CME

Bioterrorism: A Clinical Reality

Robert J. Leggiadro, MD

The intentional delivery of *Bacillus anthracis* spores through mailed letters or packages established the clinical reality of bioterrorism in the United States in autumn 2001. An understanding of the epidemiology, clinical manifestations, and management of the more credible biologic agents is critical to limiting morbidity and mortality from a bioterrorism attack.[1-5]

Children may be particularly vulnerable to a bioterrorist attack for several reasons.[6] They have a more rapid respiratory rate, a lower breathing zone, increased skin permeability, higher ratio of skin surface area to mass, and less fluid reserve than adults. Accurate and rapid diagnosis may be more difficult in children because of their inability to describe symptoms. Their caretakers may become ill or require quarantine during a bioterrorist event. Preventive and therapeutic agents recommended for adults exposed or potentially exposed to agents of bioterrorism have not been studied in infants and children.[7]

CME EDUCATIONAL OBJECTIVES

1. Recognize clues to a bioterrorism event.
2. Review the clinical features of and diagnostic methods for the critical biological agents.
3. Explain the management and prevention strategies for the critical biological agents.

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EPIDEMIOLOGY

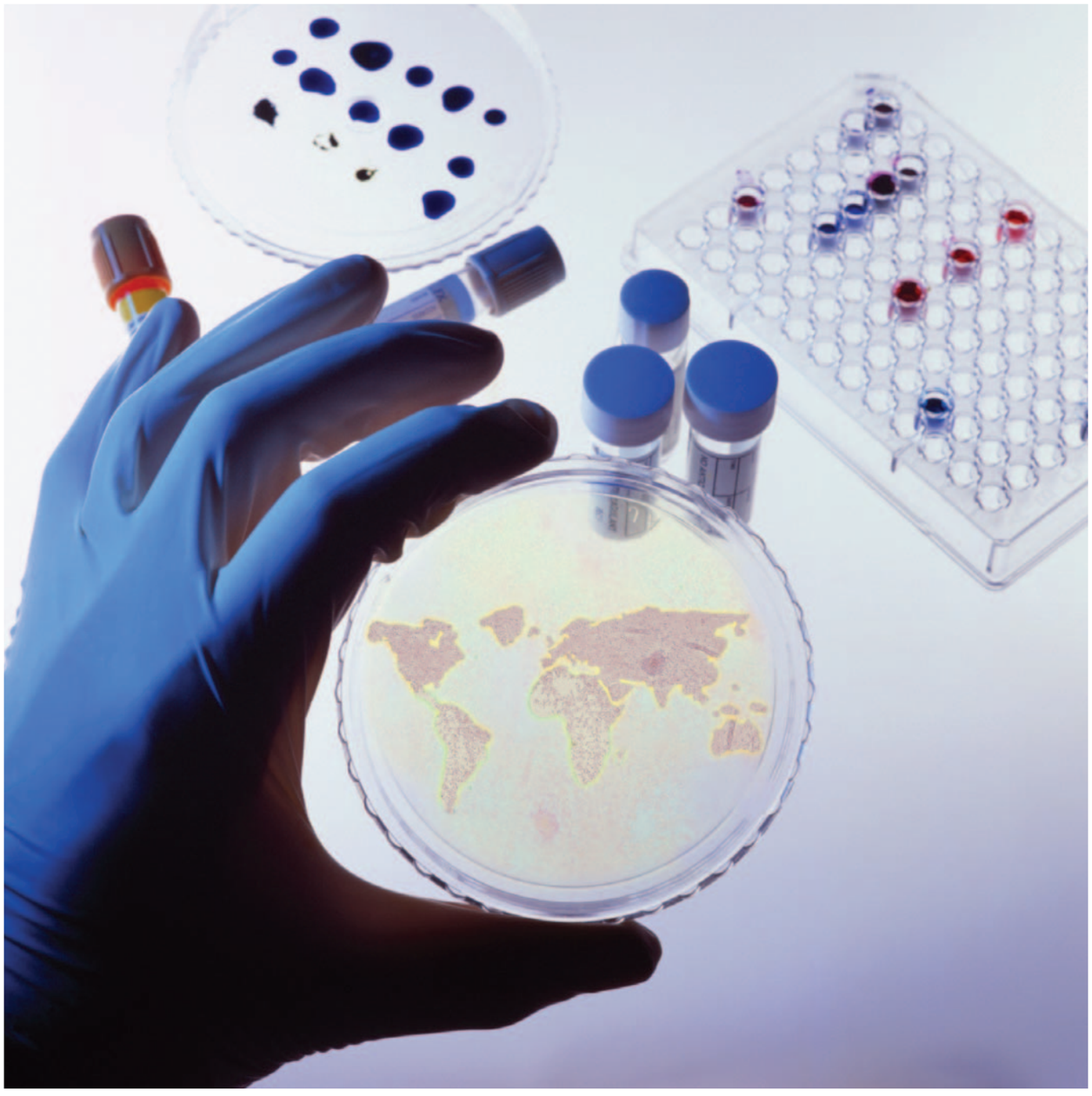
Several epidemiologic clues may be helpful in determining whether further investigation into an outbreak as a potential biologic attack is warranted. A large epidemic, especially in a discrete population; more severe disease than expected for a given pathogen; and a disease unusual for a given geographic area (eg, pulmonic tularemia in an urban setting) are major indicators. An outbreak of generalized vesicular rash disease in patients immune to varicella could indicate a release of smallpox, and a large number of patients with influenza-like illness in the summer might point to an anthrax attack. A cluster of patients with signs and symptoms of botulism with a common geographic exposure, but without a common dietary history, could signal an intentional botulinum toxin release. Multiple simultaneous epidemics of various diseases, outbreaks with both human and zoonotic consequences, and unusual strains or susceptibility profiles are additional helpful parameters. Rapid diagnosis and communication among healthcare providers, public health agencies, and the public when patients seek medical attention for an illness that might be caused by an agent of terrorism are critically important.[8]

