiratory tract and alveolar filling in 36 to 72 hours after exposure.

When ingested, ricin causes severe gastrointestinal symptoms, such as nausea, vomiting, and diarrhea. With large toxin exposures, this may be associated with gastrointestinal hemorrhage and hepatic, splenic, and renal necrosis. Death can occur from hypovolemic shock [73]. Ricin toxin may also cause disseminated intravascular coagulation, microcirculatory failure, and multiple organ failure if given intravenously in laboratory animals.

Diagnosis

Diagnosis of ricin poisoning would be primarily clinical and epidemiologic. ELISA testing can be performed on serum, but this modality would not be widely available in most laboratories [74]. Acute and convalescent sera could be obtained from survivors to measure antibody response for diagnostic confirmation.

Infection control precautions

This toxin-mediated syndrome has no potential for person-to-person spread. Patients who are grossly contaminated may need to change their clothes and wash with soap and water.

Treatment and prophylaxis

Treatment of ricin poisoning is supportive. Respiratory support may be needed for pulmonary edema. Gastric decontamination with charcoal may have some benefit for ingestions. Fluids may be required to replace gastrointestinal losses. Vaccines against ricin toxin are currently under development [75].

Epsilon toxin of Clostridium perfringens

History and significance

Clostridium perfringens is an anaerobic, gram-positive, spore-forming bacillus. This ubiquitous organism is present in soil throughout the world and has been found in the stool of virtually every vertebrate organism ever tested [76]. *Clostridium* species can produce various toxins, and these are responsible for illness. Enterotoxin-producing strains of *C perfringens* type A cause a mild form of food poisoning that is common worldwide. Large amounts of this toxin could be produced for intentional exposure.

Clinical presentation

Within hours of exposure, gastrointestinal symptoms such as watery diarrhea, nausea, and abdominal cramps will develop. Fever is rare. Spontaneous resolution typically occurs within a day, and fatalities are rare. The *C perfringens* enterotoxin can act as a superantigen and is a potent stimulator of human lymphocytes. Large exposure through aerosol or ingestion could lead to more severe systemic symptoms.

Diagnosis

Enterotoxin can be detected in stool with latex agglutination or ELISA, but these tests are not widely available. Cultures are not of value because *C perfringens* is normally found in stool.

Infection control precautions

Because this is a toxin-mediated syndrome, no potential exists for person-to-person spread.

Treatment and prophylaxis

Treatment is supportive.

Staphylococcus enterotoxin B

History and significance

Staphylococcal enterotoxin B (SEB) is a common cause of food poisoning caused by a heat-stable toxin produced by the ubiquitous organism *Staphylococcus aureus*. The toxin is relatively stable in aerosols (more stable than botulinum toxin); even low doses can cause symptoms when inhaled. Although rarely fatal, a high percentage of those exposed could become seriously ill within a few hours. It could also be used to contaminate food or water supplies.

Clinical presentation

SEB is a potent activator of T cells, and most of the clinical manifestations are mediated by the patient's own immune system. Symptoms begin 3 to 12 hours after exposure. Typical symptoms are high fever, headache, myalgia, prostration, and dry cough. Vomiting and diarrhea may result from swallowed toxin. Patients may be incapacitated for up to 2 weeks. In severe cases, pulmonary edema or adult respiratory distress syndrome may develop. In rare cases, death occurs from dehydration.

Diagnosis

The diagnosis of SEB intoxication is primarily clinical and epidemiologic. Practically speaking, a specific diagnosis of SEB would be very difficult. The symptoms are nonspecific and overlap with many other clinical syndromes, including those of other bioterrorism agents. Because of the short

incubation period, this agent is more likely to cause a sudden cluster of cases in a localized area compared with many other bioterrorism agents. The toxin may be identified with ELISA of nasal swabs after aerosol exposure, or the antigen can be detected in urine [61]. Neither of these tests is readily available.

Infection control precautions

Because this is a toxin-mediated syndrome, no potential exists for person-to-person spread. However, if patients are grossly contaminated after a recent exposure, health care workers could be exposed to the toxin on skin or clothing. A simple change of clothes and shower with soap and water would provide adequate decontamination.

Treatment and prophylaxis

Treatment is supportive. Some patients may require rehydration for fluid losses, although care must be taken to avoid pulmonary edema in more severe intoxications. Ventilatory support may be required in severe cases. Vaccines are under development.

Food-borne and waterborne pathogens

History and significance

Although most agents considered more likely to be used for bioterrorism would be disseminated through aerosol, food- or waterborne agents could be used. In fact, Shigella and Salmonella have already been used in intentional exposures in the United States. Shigella was used to contaminate donuts given to fellow workers by a disgruntled employee and caused 12 cases of diarrhea [77]. Salmonella was used by a religious commune in Oregon to contaminate local salad bars, leading to more than 750 cases of gastroenteritis [78].

