

The Threat of Bioterrorism, Clinical Recognition and Management

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Abstract: Bioterrorism is an emerging public health and infection control threat. Potential biological agents include smallpox, plague, botulinum toxin, brucellosis, Q fever, viral encephalitis, haemorrhagic fever and staphylococcal enterotoxin B. An understanding of the epidemiology, clinical manifestation, and the management of the more likely candidate agent is critical to limiting morbidity and mortality from biological events. Effective response requires an increase index of suspicion for usual diseases or syndromes, with prompt reporting to health authorities to facilitate recognition of outbreak and subsequent intervention. The clinical manifestation and management is discussed in this review.

Key Words : *Biological warfare, Bioterrorism.*

Introduction

Biological weapons include any organism or toxin found in nature that can be used to incapacitate, kill or otherwise impede an adversary. Biological weapons are characterized by low visibility, high potency, substantial accessibility, and relatively easy delivery. Prior to the 20th century, biological warfare took on 3 main forms: (1) deliberate poisoning of food and water with infectious material, (2) use of microorganisms or toxins in some form of weapon system, and (3) use of biologically inoculated fabrics.

In the 12th century AD, during the battle of Tortona, Barbarossa used the bodies of dead soldiers to poison wells. In the 14th century AD during the siege of Kaffa, the attacking Tartar force hurled the corpses of those who died of plague into the city to attempt to inflict a plague epidemic upon the enemy¹. Biological warfare became more sophisticated against both animals and humans during the 1900s. During World War I, the Germans developed anthrax, glanders, cholera, and a wheat fungus for use as biological weapons. In 1925, the Geneva Protocol was signed by 108 nations, including the 5 permanent members of the UN Security Council. This was the first multilateral agreement that extended prohibition of chemical agents to biological agents². No method for verification of compliance was addressed. Currently, 17 countries are suspected of having an offensive BW program. Dissemination of BW agents may occur by aerosol sprays, explosives (artillery, missiles, detonated bombs), or food or water contamination. *Preliminary criteria for suspicious outbreak of disease that could provide indications of a possible biological weapons include the following :* (i) Disease (or strain) not endemic; (ii) Unusual antibiotic resistance patterns; (iii) Atypical clinical presentation; (iv) Case distribution geographically and/or temporally inconsistent (eg, compressed time course); (v) Other inconstant elements (eg. number of cases, mortality and morbidity rates, deviations from disease occurrence baseline)

Anthrax

Bacillus anthracis is a large, aerobic, gram-positive, spore forming, nonmotile bacillus. Infection occurs predominantly through the cutaneous route and only rarely via the respiratory or gastrointestinal (GI) route³.

(i) *Cutaneous* : more than 95% of cases of anthrax are cutaneous. After inoculation, the incubation period is 1-5 days. The disease first appears as a small papule that progresses over 1-2 days to a vesicle containing serosanguinous fluid with many organisms and a paucity of leukocytes. The vesicle ruptures,

leaving a necrotic ulcer. The ulcerbase develops a characteristic 1- to 5-cm black eschar⁴. (The black appearance of the eschar gives anthrax its name [Greek *anthrakos* = coal].

(ii) *Inhalation* : Also known as **wool sorter's disease**. Initial manifestations are nonspecific and this is followed by the sudden onset of increasing respiratory distress with dyspnea, stridor, cyanosis, increased chest pain, and diaphoresis. pneumonia is an uncommon finding. Mortality is nearly 100% despite appropriate treatment. Inhalation anthrax is the most likely form of disease to follow military or terrorist attack⁵.

