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April 2005

BIOTERRORISM:
What the Healthcare Professional Needs to Know

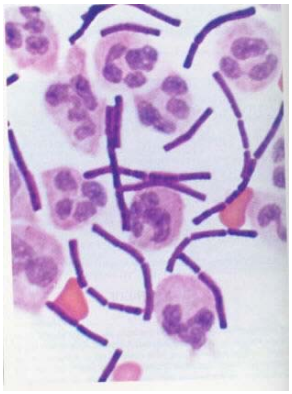
Introduction to Bioterrorism

The events that have occurred since September 11, 2001 have shown that bioterrorism is an unfortunate reality in the United States in the year 2001.

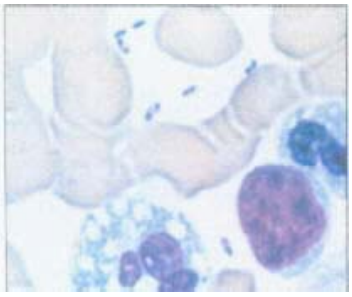
There are a large number of agents that can be used by the terrorist. Some are probable candidates and others are possible but unlikely. An additional layer of complexity for the clinician is the rather commonplace presentation of most of the biologic agents. For example, the presentation of inhalation anthrax is nearly indistinguishable from a viral URI in the initial stages.

The United States has been preparing for such threats for many decades now, but only a test of the system will prove if the system is ready or not. Interestingly, physicians and nurses – especially in Emergency care and Primary Care – are considered key elements in the strategic plan. I would venture to say that before September 11 most of you had not seriously considered your role in managing a bioterrorist attack. Even since that fateful day, most of us have been too busy with the routines of our jobs and lives to give serious consideration to this matter.

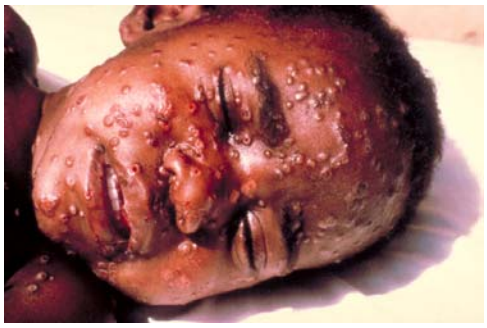
This handout has several purposes and is divided into distinct sections to help accomplish each of these goals.



Anthrax

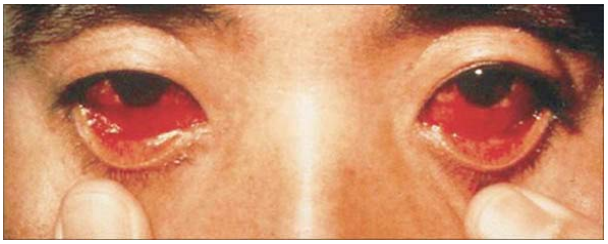


Plague (Yersinia)



Young boy with smallpox

Ebola virus



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Historical Aspects of Bioterrorism

Bioterrorism is certainly nothing new to humanity or warfare. The aboriginal use of curare and amphibian-based toxins (a Neolithic practice) started the modern interest in biologic agents for use in war. There have been numerous accounts of the use of sick persons, secreta or corpses against an enemy in order to incapacitate them or kill them outright.

A brief overview of some of these historical cases will likely aid the clinician in understanding the psyche of biologic warfare. This understanding is important for our ability to understand the potential epidemiology of an "outbreak" and to handle the psychological impact of such an attack. As we have seen in the US the nationwide psychological impact of less than 12 deaths can be devastating (especially if the media is affected directly).