Food- and waterborne agents would be less likely than airborne agents to be involved in a large-scale attack, because it is more difficult to expose large numbers of people. Standard treatment of municipal water supplies would preclude survival of most biologic agents and inactivates most biological toxins. Food-borne outbreaks are generally limited to small groups of people. However, more centralized processing of foods for mass marketing may increase the potential for widespread food-borne outbreaks, as has been shown by multistate outbreaks of Listeria and Salmonella resulting from contamination in food-processing facilities [79,80].

Salmonella species, *Shigella dysenteriae*, *Escherichia coli* O157:H7, and *Vibrio cholerae* are all bacterial causes of food-borne gastroenteritis. *Salmonella*, *Shigella*, and *E coli* all cause illness sporadically in the United States [81]. Cholera is a cause of severe gastroenteritis in developing countries but is only occasionally imported into the United States.

Cryptosporidium parvum is a protozoal organism that is also associated with diarrhea. *C parvum* can be spread by contamination of food or water

and has been involved in outbreaks related to swimming pools. Because it is resistant to chlorine, *C parvum* can survive in swimming pools and municipal water supplies. *C parvum* was associated with a massive outbreak caused by contamination of the municipal water supply in Milwaukee, Wisconsin, in 1993 [82]. More than 400,000 people became ill, resulting in more than 40,000 health care visits and 4000 hospitalizations.

Clinical presentation

These infections generally present with diarrhea, sometimes associated with nausea, vomiting, fever, and abdominal cramps. The incubation period is approximately 1 to 3 days. Gastroenteritis caused by *Shigella* is often associated with blood or mucus in the stool. *Salmonella typhi* and *S paratyphi* can produce a typhoidal syndrome, with gradual onset of fever, headache, malaise, myalgias, and constipation. Diarrhea is uncommon. Cholera is associated with severe watery diarrhea, which can cause death from dehydration within hours.

E coli O157:H7 is notable for being associated with bloody diarrhea, but Salmonella or Shigella can also be associated with this condition [83]. *E coli* O157:H7 produces a Shiga toxin associated with development of hemolytic uremic syndrome (HUS) [84]. HUS is characterized by hemolytic anemia, thrombocytopenia, and renal insufficiency. Approximately 6% of people with bloody diarrhea caused by *E coli* O157:H7 will develop HUS, but the rate is higher (about 10%) in children younger than 10 years. The mortality rate associated with HUS is 3% to 5%.

C parvum typically causes watery diarrhea associated with crampy abdominal pain. The incubation period is usually approximately a week but can sometimes extend up to several weeks. Illness can sometimes last for many weeks.

Diagnosis

Routine stool cultures for enteropathogens will identify agents such as *Salmonella* and *Shigella*. Many laboratories do not routinely test for *E coli* O157:H7 and other Shiga toxin–producing strains of *E coli*, so the laboratory should be notified if this agent is suspected (eg, afebrile patient with bloody diarrhea). *E coli* O157:H7 appears as a colorless colony on sorbitol MacConkey agar. These colonies can be tested for O157 antigen using a commercial kit. Stool cultures can also be tested directly for Shiga toxin using a commercial kit. *V cholerae* requires special media to grow, so the laboratory should be notified if cholera is suspected. *C parvum* can be identified with a modified acid-fast stain of stool or with fluorescent stain.

Infection control precautions

Standard body fluid precautions should prevent spread of these organisms. Patients should be instructed to be extra vigilant about handwashing after using the bathroom.

Treatment and prophylaxis

Treatment of these infections is generally supportive. Most infections with *Salmonella* and *Shigella* are self-limited and will resolve without specific treatment within a few days. Antimicrobial treatment may reduce the duration and severity of symptoms. *Salmonella* is susceptible to quinolones, azithromycin, and third-generation cephalosporins. Resistance to trimethoprim-sulfamethoxazole seems to be increasing, and antimicrobial-resistant organisms seem likely to be used in a bioterrorism event. *Shigella* is susceptible to fluoroquinolones, trimethoprim-sulfamethoxazole, and azithromycin. *E coli* O157:H7 infection should not be treated with antimicrobials or antimotility agents, because treatment may increase toxin production and thereby increase the risk for hemolytic uremic syndrome. Treatment of cholera typically requires large amounts of intravenous fluids and replacement of electrolytes. Oral administration of ciprofloxacin or doxycycline is effective for cholera. No antimicrobial agent has proven efficacy for *C parvum* infection, although paromomycin and azithromycin have been used in patients who have AIDS experiencing chronic diarrhea caused by this organism.

Category C agents

Nipah virus

History and significance

In April 1999, an outbreak of 257 cases of encephalitis (100 fatal) was reported in Malaysia [85]. A previously unrecognized paramyxovirus called *Nipah* was identified as the cause. Pigs appeared to be the primary source of human infection in this outbreak.

Clinical presentation

Patients in the reported outbreak presented with fever, headache, and myalgias and eventually developed signs of meningitis or encephalitis. A few patients had respiratory symptoms.

Diagnosis

Identification of Nipah virus requires specialized testing in a reference laboratory, such as the CDC or USAMRIID. IgM antibodies can be detected in blood and CSF. Better diagnostic tests for this recently discovered agent are under development [86].

