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BIOTERRORISM: PRIORITY AGENTS

UNLESS YOU'VE BEEN living on Mars with a broken interplanetary radio, you're aware of the two October cases of inhalational anthrax in Florida — the first in the United States since 1976 — and of cases of cutaneous anthrax in New York City.[1] Anthrax is a disease of such rarity in the U.S. that any case appropriately triggers conjecture about bioterrorism, and in these cases, ongoing investigation by public-health and criminal-justice officials has not quelled the suspicion.

Faithful readers of these pages have been apprized of the possibility of bioterrorism, i.e., the deliberate use of microorganisms to cause disease with the intention of achieving a political end. Unfortunately, we don't know where, when, or with what agent a bioterrorist might strike. And because it is impractical to maintain stocks of antibiotics and vaccines sufficient to protect every citizen in every locale from every possible biological agent for an indefinite period of time, the only workable, long-term strategy is to be able to detect an event as early as possible, to respond quickly, and to bring resources to bear efficiently.

The cornerstone of our disease-surveillance system is a cadre of physicians, physician assistants, nurse practitioners, and clinical laboratorians who will recognize the public-health implications of reportable diseases, clusters of illnesses, and some unusual illnesses, and who will notify health department officials so that public-health investigation and action can be undertaken expeditiously. The importance of alert clinicians is underscored by the recent diagnosis and reporting of inhalational anthrax by the Florida physician who spotted the causative agent on Gram-stained cerebrospinal fluid.

Although nearly any microbe could be put to nefarious use, CDC has classified 6 diseases as "Category A," i.e., highest priority, because they can be easily disseminated or transmitted person to person; cause high mortality, with potential for major public-health impact; might cause public panic and social disruption; and require special action for public-health preparedness. The following is a quick overview of the Category A diseases, suspicion of any of which should prompt an immediate call to the local health department.[2]

Anthrax. A nonspecific prodrome (i.e., fever, dyspnea, cough, and chest discomfort) follows inhalation of infectious spores. Approximately 2–4 days after initial symptoms, sometimes after a brief period of improvement, respiratory failure and hemodynamic collapse ensue. Inhalational anthrax also might include thoracic edema and a widened mediastinum on chest radiograph. Gram-positive bacilli can grow on blood culture, usually 2–3 days after onset of illness. Cutaneous anthrax follows deposition of the organism onto the skin, occurring particularly on exposed areas of the hands, arms, or face. An area of local edema becomes a pruritic macule or papule, which enlarges and ulcerates after 1–2 days. Small, 1- to 3-mm vesicles may surround the ulcer. A painless, depressed, black eschar usually with surrounding local edema subsequently develops. The syndrome also may include lymphangitis and painful lymphadenopathy.[3]

Plague. Clinical features of pneumonic plague include fever, cough with muco-purulent sputum (Gram-negative rods may be seen on Gram stain), hemoptysis, and chest pain. A chest radiograph will show evidence of bronchopneumonia.[4]

Botulism. Clinical features include symmetric cranial neuropathies (i.e., drooping eyelids, weakened jaw clench, and difficulty swallowing or speaking), blurred vision or diplopia, symmetric descending weakness in a proximal-to-distal pattern, and respiratory dysfunction from respiratory muscle paralysis or upper airway obstruction without sensory deficits. Inhalational botulism would have a similar clinical presentation as

Microbiology and epidemiology of selected BT agents [3-8]

Agent	Microbiology	Reservoir	Incubation	Transmission
Anthrax	*Bacillus anthracis*, a spore-forming Gram-positive rod	livestock and wildlife, spores viable in soil for years	Average: 1-7 days Range: 1-60 days	inhalation and/or ingestion of spores, cutaneous contact with infected animal
Plague	*Yersinia pestis*, a Gram-negative rod	wild rodents	1-7 days (longer in immunocompromised individuals)	bubonic: bites from infected fleas pneumonic: person-to-person by respiratory droplets
Smallpox	Variola virus, an *orthopoxvirus*	officially, only in designated freezers	7-19 days	respiratory
Botulism	neurotoxins produced by the anaerobic Gram-positive rod *Clostridium botulinum*	spores, ubiquitous in soil	12-36 hours to several days	ingestion of preformed toxin
Tularemia	*Francisella tularensis*, a Gram-negative rod	wild animals (rabbits, beavers, various ticks)	average: 3-5 days range: 1-14 days	tick bites, handling or eating insufficiently cooked meats, drinking contaminated water, inhalation of contaminated soil
Hemorrhagic fever	Ebola and Marburg, filoviruses	unknown. Bats?	average: 5-10 days range: 2-19 days	contact with body fluid of infected person