The emergence of mosquito-borne West Nile virus encephalitis in New York City in the summer of 1999 is an example of a naturally occurring outbreak that had elements of a potential bioterrorist attack.[9-11] This outbreak represented a disease occurring in an unusual (previously nonendemic) area, as well as one with zoonotic (birds) in addition to human consequences. It marked the first documented appearance of West Nile virus in the Western hemisphere and the first arboviral outbreak in New York City since the yellow fever epidemics of the 19th century.[10] A large avian die-off, affecting primarily crows, preceded the outbreak in humans by at least several weeks.

CRITICAL BIOLOGIC AGENTS

The list of potential biologic terrorism agents has been prioritized into three categories (A, B, and C) by the Centers for Disease Control and Prevention (CDC) on the basis of the risk to national security.[9] Biologic agents are classified as high risk or Category A because they can 1) be easily disseminated or transmitted person-to-person; 2) cause high mortality with potential for major public health impact; 3) might cause public panic and social disruption; or 4) require special action for public health preparedness.

In addition to anthrax, Category A agents include smallpox, plague, tu-



laraemia, botulism, and hemorrhagic fever viruses.

ANTHRAX

B. anthracis is a large sporulatory, gram-positive rod with three distinct life cycles featuring multiplication of spores in soil, animal (herbivore) infection, and human infection.[12]

In February 2006 the Pennsylvania Department of Health reported to CDC and the New York City Department of Health and Mental Hygiene a case of inhalation anthrax in a man who lived in New York City.[13] After a 3-week trip to the Ivory Coast in December 2005, he had returned to New York with four hand-dried goat hides wrapped in a plastic bag. He made traditional African drums from these hides in a windowless workspace with poor ventilation and without personal protective equipment.