Infection control precautions

Person-to-person spread of Nipah virus has not been identified. However, virus has been isolated from respiratory secretions and urine of patients infected with Nipah virus [87]. Pending further study of the potential for person-to-person spread, strict isolation would be prudent for patients suspected of being infected with this virus.

Treatment and prophylaxis

Treatment is primarily supportive. A small, open-label trial conducted during the outbreak in Malaysia showed a 36% reduction of mortality among patients who had acute Nipah virus encephalitis with ribavirin [88].

Hantaviruses

History and significance

Hantaviruses are in the family Bunyaviridae, which also comprises California encephalitis virus and several hemorrhagic fever viruses. Hantaviruses are found in many rodent species worldwide. Hantavirus and several related viruses cause a syndrome of fever, thrombocytopenia, and renal insufficiency; the disease occurs primarily in Eastern Asia. Sin nombre virus (SNV), a similar virus, was identified as the cause of several cases of severe pulmonary edema and shock (hantavirus pulmonary syndrome) in the southwestern United States in 1993 [89]. Aerosols of virus-contaminated rodent urine or feces seemed to be the mechanism of transmission in these cases. Because aerosol transmission is possible, the virus is believed to have potential for weaponization.

Clinical presentation

Hantavirus pulmonary syndrome (HPS) begins with a viral prodrome of fever and myalgias. Respiratory symptoms, including cough and dyspnea, begin after several days. Laboratory investigations may reveal an elevated hematocrit, leukocytosis, mild thrombocytopenia, and elevated liver transaminases. In severe cases, the illness progresses to pulmonary edema, with respiratory failure and shock [90].

Diagnosis

Hantaviruses are difficult to isolate in viral culture. In the acute phase of the disease, the clinical diagnosis may be confirmed through serology or PCR. ELISA and IFA are available to identify antibody to hantaviruses [91]. An immunoblot assay is also available.

Infection control precautions

Person-to-person transmission of naturally occurring SNV in the United States has not been identified. However, it has been identified in Argentina, including a fatal infection in a physician who also transmitted the virus to his family [92,93]. Because of the potential for person-to-person spread of a virus used in an intentional attack, using respiratory isolation would be prudent for persons who have suspected HPS related to a bioterrorism event.

Treatment and prophylaxis

Treatment of HPS is primarily supportive. Extracorporeal membrane oxygenation has been used in severe cases [94]. An open-label trial of ribavirin

for HPS failed to show any benefit. Controlled trials of ribavirin are ongoing. Vaccines are under development.

Other agents

Several arthropod-borne viruses might have potential for use as bioweapons, including the flaviviruses that cause yellow fever and tick-borne encephalitis. Person-to-person transmission of flaviviruses does not appear to occur, except through the arthropod vectors.

Yellow fever is a mosquito-borne virus of historical interest because of large outbreaks that played a role in development of the Americas. The disease has been greatly diminished through mosquito control and vaccination, although sporadic outbreaks still occur. The severity of illness can range from a mild self-limited viral syndrome to a fatal hemorrhagic fever [95]. After an incubation period of several days, symptoms begin as fever, headache, and myalgias. Conjunctivitis, relative bradycardia, and leukopenia may be present. Jaundice occurs secondary to hepatitis, and gastrointestinal bleeding may also occur. Death can occur 7 to 10 days after onset. Treatment of yellow fever is supportive. The illness is preventable with the attenuated 17D vaccine, which produces immunity in approximately 95% of those vaccinated.

Tick-borne encephalitis occurs in many areas of Europe and Asia. Infection can also occur from consumption of unpasteurized milk products. Most infections are asymptomatic or only mildly symptomatic, but a small fraction of infected individuals can develop encephalitis. Only approximately 1% of encephalitis cases are fatal, mostly in elderly individuals [96]. No specific therapy exists for flavivirus encephalitis.

Multidrug-resistant tuberculosis has become a significant problem in many areas of the world over the past several decades. Although illness progression and person-to-person transmission occur slowly, the ability to disseminate through aerosol and difficulty treating multidrug-resistant strains could make the organism attractive as a bioweapon. Treatment options for highly resistant strains are severely limited [97].

Summary

Various agents have potential for use as weapons of bioterrorism. Knowledge of the likely organisms may be useful in preparations to mitigate the effects of a bioterrorism event. Recognizing the clinical presentation of these organisms could help physicians identify infection quickly, allowing more appropriate management and possible prophylaxis of other individuals who may have been exposed. Although many of these agents do not have specific treatments, those that do are important to recognize. Which infections require isolation is also important to know because of potential for person-to-person spread.

If a bioterrorism event occurs, the expertise of emergency physicians and infectious disease specialists will be critical to mitigate the effects of the disaster. Emergency physicians will be on the front line when large numbers of ill and potentially contagious patients present for care. Infectious disease specialists will be essential in providing expertise for specialized diagnostic testing, identifying treatment options when resources may be limited, and advising on infection control and prophylaxis. Disaster planning for bioterrorism should incorporate consideration of surge capacity, infection control, and mobilization of resources for vaccination, antimicrobial treatment, and prophylaxis for large numbers of people.

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