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foodborne botulism; however, the gastrointestinal symptoms that accompany foodborne botulism may be absent.[5]

Smallpox (variola). The acute clinical symptoms of smallpox resemble other acute viral illnesses, such as influenza, beginning with a 2- to 4-day nonspecific prodrome of fever and myalgias before rash onset. Several clinical features can help clinicians differentiate varicella (chickenpox) from smallpox. The rash of varicella is most prominent on the trunk and develops in successive groups of lesions over several days, resulting in lesions in various stages of development and resolution. In comparison, the vesicular/pustular rash of smallpox is typically most prominent on the face and extremities, and lesions develop at the same time.[6]

Inhalational tularemia. Inhalation of *F. tularensis* causes an abrupt onset of an acute, nonspecific febrile illness beginning 3-5 days after exposure, with pleuropneumonitis developing in a substantial proportion of cases during subsequent days.[7]

Hemorrhagic fever (such as would be caused by Ebola or Marburg viruses). After an incubation period of usually 5-10 days (range: 2-19 days), illness is characterized by abrupt onset of fever, myalgia, and headache. Other signs and symptoms include nausea and vomiting, abdominal pain, diarrhea, chest pain, cough, and pharyngitis. A maculopapular rash, prominent on the trunk, develops in most patients approximately 5 days after onset of illness. Bleeding manifestations, such as petechiae, ecchymoses, and hemorrhages, occur as the disease progresses.[8]

Diagnostic studies for category A bioterrorism diseases [3-8]

Agent	Diagnostic Studies
Anthrax	Widened mediastinum on chest x-ray Gram-positive bacilli on unspun blood smear Growth of large Gram-positive bacilli with preliminary identification of Bacillus species from blood, CSF, nasal swab, sputum, or wound culture from cutaneous lesion Pathology showing hemorrhagic mediastinitis, hemorrhagic thoracic lymphadenitis, hemorrhagic meningitis
Plague	Sputum, blood or lymph node aspirate Gram-negative bacilli with bipolar ("safety pin") staining on Wright, Giemsa or Wayson stain Rapid diagnostic testing available at CDC Pulmonary infiltrates or consolidation on chest x-ray Pathology showing lobular exudates, bacillary aggregation and areas of necrosis in pulmonary parenchyma
Smallpox	Electron microscopy examination of vesicular or pustular fluid or scab in high containment (Biosafety Level 4) facility Definitive identification requires growth of virus, further characterization by PCR and RFLP
Botulism	Clinical diagnosis is foundation for early recognition; routine laboratory testing unremarkable EMG with normal nerve-conduction velocity, normal sensory nerve function, a pattern of brief, small-amplitude motor potentials, and incremental response (facilitation) to repetitive stimulation Serum or stool tested at Oregon State Public Health Laboratory using mice bioassay (takes several days)
Tularemia	Small Gram-negative coccobacilli in direct stain of respiratory secretions Sputum and blood culture using cysteine-enriched medium Rapid testing with DFA, PCR or antigen-detection procedures Peribronchial infiltrates leading to bronchopneumonia in ⩾1 lobe on chest x-ray, often with pleural effusion and enlarged hilar nodes Histological findings of acute suppurative necrosis followed by granulomatous reactions. Target organs include lungs, lymph nodes, spleen, liver, and kidney
Hemorrhagic fever	ELISA for IgG, IgM, or viral antigen; viral isolation, PCR post-mortem: immunohistochemistry, viral isolation, PCR

ADDITIONAL RESOURCES

A wealth of information, in addition to valuable bioterrorism-related links, is available on our web site *http://www.ohd.hr.state.or.us/acd/bioterr/home.htm*.

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