

Bioterrorism: Medical and Public Health Perspectives

Overview and Historical Perspective

As weapons, biological agents have a number of advantages. There is the potential for wide dissemination with mass casualties at low cost. Perpetrators can protect themselves as delayed onset allows time to escape. Finally the panic that is engendered wreaks more havoc, often, than the weapon itself. Prior to 9/11 there was a belief that bioterrorism in the US would never happen. Because biologic weapons were seldom used, the technology was difficult, and it was thought of as morally wrong, this unthinkable concept was dismissed. However, biological weapons have historically been used in attacks that were considerably more debilitating than the anthrax attacks of immediate post-9/11 era. The first recorded case of biologic warfare occurred in 1347 when Tartars holding the city of Kaffa under siege catapulted the bodies of plague victims over city walls in an attempt to cause an outbreak of plague among the inhabitants. In 1700 during the French and Indian Wars, Native Americans were given blankets contaminated with small pox- a disease to which they had no natural immunity. More recently, the Ranjeesh Cult in Dulles, Oregon contaminated salad bars with Salmonella in an attempt to rig an election. It was the most effective bioterrorist attack of the modern era and affected 400-500 people. And, as you all remember, in 2001 anthrax attacks occurred in New York, Florida and Washington, DC. The perpetrator of those attacks has never been identified.

The United States has a history of bioweapons research. From 1943-1969 the US had an active offensive program. Nixon ended the program and in 1972 the US signed the Biological Weapons Convention. The US maintains an active bioweapons defense program. Other nations with confirmed bioweapons programs include Iraq and the former Soviet Union, which in the 1970's began a massive production program for bioweapons. Nations with probable programs include China, Iran, N. Korea, Libya, and Syria while Israel, Egypt, and Cuba possibly may have programs.

Characteristics of Ideal Biologic Weapon Biowarfare: Potential Agents

The ideal bioweapon is silent, odorless, and tasteless, inexpensive, easy to produce, hardy, transmitted person to person, causes lethal or disabling disease and has no effective treatment or prophylaxis. While no one agent meets all these criteria several agents meet many of them. Potential biowarfare agents include:

Bacterial:

Anthrax
Brucellosis
Plague

Q fever
Tularemia

Viral:

Smallpox
Viral Hemorrhagic Fever

Toxins:

Botulism
Ricin
Staph enterotoxin B

ANTHRAX

Bacillus anthracis a non-motile Gram positive rod. It produces three exotoxins: **Edema Factor (EF)**, **Lethal Factor (LF)**, and **Protective Antigen (PA)**. PA binds to specific cell surface receptors and upon proteolytic activation forms a membrane channel that mediates entry of EF and LF into the cell. EF and PA form a toxin referred to as **edema toxin**. LF and PA form **lethal toxin**. Lethal toxin is the dominant virulence factor produced by *Bacillus anthracis* and is the major cause of death in infected animals.

Clinically anthrax may be manifest as one of three types depending upon the route of inoculation:

1. Cutaneous
2. Inhalational
3. Intestinal

Cutaneous Anthrax is the most common manifestation of anthrax infection accounting for 95% of all cases in developed countries. The route of infection is the direct inoculation of skin by spores with an incubation period of 1-7 days (up to 14d). Clinical findings are characteristic and the diagnosis is not often missed by physicians familiar with the disease. The infection begins as a pruritic macule which enlarges and within 1-2 days develops into a round ulcer surrounded by vesicles. A **black eschar** then develops with associated edema and over 1-2 weeks softens and separates leaving a permanent scar. In untreated infection there is a ~5-20% fatality rate. Diagnosis can be made clinically by an experienced physician. Confirmation may include gram stain with culture or PCR of vesicular fluid at the border of skin lesion; skin biopsy with culture and PCR or immunohistochemistry; or serology looking for IgG antibody to protective antigen.