This represents the first case of naturally-acquired inhalation anthrax in the United States since 1976. The likely source of infection was exposure to *B. anthracis* spore-containing aerosols

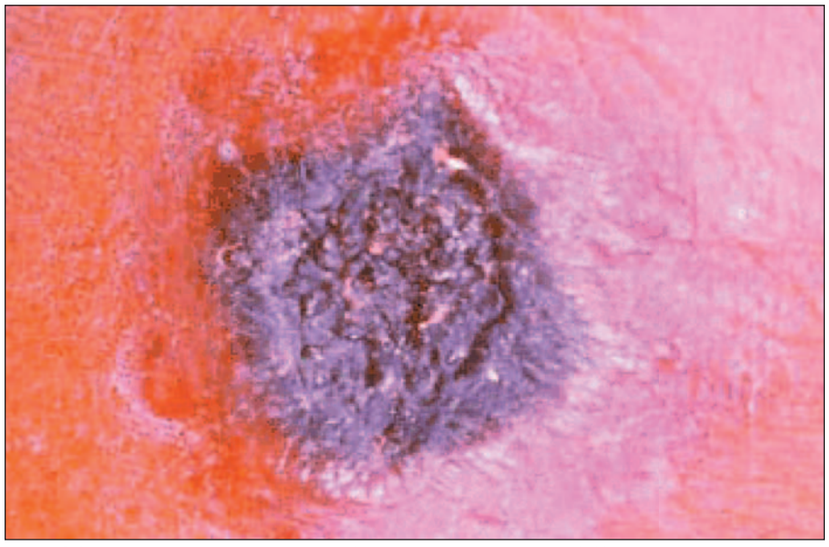


Figure 1. Cutaneous anthrax-eschar lesion. Public Health Image Library, CDC.

generated by mechanical scraping of a contaminated animal hide in a nonventilated workspace.

The three forms of human anthrax are cutaneous, inhalational, and gastrointestinal. The most common form is cutaneous, which is acquired through contact with an infected animal or animal products. The much less common inhalational form results from the deposition of spores in the lungs, and gastrointestinal anthrax occurs after the ingestion of infected meat. Because human-to-human transmission of anthrax has not been reported, standard precautions are recommended for hospitalized patients with all forms of anthrax infection.[14,15]

Industrial processing of animal hair or hides accounted for 153 of 236 (65%) anthrax cases reported to the CDC from 1955 to 1999. The majority of the cases were cutaneous anthrax. Improvements in industrial hygiene and introduction of practices such as improved ventilation, decreased use of imported animal materials, and vaccination of at-risk workers has helped limit the incidence of industrial inhalational anthrax.[13]

The clinical features and course of the first 10 confirmed cases of inhalational anthrax associated with bioterrorism in the United States in fall 2001 were reported.[16] Epidemiologic investigation indicated that the outbreak was a result of intentional delivery of *B. anthracis* spores through mailed letters or packages. The incubation period ranged from 4 to 6 days. Several clinical features of these patients were not emphasized in earlier reports of inhalational anthrax, a previously rare disease. Drenching sweats, nausea, and vomiting were common manifestations of the initial phase of illness in this outbreak. Pleural effusions were a remarkably consistent clinical feature. No predominant underlying diseases or conditions were noted.

None of the 10 patients had an initially normal chest radiograph. In addition to the characteristic feature, mediastinal widening, paratracheal or hilar fullness, pleural effusions, and parenchymal infiltrates were noted. Computed tomography of the chest was more sensitive than chest radiography in revealing mediastinal lymphadenopathy. Additionally, an elevation in the proportion of neutrophils or band forms represented an early diagnostic clue.

The 55% survival rate in these patients was higher than previously reported (<15%). Limited data on treatment of survivors suggest that early treatment with a fluoroquinolone and at least one other active drug (eg, rifampin, clindamycin, or vancomycin) may improve survival.[15,17]

Nasal congestion, rhinorrhea, and sore throat, infrequently seen in this series, might help distinguish influenza-like illness from inhalational anthrax.[18] Newer diagnostic methods for *B. anthracis* infection include polymerase chain reaction (PCR), immunohistochemistry, and sensitive serologic tests. Recommendations for antibiotic treatment of inhalation anthrax include use of either ciprofloxacin or doxycycline, plus one or two additional antibiotics known to be active in vitro against *B. anthracis.* Additional antibiotics include clindamycin, vancomycin, imipenem, meropenem, chloramphenicol, penicillin, ampicillin, rifampin, and clarithromycin. Corticosteroids should be considered for meningitis or significant mediastinal edema.[19,20]