Treatment : Most naturally occurring strains of anthrax are sensitive to penicillin, and penicillin historically has been the preferred therapy for the treatment of anthrax. Experts currently recommend initiation of ciprofloxacin or other fluoroquinolones in adults with presumed inhalation anthrax infection. Following a terrorist attack, resistance to penicillin and tetracycline class antibiotics is assumed until laboratory testing demonstrates otherwise. In adults, ciprofloxacin 400mg IV q12h is recommended. Traditionally, ciprofloxacin and other fluoroquinolones are not recommended for use in children younger than 16-18 years because of a link to permanent arthropathy in adolescent animals and transient arthropathy in small number of children. Balancing these small risks against the real risk of death and resistant strains of *B anthracis*, experts recommend that ciprofloxacin be given to a pediatric population for initial therapy or postexposure prophylaxis following anthrax attack. In children, ciprofloxacin at 20-30 mg/kg/d IV in 2 daily doses (not to exceed 10g/d) is recommended. If antibiotic susceptibility testing allows, substitute intravenous penicillin for the fluoroquinolones. For adults and children older than 12 years, penicillin G at 4 million U IV q4h is recommended for 60 days. Doxycycline at 100mg IV q12h for 60 days is an acceptable alternative for adults. For children younger than 12 years, penicillin G is dosed 50,000 U/kg q6h for 60 days.

Prevention : No FDA-approved chemoprophylactic regimens are available following exposure to an anthrax aerosol. For postexposure prophylaxis, experts recommend the same oral regimen as that recommended for treatment of mass casualties⁷. A licensed vaccine, an aluminum hydroxide-adsorbed preparation, is derived from culture fluid supernatant taken from an attenuated strain. The vaccination series consists of 6 subcutaneous doses at 0, 2, and 4 weeks, then at 6, 12, and 18 months, followed by annual boosters. If information indicates that a BW attack is imminent or may have occurred, prophylaxis of unimmunized

individuals with ciprofloxacin (500 mg PO bid) or doxycycline (100mg PO bid) is recommended. Should an anthrax attack be confirmed, continue chemoprophylaxis for at least 4 weeks and until all those exposed receive 3 doses of vaccine (at 0, 2, and 4 wk).

Plague

Plague is a zoonotic infection caused by *Yersinia pestis*, a gram-negative coccobacillus. Throughout history, the oriental rat flea (*Xenopsylla cheopis*) has been largely responsible for spreading bubonic plague.

Clinical features : Plague is characterized by the abrupt onset of high fevers, painful lymphadenopathy, and bacteremia. Septicemic plague sometimes can ensue from untreated bubonic plague or, de novo, after a fleabite. Patients with the bubonic form of the disease may develop secondary pneumonic plague. Pneumonic plague is the most severe form of disease and, untreated, has a mortality rate approaching 100%. If *Y. pestis* were used as BW agent, it most likely would be inhaled as an infectious aerosol and result in primary pneumonic plague (epidemic pneumonia)⁸. If fleas were used as carriers of disease, bubonic or septicemic plague would result. Patients typically have a productive cough with blood-tinged sputum within 24 hours of symptom onset.

Treatment : Isolate patients with plague for the first 48 hours after treatment initiation. If pneumonic plague is present, continue isolation for 4 days. Since 1948, streptomycin has been the treatment of choice for bubonic, septicemic, and pneumonic plague. It is administered in a dose of 30 mg/kg/d IM divided bid. In patients with meningitis or hemodynamic instability, intravenous chloramphenicol (50-75 mg/kg/d) divided qid dose is added. Gentamicin has had much less clinical usage but can be used as an alternative to streptomycin. Treatment is continued for a minimum of 10 days or 3-4 days after clinical recovery. In patients with very mild bubonic plague who are not septic, tetracycline can be used orally at a dose of 2 g/d divided qid for 10 days. Doxycycline, ofloxacin, and ceftriaxone have been demonstrated to be effective in animal models⁹.

Prevention : Contacts of patients with pneumonic plague and individuals who have been exposed to aerosols are treated with tetracycline 15-30 mg/kg/d divided qid for 6 days. If tetracycline is not available, doxycycline 100mg bid is an effective alternative. Only individuals at high risk for plague should be immunized with a licensed, killed, whole cell vaccine¹⁰.