200 BCE – on	Corpses are used by Roman legions to contaminate water supplies of towns being seiged. A practice considered standard up through the Napoleonic Wars (early 1800s).
1300s	Siege forces catapult corpses of **plague** victims over the walls of the city of Kaffa.
1700s	British use blankets contaminated by **smallpox** victims to infect the Native Americans in the French and Indian War.
1930s & 1940s	Japan extensively field-tested numerous biologic agents against the Chinese. One incident involved the use of 15 million **plague**-infested fleas. Food supplies were contaminated with **Vibrio**.
1960s – 1970s	Viet Cong used excrement on pungi sticks to cause sickness (and delayed death) in American GI's. Adolph Hitler banned the use and experimentation in biologic weapons.
1940s	• US had made > 5000 **anthrax** bombs for use in WWII if needed • US experimented in NYC and SF releasing biologics into the general public in various forms to study the epidemiology • Stanford had an outbreak of resistant *S mascescens* • Program halted in 1970
1980s	• Religious community in rural Oregon convicted of poisoning the food and water supply of several towns with "research-grade" *Salmonella*
1995	• Ohio man arrested for purchasing large quantities of anthrax through a supply company on the internet

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Anthrax (*Bacillus anthracis)*

Anthrax is not the most important agent because of the recent infections in the United States. It is the most important biologic agent because it is the easiest to use to cause such infections. An aerobic, gram-positive rod that is ubiquitous in herbivorous animals (especially domesticated animals) and the soil. The organism is 1 – 8 micrometers long and the spore form is 1 micrometer round.

Anthrax

Incubation period	1 – 5 days most typical Cases have occurred at least 58 days post exposure	
Testing	• Gram stain & culture of body fluids (sputum rarely +) • Gram stain should be diagnostic! ○ Experience level of person looking at specimen critical • PCR available through PHLN (Public Health Lab Network - CDC) • Widened mediastinum on CXR	
Clinical Syndromes	Lethality	Clinical Symptoms
Cutaneous	• 20% untreated • < 1% treated	• Most common form • Entry from contamination through broken skin layer. • Vesicle development initially • Depressed ulcer with localized edema • Deep black eschar development • Heals generally without scarring
Inhalation	• 100% untreated • 89% treated • 40% early Tx	• URI symptoms with dyspnea, fatigue, fever • Chills, nausea and emesis not uncommon • Rapid development of respiratory collapse, high fevers, shock • Death often in hours after above symptoms
Gastrointestinal	• 100% untreated • 90% treated	• Upper GI ulcer (esophagus, stomach) • Nausea, emesis, fevers, bloody diarrhea • Obstructive symptoms not uncommon • Rapid fatality
Vaccine	• Produced and FDA approved (military use only) • No public availability at this time • 6 shot series, then annual booster • May confer immunity to exposed persons	

Stage 1 inhalation anthrax consists of symptoms generally not distinguishable from other URIs including influenza. Stage 2 make it more evident that another process may be ongoing but generally lasts only several hours. Needless to say a high index of suspicion is needed to treat this disease effectively. There is no person-to-person spread of the disease.

This organism generally causes illness within days of exposure but has the capability to cause disease weeks after exposure. The biologic weapon factory disaster at Sverdonosk had one case of inhalation anthrax 58 days after the initial incident. This is the basis for postexposure prophylaxis and treatment of patients for sixty (60) days.

Therapy is not without consequences – especially in the case of postexposure prophylaxis. In the case of the 5800 postal workers offered postexposure therapy, at least 19% have reported serious side effects, 2% have sought medical treatment for side effects and 8% have discontinued therapy on their own.

Principles of anthrax therapy:

- Patients need to be treated for sixty days (as indicated above)
- Cipro is the only FDA approved drug and has the widest activity against all strains of *B anthracis* and is the initial choice in patients with inhalation or GI disease
- Many other antibiotics have good *in vitro* activity, however
- **Cephalosporins are contraindicated in the treatment of anthrax**
    - High cephalosporinase levels appear within days of therapy
    - Induction of resistance to other antibiotics
- Treatment guidelines for adults are for all adults – pregnant and immunocompromised included
    - Cipro and doxycycline are recommended despite their general contraindication in pregnancy
- Adolescents (and children) should also be treated with Cipro and doxycycline – antibiotics that are otherwise contraindicated in this age group