Cutaneous anthrax is characterized by a skin lesion evolving from a papule, through a vesicular stage, to a depressed black eschar, often surrounded by significant edema and erythema (see Figure 1, page 353).[5,21,22] The lesion, which may mimic a spider bite, is usually painless and located on exposed parts of the body (ie, face, neck, and arms). The incubation period ranges from 1 to 12 days but is commonly less than 7 days. Fatalities are rare (<1%) with effective antimicrobial therapy. Cutaneous anthrax occurred in a 7-month old infant who was exposed at his mother's workplace as a result of the fall 2001 attack. This infant displayed severe microangiopathic hemolytic anemia with renal involvement, coagulopathy, and hyponatremia, which were unusual findings with cutaneous anthrax.[23]

The organism grows readily on sheep blood agar and forms rough, gray-white colonies 4 to 5 mm in size with characteristic comma-shaped or "comet tail" protrusions.[12] Biosafety level 2 conditions for safe specimen processing in the microbiology laboratory and prompt

confirmation of suspected isolates at CDC or the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) in Fort Detrick, Frederick, Maryland, are warranted.[14,24]

Postexposure vaccination with an inactivated, cell-free anthrax vaccine may be indicated, along with ciprofloxacin, doxycycline, or amoxicillin chemoprophylaxis after a proven biologic event.[15,25] Recommendations for postexposure prophylaxis (and prolonged therapy following initial therapy for inhalational or cutaneous anthrax) include three options: 1) a 60-day course of antibiotics followed by careful clinical observation, 2) extension of antibiotic therapy to 100 days, or 3) extension antibiotic therapy to 100 days combined with administration of anthrax vaccine in three doses at 2-week intervals.[19,20] Pre-exposure vaccination may be indicated for the military and other select populations or for groups for which a calculable risk can be assessed.

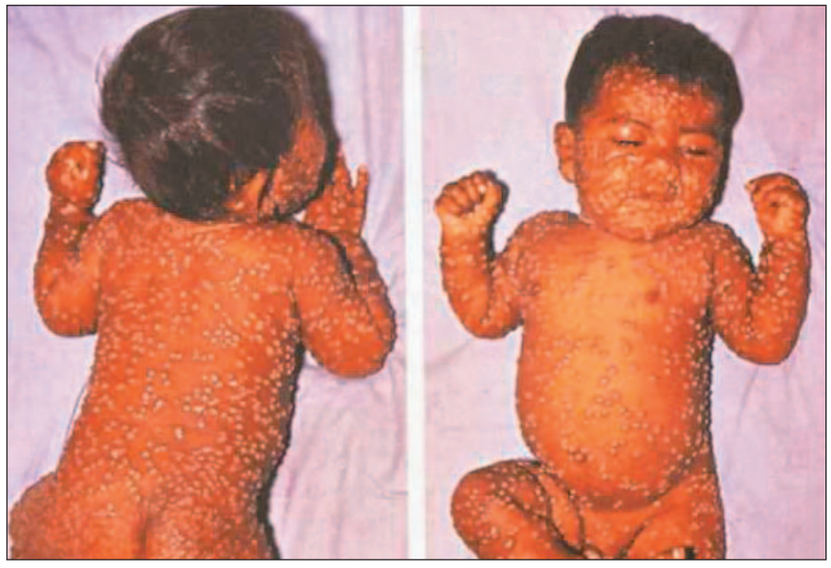


Figure 2. The lesions of smallpox are at the same stage of development on each area of the body, are deeply embedded in the skin, and are more densely concentrated on the face and extremities. From Henderson DA. Smallpox: clinical and epidemiologic features. *Emerg Infect Dis.* 1999;5(4):537-539. (CDC.)

SMALLPOX

After a worldwide eradication program, the last known endemic case of smallpox occurred in Somalia in 1977, and the World Health Organization declared smallpox eradicated in 1980.[26] No animal reservoir exists. Current recognized stocks of variola virus are authorized only at the CDC in Atlanta and a Russian state laboratory in Koltsovo. However, it is speculated that additional variola isolates, either long held unreported or acquired through security breaches, also may exist. Because vaccination against smallpox ceased in the United States in 1972, virtually the entire population now would be considered susceptible because immunity wanes over time. Release of an aerosol would be the most likely route of transmission during an act of bioterrorism.