Cholera

Cholera is an acute and potentially severe GI disease caused by *Vibrio cholerae*. *V. cholerae* is a short, curved, motile, gram-negative, nonsporulating rod. Two serogroups (O1, O139) have been associated with cholera in humans. The O1 serotype exists as 2 biotypes, classical and El Tor¹¹. They do not invade the intestinal mucosa but rather adhere to it. Cholera is the prototype toxigenic diarrhea, which is secretory in nature.

Clinical Features : Infection generally occurs within a week of exposure and is classically of abrupt onset following a brief nonspecific prodrome. The syndrome is characterized by sudden onset of nausea and vomiting and profuse diarrhea with a classic rice water appearance. The rapid loss of body fluids often leads to toxemia and frequent cardiovascular collapse.

Treatment : Treatment depends on replacement of fluids and electrolyte losses. This is best accomplished using oral rehydration therapy, but intravenous fluid replacement is occasionally necessary for persistent vomiting or high rates of stool loss (10mL/kg/h). Antibiotics shorten the duration of diarrhea and reduce fluid losses.

Tetracycline (500 mg q6h for 3d) or doxycycline (300mg once or 100mg bid for 3d) is an acceptable alternative. However, due to resistance, ciprofloxacin (500mg q6h for 3d) or erythromycin (40mg/kg/d divided qid for 3d) also has been accepted¹².

Prevention : A licensed, killed vaccine is available for use in those considered to be at risk for exposure. The vaccination schedule is an initial dose followed by another dose 4 weeks later, with booster doses every 6 months. An inactivated oral vaccine (WC/rBs) is safe and provides rapid short-term protection. WC/rBs requires 2 doses and has approximately 85% efficacy lasting 2-3 years for both El Tor and classic biotypes.

Brucellosis

Brucellosis is a zoonotic infection of domesticated and wild animals caused by an organism of the genus *Brucella*. The ease of transmission by aerosol suggests that *Brucella* species may be useful as a BW agent¹³. The disease often becomes chronic and may relapse, even with appropriate treatment.

Brucella species are small, nonmotile, nonsporulating, aerobic, gram-negative coccobacilli that may represent a single species. Only *Brucella melitensis*, *Brucella suis*, *Brucella abortus*, and *Brucella canis* cause disease in man. *Brucella* species can enter mammalian hosts through skin abrasions or cuts, the conjunctiva, the respiratory tract, and the GI tract.

Clinical Features : Patients usually have nonspecific symptoms such as fever, sweats, fatigue, anorexia, and muscle or joint aches. Neuropsychiatric symptoms, focal infection of bones, joints, or the genitourinary tract may occur. Cough and pleuritic chest pain also may be noted. Pyelonephritis, cystitis, and in males, epididymo-orchitis may occur. Hepatitis and rarely, liver abscess also occur. *Brucella* endocarditis, a rare but feared complication, accounts for 80% of deaths from brucellosis.

Treatment : Therapy with a single drug has resulted in a high relapse rate, so use combined antibiotic regimens is used whenever possible. A 6-week regimen of doxycycline 200mg/d PO with the addition of streptomycin 1g/d IM for the first 2 weeks is effective in most adults with most forms of brucellosis. Patients with spondylitis may require longer treatment. A 6-week oral regimen with both rifampin 900 mg/d and doxycycline 200mg/d is effective. Endocarditis likely is best treated with a combination of rifampin, streptomycin, and doxycycline for 6 weeks.

Q Fever

Q fever is a zoonotic disease caused by *Coxiella burnetii*, a rickettsialike organism of low virulence but remarkable infectivity. The potential of *C. burnetii* as a BW agent is related directly to its infectivity. It has been estimated that 50 kg of dried *C. burnetii* would produce casualties at a rate equal to that of similar amounts of anthrax or tularemia organisms¹⁴.

Clinical Features : Q fever in humans may be manifested by asymptomatic seroconversion, acute illness, or chronic disease. Dever, chills, and headache are the most common signs and symptoms. Diaphoresis, malaise, myalgias, fatigue, and anorexia are also common. Encephalopathic symptoms and acute hepatitis have been reported. Chronic infection with *C. burnetii* usually is manifested by infective endocarditis, which also is the most severe complication of Q fever.