Inhalational Anthrax is very rare with only 18 cases in the US between 1900-1978 and none reported at all from 1978 until October 2001. The route of infection is inhalation of spores (1-5 Microns) into terminal bronchioles and alveoli where they may live for up to weeks. Next, spores are taken up by macrophages and are brought to regional lymph nodes. In the lymph nodes, spores germinate producing actively growing anthrax, which proliferates in macrophages, secretes toxins, and enters the bloodstream. The regional lymph nodes grow and hemorrhage during this infectious stage. The initial symptoms resemble flu with malaise, fever, cough and body aches. Later symptoms include high fever, vomiting, respiratory distress and **necrotizing hemorrhagic mediastinitis**. The disease can be fatal within 24-36 hours. Diagnosis can be difficult as inhalational anthrax has non-specific physical findings. Chest X-Ray may reveal mediastinal adenopathy and pleural effusions. Gram stain, culture, and PCR of blood, pleural fluid and CSF may produce the diagnosis. Suspected cultures should be sent to NYCDOH and/or CDC- both of which are now capable of making diagnoses. Antibiotics are effective against vegetative *B. anthracis* but not against the spore form. Unfortunately, in "advanced disease" the mortality rate is 100% despite the most aggressive therapy. Mortality decreases with early treatment. 6/11 cases in the 2001 outbreak survived with early aggressive therapy.

Intestinal Anthrax is rare but has been associated with epidemics usually occurring during periods of extreme hardship when meat from animals dying of anthrax is eaten. The incubation period is 3-7 days and there are two clinical presentations: abdominal and oropharyngeal. The symptoms of abdominal anthrax are initially nonspecific with nausea, vomiting, anorexia and fever. With progression of disease abdominal pain, hematemesis, and bloody diarrhea develop which progresses in turn to shock, cyanosis, and death. In the oropharyngeal form edema and tissue necrosis occur in the cervical area. The main clinical features are sore throat, dysphagia, fever, lymphadenopathy, and toxemia. Diagnosis includes culture of vomitus or feces.

Anthrax **vaccine** was originally made in 1970 and is a sterile filtrate of cultures from an avirulent strain of anthrax that elaborates protective antigen. The vaccine is 100% effective against cutaneous infection, and "possibly" effective against inhalational disease. Field tests of mill workers in the US showed a 92.5% effectiveness. Current stocks of vaccine are limited. **Prophylaxis** comes in two types: *pre-exposure*- vaccination of people at high exposure risk (US military since 1997, CDC Lab. Response Network, decontamination workers, occupations with high risk of exposure to contaminated animals) and *postexposure*- vaccination of people exposed to aerosolized anthrax spores to prevent germination and progression to inhalational anthrax (victims of the 2001 anthrax attack). Additionally, disease can be prevented if antibiotic therapy is continued until all spores have been cleared or controlled by the immune system. As spores can live for up to 100 days post exposure in mediastinal lymph nodes it is recommended that exposed individuals stay on antibiotics (Cipro) for 100 days (if not vaccinated - 30 days with three vaccine doses 0,2,4 weeks post exposure).

SMALLPOX (*Variola Major*): A Bioweapon for the future

Factors that make smallpox a good bioweapon include aerosol transmission with rapid person to person spread, severe morbidity and mortality especially in non-immune populations (and worldwide immunity has waned since the disease was eradicated), clinical inexperience (most practicing physicians have never seen a case), potential to overwhelm medical care and public health systems, and a high secondary attack rate. Despite the fact that natural smallpox was eradicated in the late 1970's, the Soviet Union actively weaponized their stocks in the 1970's and 1980's. The fate of much of that material is unknown and it is believed that several other countries have hidden stocks of virus.