Smallpox is ordinarily transmitted by respiratory secretions and requires person-to-person contact. The incubation period is generally 12 to 14 days, with a range of 7 to 17 days. The prodromal illness of classic variola major features an acute onset of malaise, fever, rigors, vomiting, headache, and backache. Two to 3 days later, a discrete rash appears on the face, hands, forearms, and mucous membranes; it spreads to the legs and then centrally to the trunk during the second week of illness. Lesions progress from macules to papules to pustular vesicles during the course of 1 to 2 days. Umbilicate scabs form 8 to 14 days after onset and leave depressions and depigmented scars.[27]

An outbreak of generalized vesicular rash disease in patients immune to varicella could indicate a release of smallpox, and a large number of patients with influenza-like illness in the summer might point to an anthrax attack.

In contrast to varicella (chickenpox), the rash of smallpox is centrifugal, with a concentration of lesions on the face and extremities, including the palms and soles, which is different from the truncal predominance in varicella (see Figure 2). Smallpox lesions are also synchronous in stage of development, whereas the lesions of chickenpox appear in crops every few days, which result in lesions at very different stages of maturation in a given area of the skin. Any confirmed case of smallpox represents an international emergency and must be reported to national authorities through local and state health departments.[26]

Historically, the mortality associated with smallpox was 30% for unvaccinated contacts, and currently no antiviral therapy of proven efficacy has been developed. Supplies of vaccinia vaccine and vaccinia immune globulin are available only through the CDC.[26] Postexposure vaccination and strict quaran-

tine are indicated for all household and other face-to-face contacts of suspected smallpox cases.[26]

In a limited outbreak with few cases, hospitalized patients should receive care in negative-pressure rooms with high-efficiency particulate air (HEPA) filtration. In addition, precautions using gloves, gowns, and masks are indicated. Home isolation and care are appropriate for most patients in larger outbreaks.[26]

Between January 24 and October 31, 2003, 37,901 volunteers in 55 jurisdictions received 38,885 smallpox vaccinations through the U.S. Department of Health and Human Services program, with a take rate of 92%.[28] The Vaccine Adverse Event Reporting System (VAERS) received 822 adverse event reports related to these vaccines, an overall reporting rate of 217 per 10,000 vaccinees. Also, 722 nonserious reports to VAERS included mild systemic and self-limited local reactions, including fever, rash, pain, and headache.

No cases of preventable life-threatening adverse reactions, such as eczema vaccinatum, progressive vaccinia, or fetal vaccinia were reported. There were no cases of vaccinia contact transmission. No vaccinee or contact of this program received vaccinia immune globulin. Rigorous smallpox vaccine safety screening, educational programs, and older vaccinees may have contributed to low rates of preventable life-threatening adverse reactions.[28]

There were 100 adverse events designated as serious, resulting in 85 hospitalizations, two permanent disabilities, 10 life-threatening illnesses, and three deaths. Among the serious adverse events, 21 cases were classified as myocarditis and/or pericarditis and 10 as ischemic cardiac events that were not anticipated on historical data. Two cases of generalized vaccinia and one case of postvaccinial encephalitis were also detected.[28]

PLAGUE

Plague, a zoonotic illness caused by the gram-negative bacillus *Yersinia pestis* is primarily a disease of rodents, with transmission occurring through infected fleas. Human disease is acquired through rodent flea vectors, as well as respiratory droplets from animals to humans and humans to humans. Plague is transmitted to humans in the United States primarily via the bites of fleas from infected rodents. From 1990 to 2005, a total of 107 cases of plague were reported in the United States, a median of seven cases per year, most commonly from Arizona, California, Colorado, and New Mexico.[29] Indications of a deliberate release of plague bacilli would include the occurrence of cases in locations not known to have enzootic infection, in people without known risk factors, and in the absence of previous rodent deaths.[30] Travelers can acquire plague in one area and become ill in another area where plague is not endemic (ie, peripatetic plague).[8]

The emergence of mosquito-borne West Nile virus encephalitis in New York City in the summer of 1999 is an example of a naturally occurring outbreak that had elements of a potential bioterrorist attack.