Anthrax Therapy **Treatment Guidelines: For ALL Adults (Including Pregnancy)**		
	Initial Therapy	
Inhalation or GI Anthrax	Cipro 500 mg IV q 12h OR Doxycycline 100 mg IV q 12 h + other antibiotics	60 d
Cutaneous Anthrax	Cipro 500 mg PO BID OR Doxycycline 100 mg BID + other antibiotics	60 d
Postexposure Prophylaxis	Cipro 500 mg PO BID OR Doxycycline 100 mg BID + other antibiotics	60 d

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Tularemia (*Fransciella tularensis*)

Incubation period	3 – 5 days (as long as 21 days)	
Testing	• Largely a clinical diagnosis • Cultures of affected body fluids or biopsy specimens • Serologic testing available through PHLN	
Clinical Syndromes		
• Infection through skin, mucous membranes and lungs • Syndromes include bronchitis, pharyngitis, lymphangitis • Ocuglandular form in hunters, abattoirs • Typhoidal form (illness without specific site)		
	Lethality	*Clinical Symptoms*
	• 30 – 60% if untreated	• Acute onset of febrile illness with malaise • Severe respiratory illness in healthy persons • Dramatic WBC elevation • Pulmonary symptoms of dry cough, dyspnea and chest pain. Pleural effusions common. • Eventual sepsis and multi-system organ failure
Vaccine	• Live, attenuated vaccine under development • FDA investigation now • No protection against ulceroglandular form • Unclear the degree or significance of side-effects	

The organism responsible for tularemia (*F tularensis*) is a small, gram-negative coccobacillus. It is found in many animals common throughout the world, and it is common throughout the United States. Zoonotic disease has been known since the early 1900s, when the disease was initially thought to be a variant of plague. The organism can survive in the soil for at least 270 days.

The recommended treatment of tularemia varies according to the extent of the outbreak. The most effective therapies are unable to be administered in mass quantities.

Contained Casualty Situation		**Tularemia Therapy**
	Preferred Agents	Alternative Agents
Adults (ALL)	Streptomycin 1 gm IM BID OR Gentamicin 5 mg/kg IM/IV QD	• Doxycycline 100 mg IV q 12h • Chloramphenicol 15 mg/kg IV QID • Cipro 400 mg IV q 12h
Mass Casualty Situation & Postexposure Prophylaxis		
Adults (ALL)	• Doxycycline 100 mg PO BID • Cipro 500 mg PO BID	

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Plague (*Yersinia pestis*)

Plague is one of the most utilized and "successful" biologic weapons throughout history. Armies used the corpses of plague victims to infect their enemies. The Japanese let 15 million plague-infested fleas loose in the environment over a town in China. The Black Death (1346) was responsible for killing more than 1/3 of the population of Europe.

Incubation period	1 – 10 days (typical 2 – 3 days)	
Testing	• Gram stain and culture of body fluids ○ Gram-negative organism with bipolar staining (safety pin) • Confirmatory serologic tests through PHLN	
Clinical Syndromes	Lethality	Clinical Presentation
	• 100% untreated • 20 – 60 % treated (in < 24h)	• "Flu-like" prodrome of fever, headache, myalgias • Progression to dyspnea, chest pain & cough • Days 2+ show respiratory failure, cyanosis and SIRS • Rat is natural reservoir but also squirrels, prairie dogs and other rodents • Rat flea is the vector to humans
Vaccine	• Licensed (inactivated, whole-cell) but no longer produced • Yearly boosters required • No protection against aerosol spread in humans	

There continues to be naturally occurring outbreaks of the plague throughout the world. These outbreaks give us some information about how the plague acts in the natural setting, but does not necessarily show us how the organism would act in a biologic attack. In 1977 in Madagascar there was one case of bubonic plague in a laboratory worker. The worker developed pneumonic disease. Although the pneumonic disease is less common it is spread person-to-person. This individual infected 18 other persons – 8 of whom died – even with quick medical attention and treatment.