Smallpox is spread by the aerosol route with infectious particles gaining entry through the oral and respiratory mucosa. There is migration to regional lymph nodes, replication then an initial asymptomatic viremia which occurs 3-4 days after exposure. The virus then multiplies in the reticuloendothelial tissues leading to a secondary viremia by about day 8. Symptoms begin with the abrupt onset of high fever, malaise, rigors, vomiting, backache and headache followed 2-3 days later by a maculopapular rash. Importantly, patients are generally not infectious until the rash appears. The rash of smallpox is characteristic although it may be confused with chickenpox. It starts as a maculopapular rash which is deeply embedded in the dermis on the face (including the oral mucosa) and then spreads down and out to the arms,

trunk and legs. Lesions are often found on the palms and soles. The rash develops from a maculopapular eruption to vesicles and then pustules just like in chickenpox. However, the lesions in smallpox develop at the same time (synchronous) unlike chickenpox in which different lesions are at different stages of development (cropping).

Diagnosis requires an astute physician to distinguish smallpox from chicken pox. Important differences between the two include:

	Variola	Varicella
Incubation	7-17 days	14-21 days
Prodrome	2-4 days	Minimal
Distribution	Centrifugal	Centripetal
Evolution	Synchronous	Cropping
Depth of Lesion	Dermal	Subcutaneous

A swab of vesicular/pustular fluid can be cultured for smallpox at the CDC's BSL4 laboratory (this is not something you want to try at home). A PCR assay is also available through the CDC. Once a single case is diagnosed an international emergency will occur. Therefore, immediate reporting to public health authorities is required for even suspected cases. Strict **quarantine** of suspected cases with both respiratory and contact isolation procedures is mandatory. There is **no proven treatment** although cidofovir is effective in vitro.

Smallpox vaccine was first developed in England by Edward Jenner from the pustules of milkmaids with cowpox. Modern vaccine (Dryvax) is administered by a bifurcated needle which is repetitively jabbed (15 times) into the skin of the person to be inoculated. The needle must draw blood to be effective. High levels of protection are present for 3 years but the immune response to variola wanes over time. It is not clear if people vaccinated in the early 1970s will still be protected. The vaccine is not benign. **Side effects** include- muscle aches, fatigue, headache, nausea, fever, pain at injection site, regional lymphadenopathy. Acute viral illness can occur with vaccine and is a real risk to be considered. **Contraindications** to vaccine use include immunodeficiency- high risk of side effects (progressive vaccinia), eczema- including a past history (eczema vaccinatum), pregnancy, allergies to polymyxin B (an antibiotic used in the preparation of the vaccine), and acute or chronic skin conditions. Adverse reactions in the general population are rare, but actually occur. Inadvertent inoculation of an unimmunized contact is most common occurring in 1/1700 primary vaccinees. Postvaccinial encephalitis occurs in 1/80,000 primary vaccinees and death in 1/million. Vaccinia immune globulin (VIG) can be used to attempt to ameliorate the adverse effects of the vaccine; however, supplies of VIG are limited. They are obtained from vaccinated donors and the pool is very small. The US currently has enough vaccine to vaccinate everyone in the case of an attack. Recent studies suggest that the vaccine is as effective at a 1:5 dilution as undiluted which will further increase the supply.

Public Health Response to Bioterror

Public health infrastructure is critical in responding to a suspected bioterror event. Detection of a potential outbreak is critical as is follow up to confirm its existence and to identify the etiology (intentional vs. natural). Once an outbreak is detected, members of the medical community, law enforcement, and other agencies will be notified and an epidemiologic and criminal investigation will be carried out. An active surveillance program will be put in place to track morbidity and control measures implemented. Cooperation is crucial in identifying and containing a potential bioterror event. Medical personnel are asked to help by being aware of and reporting any increases in unexpected illnesses or deaths (this is how West Nile was identified). Finally prevention is worth a pound of cure. In order to prevent a bioterror event we need to strengthen and enforce the UN's biologic and chemical weapons conventions, restrict the sale of potential bioweapons organisms and safeguard research stocks, enhance worldwide intelligence capacity to identify terrorists working with bioweapons, and address the human rights issues that foster terrorism in the first place.