The three clinical forms of human plague are bubonic, primary septicemic, and pneumonic. Bubonic plague, characterized by the development of acute regional lymphadenopathy (the buboe), is the most frequent clinical form and accounts for 80% to 90% of U.S. cases.[29] However, the pneumonic form would be the most likely manifestation as a result of release of an aerosol during a biologic attack.[30,31] This clinical form is now the least common, but it has the highest mortality; it is almost always fatal if antibiotics are not begun within 24 hours of the onset of symptoms. Septicemic plague without obvious lymphadenopathy may be more difficult to diagnose than bubonic plague because of nonspecific manifestations (ie, fever, chills, abdominal pain, nausea, vomiting, diarrhea, tachycardia, tachypnea, and hypotension).[30] Delay in both diagnosis and appropriate therapy may lead to death.

The incubation period for primary pneumonic plague is 1 to 3 days. Fever, chills, headache, and rapidly progressive weakness are characteristic of all clinical forms of plague. Cough, dyspnea, and hemoptysis are distinctive for primary pneumonic plague. The sudden appearance of a large number of previously healthy patients with fever, cough, shortness of breath, chest pain, and a fulminant course leading to death should suggest immediately the possibility of pneumonic plague or inhalational anthrax. The presence of hemoptysis would suggest plague.[30,32]

Y. pestis may be identified in clinical specimens by Gram, Wright-Giemsa, Wayson, and immunofluorescence staining methods, in addition to standard bacterial culture. Appropriate clinical specimens include lymph node aspirates and blood, as well as tracheal washes or sputum smears if pneumonic plague is suspected. Tests that would be used to confirm a suspected diagnosis, including antigen detection, IgM enzyme immunoassay, and PCR assay, are available only through state health departments, the CDC, and military laboratories.[30]

Effective therapy is available in the form of streptomycin, gentamicin, chloramphenicol, doxycycline, or ciprofloxacin.[30] Parenteral aminoglycoside therapy is recommended in a contained

casualty setting (modest number of patients requiring treatment); oral antiobiotic therapy is recommended in a mass casualty scenario. The potential benefits of doxycycline and ciprofloxacin in the treatment of pneumonic plague infection in children substantially outweigh the small risks.[30,33] An inactivated, whole-cell *Y. pestis* vaccine was discontinued by its manufacturers in 1999 and is no longer available.[30]

In addition to standard precautions, droplet precautions are indicated for all patients with suspected plague until pneumonia is excluded and appropriate therapy has been initiated. Droplet precautions should be continued in patients with confirmed pneumonic plague for 48 hours after the initiation of appropriate therapy.[30] Only standard precautions are recommended for bubonic plague.

TULAREMIA

The etiologic agent of this zoonotic illness is *Francisella tularensis*, a gram-negative coccobacillus. The disease may be acquired from ticks and deer flies, contact with animals such as rabbits and rodents, ingestion of contaminated water, or inhalation of aerosols. In a bioterrorist event, inhalation of an aerosol would be the most likely route of infection.[32,34] Human-to-human transmission of tularemia has never been reported. The annual incidence of tularemia in the United States is fewer than 200 cases; all suspected or confirmed cases must be reported to health authorities. Arkansas (23%), Missouri (19%), South Dakota (7%), and Oklahoma (7%) account for 56% of all reported tularemia cases in the United States.[35]

Clinical forms of the disease include ulceroglandular, glandular, oculoglandular, oropharyngeal, pneumonic, and typhoidal, the type reflecting the organism's portal of entry.[36] Either pneumonic alone or typhoidal, with or without a pneumonic component, would be the most likely clinical manifestation of tularemia as a result of aerosol release during a biologic attack.[32,34] The incubation period for tularemia is 3 to 6 days, with a range from 1 to 21 days. Typhoidal tularemia may manifest as fever of unknown origin. Standard precautions are indicated for hospitalized patients with all forms of tularemia.[34]