Treatment : Tetracycline has been the mainstay of therapy since the 1950s. Macrolide antibiotics, such as erythromycin and azithromycin, are also effective. In cases of infective endocarditis at least 2 years of therapy are required, usually with a tetracycline combined with rifampin or a quinolone, although trimethoprim-

sulfaethoxazole also has been used¹⁵.

Prevention : Although an effective vaccine (Q-Vax) is licensed in Australia, all Q fever vaccines used in the US are investigational. Q fever can be prevented by immunization.

Smallpox

Variola, the causative agent of smallpox, is the most notorious of the poxviruses (family Poxviridae). In 1980, the World Health Organization (WHO) declared endemic smallpox eradicated, with the last occurrence in Somalia in 1977. Variola represents a significant threat as a BW agent. Currently, 2 WHO-approved and inspected repositories remain: the CDC in the US and Vector Laboratories in Russia; however, clandestine stockpiles may exist. Variola virus is highly infectious by aerosol, environmentally stable, and can retain infectivity for long periods¹⁶.

Clinical Manifestations : After a 7- to 17-day incubation period, symptoms begin acutely with high fever, headache, rigors, malaise, myalgias, vomiting, and abdominal and back pain. After 2-3 days, an exanthem develops. The lesions progress synchronously from macules to papules to vesicles to pustules. Centrifugal distribution of the rash is an important diagnostic feature.

Treatment : Strict quarantine with respiratory isolation for 17 days is applied to all people in direct contact with the index case or cases. All personnel exposed to either weaponized variola or clinical cases must be vaccinated immediately. Vaccinia immune globulin (VIG) is given to patients who cannot receive the vaccine. Treatment of smallpox is mainly supportive. The antiviral agent, cidofovir, is effective in vitro and may be involved in treatment of symptomatic illness.

Prevention : Smallpox vaccine (attenuated vaccinia virus) is administered by intradermal inoculation with a bifurcated needle. The permanent scar results from a process known as scarification.

Viral Hemorrhagic Fevers

Viral hemorrhagic fevers are caused by 4 families of viruses, which include the Arenaviridae (Lassa, Argentine, Bolivian, Brazilian, Venezuelan hemorrhagic fevers), Bunyaviridae (Rift Valley, Crimean-Congo, Hantaan), Filoviridae (Marburg, Ebola 4 Fs), and Flaviviridae (Yellow, Dengue, Kyasanur Forest, Omsk HFs). The best known of the viral hemorrhagic fever agents is Ebola virus. All agents are highly infectious via the aerosol route, and most are stable as respiratory aerosols. Thus, they possess characteristics ideal for use by terrorists.

Clinical Manifestations : All viral hemorrhagic fevers primarily target vascular beds. They produce microvascular damage and enhance vascular permeability. Clinical manifestations include fever, myalgia, prostration, conjunctival injection, mild hypotension to severe shock, and mucosal and petechial hemorrhages, Neurologic, hematopoietic, hepatic, and pulmonary involvement can be found with more severe disease.

Treatment : Treatment for a viral hemorrhagic fever is largely supportive. Patients benefit from rapid nontraumatic hospitalization to prevent damage to the capillary bed. Sedative and pain-relieving medications are helpful, but aspirin and other antiplatelet agents should be avoided. Avoid intravenous lines and catheters unless absolutely necessary. Secondary infections should be sought and aggressively treated. Immunosuppressive agents such as steroids are contraindicated. The treatment for bleeding is controversial. Generally, mild bleeding should not be treated, whereas severe hemorrhage requires appropriate replacement therapy.

Specific treatment with ribavirin has been used and currently is

being investigated as therapy for Lassa fever, Hantavirus, Crimean-Congo, and Rift Valley Fever. The dosage is 130mg/kg IV followed by 15mg/kg q6h for 4 days, then 7.5mg/kg q6h for 6 days. Treatment is most effective if begun within 7 days⁸. Ribavirin has poor activity against the filoviruses and flaviviruses.