Contained Casualty Situation		**Plague Therpay**
	Preferred Agents	Alternative Agents
Adults (ALL)	Streptomycin 1 gm IM BID OR Gentamicin 5 mg/kg IM/IV QD	• Doxycycline 100 mg IV q 12h • Chloramphenicol 25 mg/kg IV QID • Cipro 400 mg IV q 12h
Mass Casualty Situation & Postexposure Prophylaxis		
Adults (ALL)	• Doxycycline 100 mg PO BID • Cipro 500 mg PO BID	• Chlorampnenicol 25 mg/kg QID

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Botulism Toxin (*Clostridium botulinum* toxin)

Botulinum toxin is the only agent of biologic warfare that has approved medicinal uses. The medical preparations, however, are weak enough to pose no population threat. *C Botulinum* is an anaerobic, gram-positive, spore-forming bacterium. It is ubiquitous in the soil throughout the world.

Terrorist groups in Japan (Aum Shinrikyo) used this weapon in at least three attacks in the 1990s. The Iraqis had made 19 000 liters of toxin – more than enough to kill everyone on earth. They also deployed 10 bombs with botulinum toxin during the Gulf War. There were no reported deaths attributed to biologic weapons during this war. (Iraq also deployed 2 bombs with anthrax spores.)

There are a number of neurologic diseases that can be confused with botulism.

Botulism Facts

Incubation period	1 – 5 days (12 – 36 hours more typical)	
Testing	• Specialized laboratory testing (takes days to complete)	
Clinical Syndromes	Lethality	Clinical Presentation
	• 60% without ventilation	• Blurred vision, double vision • Dry mouth, ptosis and fatigue progress in days • Bilateral, descending flaccid paralysis • Respiratory paralsis and death (without ventilator support)
	Other Neurologic Syndromes	*Distinguishing Features*
Differential Diagnosis Considerations	• Guillain-Barre Syndrome • Miller-Fisher variant • Myasthenia gravis • Stroke • Lambert-Eaton syndrome • Tick paralysis • Poliomyelitis • CNS tumor • Psychiatric disease • Viral syndrome • Inflammatory myopathy • Diabetic complications • Hyperemesis gravidarum • Hypothyroidism • Laryngeal trauma • Overexertion	• paresthesias, preceding viral infxn, often ascending, EMG findings • recurrent, EMG findings • asymmetric, abnormal imaging • increased strength with use, lung CA • paresthesias, ascending, tick • preceding infection, asymmetric • asymmetric image, abnormal imaging • normal EMG • absence of bulbar palsy, flaccidity • elevated CK • sensory predominantly, bulbar rare • absence of bulbar palsy, flaccidity • abnormal thyroid tests • no flaccidity, dysphonia without bulbar • no bulbar palsy, flaccidity
Therapy	• Equine anti-toxin very effective – especially if given early ○ Should not be given until symptoms develop • Supportive care mainstay of therapy	

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Smallpox (*Variola major* virus)

Smallpox is a member of the orthopox virus family of viruses. The DNA viruses are among the largest (200 nm) and most complex of all viruses. Smallpox was eradicated from the earth in 1977, and the WHO recommended that vaccination be discontinued. Stores of the vaccine remain in the US (CDC, Atlanta) and Russia (Institute of Virus Preparations, Moscow). The USSR (and subsequently Russia) has admitted to continued research with smallpox as a biologic weapon. There is concern that Iraq also possesses smallpox, which is likely from the altered Soviet sources.

Smallpox has a high person-to-person transmission rate. The virus has a generation of approximately 3-4 days and each generation has an increase in infectivity of 10 – 20 times. This means that 100 persons infected with smallpox could infect 16 million persons before the first group had any symptoms. The expected number of deaths would be **4.8 million**.