The diagnosis is established most often by serologic testing, and isolation of *F. tularensis* from clinical specimens requires cysteine-enriched media or inoculation of laboratory mice. In addition to a need for special media, the laboratory should always be informed when tularemia is suspected because of the potential hazard to laboratory personnel. Suspected isolates should be confirmed by the CDC or USAMRIID through local or state health departments.[34]

Effective therapeutic agents include streptomycin, gentamicin, tetracycline, ciprofloxacin, and chloramphenicol; postexposure prophylaxis with doxycycline or ciprofloxacin may be considered.[34] A live attenuated vaccine for pre-exposure use is available through the USAMRIID.[37]

BOTULISM

Seven distinct but related neurotoxins, A through G, are produced by different strains of *Clostridium botulinum,* an anaerobic gram-positive rod. The most common types in U.S. foodborne outbreaks are A, B, and E; outbreaks with unusual botulinum toxin types (ie, C, D, F, and G, or E not acquired from an aquatic food) would suggest deliberate release.[38] Classic neuroparalytic disease is acquired through the ingestion of preformed neurotoxin. Other forms include localized infection (wound botulism) and *C. botulinum* intestinal colonization in infants with in vivo toxin production (infant botulism). Botulism in the United States occurs most often in small clusters or single cases associated with home-canned foods. Although airborne transmission of botulinum neurotoxin does not occur naturally, aerosolization of preformed toxin would be the most likely route of transmission in a bioterrorism event.[31,38] Sabotage of food supplies is also possible. Botulism is not transmitted from human to human; standard precautions are recommended for hospitalized patients.

The incubation period for food-borne botulism is generally 12 to 36 hours (range, 6 hours to 8 days). The clinical manifestations of disease acquired by inhalation would be the same as those for food-borne botulism. Early manifestations include blurred vision, diplopia, and dry mouth. Patients are afebrile with a clear sensorium.

Later clinical features indicative of more severe disease include dysphonia, dysarthria, dysphagia, ptosis, and symmetric, descending, progressive muscular weakness with respiratory failure.[38] Clinical suspicion is critical because a recognized source of exposure may be absent in a biologic attack. Botulism is a reportable disease.

A toxin neutralization bioassay in mice is used to identify botulinum toxin in serum, stool, or food. *C. botulinum* also may be cultured from stool and food. Electromyography can be helpful diagnostically. Botulinum antitoxin of equine origin, available from the CDC and state or municipal health departments, should be administered as soon as possible to patients symptomatic with botulism after testing for hypersensitivity to equine sera.[38] A pentavalent toxoid of *C. botulinum* toxin types A, B, C, D, and E is available as a vaccine under investigational drug status through the CDC or the U.S. Department of Defense.[37,38]

VIRAL HEMORRHAGIC FEVER

The term viral hemorrhagic fever (VHF) refers to a clinical illness associated with fever and a bleeding diathesis caused by a virus belonging to one of four distinct families: *Filoviridae* (eg, Ebola and Marburg), *Arenaviridae* (eg,

Lassa fever), *Bunyaviridae* (eg, Rift Valley fever), and *Flaviviridae* (eg, yellow fever). VHF agents are RNA viruses normally transmitted to humans from animal reservoirs or arthropod vectors, although the natural reservoirs and vectors of the Ebola and Marburg agents are unknown. Geographic distribution of these agents is as follows: Ebola and Marburg (Africa); Lassa (West Africa); New World arenaviruses (Americas); Rift Valley fever (Africa, Middle East): and yellow fever (Africa, Americas). Clinical features vary with the specific virus, but all are capable of causing fever, myalgia, prostration, petechiae, hemorrhage and shock.[36,39] The filoviruses, Ebola and Marburg, as well as the arenaviruses, Lassa, Junin and related viruses, are Category A biologic terrorism agents.

Treatment generally is supportive, although ribavirin has some in vitro and in vivo activity against arenaviruses and bunyaviruses but not against filoviruses or flaviviruses. VHF-specific barrier precautions, as well as airborne precautions, are recommended for any patient with suspected or documented VHF. Effective prophylaxis following exposure to an VHF agent is not available.[39]

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