Ricin

Ricin, a plant protein toxin derived from the beans of the castor plant, is one of the most toxic and easily produced of the plant toxins. The worldwide ready availability of castor beans and the ease with which toxin can be produced give it significant potential as a biological weapon.

Clinical Manifestations : Ricin is extremely toxic to cells and acts by inhibiting protein synthesis. Inhalation exposure causes primarily pulmonary symptoms, ingestion causes GI symptoms, and intramuscular exposure results in a localized reaction¹⁷. In a BW or terrorist situation, exposure is likely to occur by inhalation of a toxin aerosol. Treatment is supportive. Inhalation injury may require treatment of pulmonary edema, with respiratory support as indicated. Intravenous crystalloid infusion and pressor support may be necessary for patients with hypotension.

Botulinum Toxin

The anaerobic, spore-forming, gram-positive bacillus, *Clostridium botulinum*, produces botulinum toxins. Botulinum toxins are the most lethal toxins known, with an estimated lethal dose to 50% of the exposed population (LD50) of 0.001 mcg/kg in humans. Since botulinum toxin is so lethal and easy to manufacture and weaponize, it represents a credible threat as a BW agent. When used as a BW or terrorist agent, exposure is likely to occur following inhalation of aerosolized toxin or ingestion of food contaminated with the preformed toxin or microbial spores. Botulinum toxins bind to the presynaptic nerve terminal at the neuromuscular junction and cholinergic autonomic sites. This prevents the presynaptic release of acetylcholine and blocks neurotransmission.

Clinical Manifestations : Initial signs and symptoms include blurred vision, mydriasis, ptosis, dysphagia, dysarthria, dysphonia, and muscle weakness. After 24-48 hours, neuromuscular manifestations progress to symmetric descending paralysis and respiratory failure. Postural hypotension may occur from autonomic insufficiency. Oral exposure can be detected by analyzing serum or gastric contents with a mouse neutralization assay.

Treatment : The most serious complication of toxicity is respiratory failure. With supportive care and ventilatory assistance, fatalities should be less than 5%. For confirmed exposures, a trivalent equine antitoxin is available. After a negative skin test, the antitoxin is administered at a dose of 10mL IV over 20 minutes, which is repeated until improvement ceases¹⁸.

Prevention : A toxoid for *C botulinum* was used to immunize US military troops in the Persian Gulf War. The current schedule for immunization is at 0, 2, and 12 weeks with an annual booster. Currently, no indication exists for prophylactic use of the antitoxin except under specialized circumstances.

Mycotoxins

The trichothecene mycotoxins are highly toxic compounds produced by certain species of filamentous fungi (*Fusarium*, *Myrothecium*, *Cephalosporium*, *Trichoderma*, *Verticillium*, *Stachybotrys* species). Strong evidence suggests that trichothecenes ("yellow rain") have been used as a BW agent in Southwest Asia and Afghanistan.

Clinical Manifestations : The trichothecene mycotoxins are cytotoxic to most eukaryotic cells by way of inhibiting protein synthesis and electron transport. After exposure to the mycotoxins, early symptoms begin within minutes. Cutaneous manifestations include burning, tender erythema, edema, and blistering with progression to dermal necrosis and sloughing of large skin areas in lethal cases. Respiratory exposure results in nasal itching, pain, sneezing, epistaxis, rhinorrhea, dyspnea, wheezing, cough, and blood-tinged saliva and sputum. GI toxicity consists of anorexia, nausea and vomiting, abdominal cramping, and watery and/or bloody diarrhea. Death may occur within minutes to days depending on the dose and route of exposure.

Treatment : Treatment is supportive. If unprotected during an attack, the outer clothing should be removed within 4-6 hours and decontaminated with 5% sodium hydroxide for 6-10 hours. The skin should be washed with copious amounts of soap and uncontaminated water. The eyes, if exposed, should be irrigated with copious amounts of normal saline or sterile water. Early use of systemic steroids increases survival time by decreasing the primary injury and shocklike state that follows significant poisoning⁸.

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