Smallpox Facts

Incubation period	7 – 17 days	
Testing	• Testing of biopsy or fluid is possible by the CDC • Notify Poxvirus section of CDC (404-639-2184)	
Clinical Syndromes	Lethality	Clinical Presentation
	• 30% in unvaccinated	• Prodrome of high fever, prostration, headache, vomiting and delirium • After 2 – 3 days maculopapular rash (face, extremities) • Progression to pustules and scabs • Easy to confuse with chickenpox, bullous erythema multiforme and allergic contact dermatitis
Vaccine	• Effective vaccine not widely available • CDC has a stockpile of the vaccine but only a few million doses • Production of vaccine has likely begun	

The treatment for smallpox is mainly supportive care and antibiotics for any secondary bacterial infections. Additionally, the administration of vaccine early after exposure provides amelioration of the disease symptoms and course. There are no antivirals that have proven *in vivo* activity against smallpox. Cytosine arabinoside analogues have shown some activity *in vitro* against the virus. There are no recommendations to use these drugs in the event of smallpox infection.

Smallpox has tremendous potential as a weapon in its natural state. In addition, officials from the former USSR have testified that the virus has been successfully genetically altered, which could make it even more deadly. The efficacy of the current vaccine is uncertain.

Variola major is extremely contagious in the aerosolized form. In the event of cases, all patients and immediate contacts should be quarantined at home and watched closely for symptoms and disease progression. Cases should not be brought to the hospital or other public places to minimize the infection of other persons.

Smallpox Vaccination

Healthcare workers have recently been offered the vaccine for smallpox [made from live cowpox virus (*Vaccinia*)]. This vaccine is among the highest complication rate among current vaccine being used in the US. 3 out of 1 million will be expected to die and another 12 – 20 will be left with permanent neurologic sequelae. Less serious adverse events are also common and may lead to loss of work for those vaccinated or their household contacts.

There are a number of exclusions for receiving the smallpox vaccine, which must be strictly adhered to. Vaccination in persons with an immunocompromised state leads to more serious complications and a higher death rate. The following persons should not receive the vaccine:

- Persons with an history of eczema at any point in their life
- Persons with cancer
- Persons with solid organ transplant
- Persons with HIV/AIDS
- Women who are pregnant or breastfeeding
- Other immunocompromised persons
- Household contacts of any of the above persons.

Additionally persons with open sores, rashes or cuts should not receive the vaccine until all lesions are healed. The area of the inoculation should not be touched and should be covered with a gauze or semi-permeable covering at all times.

Autoinoculation of distant sites is not uncommon with the genitals and eyes most commonly affected. Eye lesions have a high propensity for causing permanent blindness. Great care must be taken in preventing spread to others as well. Persons with skin conditions are at significantly increased risk for developing serious and potentially lethal forms of the disease from a vaccinated person.

Viral Hemorrhagic Fevers

Viral infections would make effective biologic weapons because of a lack of therapy for most agents. Until recently it was felt that these agents were too difficult to manufacture and work with as weapons. There are reports of success, however, from Asia and from Iraq, where many ex-Soviet scientists are employed. The effects of a successful program would be devastating in terms of morbidity and mortality.

Viral organisms in general have a high person-to-person transmission – unlike many of the bacterial agents. This obviously leads to larger devastation from a smaller initial inoculation. For example, the Filoviruses (which include Ebola) have mortality rates approaching 90%. They will also spread over great distances with devastating speed.

These organisms cause a rapid version of DIC with all of the tissues becoming liquefied and cell membranes and connective tissue are literally "melted" away. The threat to healthcare workers is VERY HIGH with these organisms.

Mass Prophylaxis

The US government has well-developed plans for stockpiling medications, antidotes, vaccines and other supportive items to be delivered anywhere in the US within 12 hours of being called upon. Their main role, however, stops with the delivery of the needed items. Local governments and agencies are expected to take up from three and have a well-developed plan for the distribution of medications.

Each local government will be doubtlessly be counting on healthcare persons to staff the locations for the distribution of treatment, which will undoubtedly become triage stations as hospitals will be filled quickly with sick individuals. A basic understanding of the potential weapons and their appropriate treatment is essential for any local system to work.

Handout, Quick Summary Sheet and Patient Education Materials created by:

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