

Bioterrorism: Physician Preparedness
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Grand Rounds, Stanford University School of Medicine
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8:00am

Reference list:

- 1) Preston R. The Cobra Event. Ballantine Books, New York, 1997
- 2) Alibek K. Biohazard. Dell Publishing, New York, 1999
- 3) Mangold T, Goldberg J. Plague Wars: The Terrifying Reality of Biological Warfare. St. Martin's Press, New York, 1999.
- 4) CDC. Biological and chemical terrorism: Strategic plan for preparedness and response. NIMV@R 2000; 49(RR-4).1-14.
- 5) Franz DR, Jahrling PB, Friedlander AM, McClain DJ, et al. Clinical recognition and management of patients exposed to biological warfare agents. JAMA 1997;278:399-411.
- 6) Tucker JB. Historical trends related to bioterrorism: An empirical analysis. Emerging Infectious Diseases 1999;5(4):498-504
- 7) Franz DR, Zajtchuk R. Biological terrorism: Understanding the threat, preparation and medical response. Disease-a-Month 2000;46(2):129-90.
- 8) Russel PK. Vaccine in civilian defense against bioterrorism. Emerging Infectious Diseases 1999;5(4):531-6
- 9) Inglesby TV, Dennis DT, Henderson DA, Bartlett JG, et al. Plague as a biological weapon: Medical and public health management. JAMA 2000;283:2281-90.
- 10) Cieslak TJ, Eitzen EM. Clinical and epidemiological principles of anthrax. Emerging Infectious Diseases 1999;5(4):552-63
- 11) Inglesby TV, Henderson DA, Bartlett JG, Ascher MS, et al. Anthrax as a biological weapon: Medical and public health management. JAMA 1999;281(18):1735-46.
- 12) Henderson DA, Inglesby TV, Bartlett JG, Ascher MS, et al. Smallpox as a biological weapon: Medical and public, health management. JAMA 1999;281(22):2127-37.
- 13) Henderson DA. Smallpox: Clinical and epidemiological features. Emerging Infectious Diseases 1999;4(4):537-51.
- 14) CDC Bioterrorism and Response: <http://www.bt.cdc.gov>
- 15) Johns Hopkins Center for Civilian Biodefense Studies: <http://www.hopkins-biodefense.org>

Bioterrorism Scenario

Day 1: A professional sporting event is being played at an outdoor stadium in San Jose before an audience of 34,000. An unmarked truck drives along an elevated highway and releases an aerosol of an unknown substance, creating an invisible, odorless cloud more than a third of a mile in breadth. The incident is detected by no one.

Day 3: Hundreds of people in and around the county become ill with high fever and cough. Some of the sick self-administer OTC cold remedies; others are seen by physicians throughout the county and symptomatic treatment is prescribed. Later patients return, often by ambulance, with high fever, pleuritic chest pain, labored breathing, severe headache, and the production of bloody watery sputum. Chest X-rays show bilateral infiltrates or consolidation. Empiric broad spectrum antibiotics are being administered

Day 4: Some unexplained deaths have occurred in patients with high fever and hemoptysis. Preliminary laboratory results suggest gram-negative bacteria growing in the blood. Local health department staff are alerted by clinicians and infection control personnel. An assessment of all local hospitals reveals a total of 61 deaths and 883 inpatients with respiratory symptoms. The local media has been notified and demands access to hospital staff and administrators.

Day 5: Media reports have begun to appear nationally about the "San Jose flu", which seems mainly to affect healthy young adults. Intensive care units and isolation beds across the county are full. The recommended isolation protocols quickly fall apart as health care workers struggle to cope with the surge of patients. Direct microscopic examination of the stained smears now indicates a preliminary diagnosis of *Yersinia pestis*. The CDC, local law enforcement and FBI are notified of a presumed bioterrorist attack with plague. The mayor announces on the news that plague had been released in the city, possibly near the sports stadium. Instructions are given on how to make protective respiratory masks, that are to be used at all times. It is recommended that all those attending the game who are still well come to assigned centers to receive prophylactic antibiotics for 1 week. Thousands rush to these distribution centers before the antibiotics arrive.

Day 6: CDC laboratories confirm the agent as *Yersinia pestis*. There is evidence of continued spread of cases, and medical services are now completely overwhelmed. Chaos has ensued. Two physicians, 3 nurses and a morgue attendant have died. At this point there are effectively no antibiotics left in the city, and a stockpile delivery of antibiotics is expected soon. President Bush declares San Jose and surrounding vicinity a federal disaster area. The state begins enforcing the ban on all travel in and out of San Jose. There are 2271 cases admitted and 472 deaths.

Day 7: Makeshift hospitals have been set up in warehouses, schools and homeless shelters, and many people are dying in their houses. Hospital and city mortuaries are full. The state health department and CDC report that the bodies must be cremated. Some citizen and religious groups refuse, and private burial ceremonies are performed throughout the city. The National Guard is trying to keep order. Travel restrictions within the city are causing shortages of food and inability to deliver essential services. Several adjacent cities have reported cases and are now competing for state and federal resources. Cases are also being reported in other states and countries. At last count, San Jose has 3700 cases and 950 deaths.

DETECTING BIOTERRORISM

The Clinician's Role

Health care providers will be “first responders” in the event of a bioterrorism attack or other public health emergency. **Early detection by astute clinicians and rapid reporting to the local health department will be critical** in minimizing the impact of a bioterrorism event or other disaster.

Bioterrorism attacks are likely to present as acute outbreaks of an unusual syndrome, or outbreak of illnesses in the “wrong” season, or geographic area.

If you see patient(s) with any of the following clinical syndromes:

1. Acute severe pneumonia or respiratory distress
2. Encephalopathy
3. Acute onset neuromuscular symptoms
4. Otherwise unexplained rash with fever
5. Fever with mucous membrane bleeding
6. Unexplained acute icteric syndromes
7. Massive diarrhea with dehydration and collapse

In the setting of any of the following:

1. Atypical host characteristics:
 - Young (< 50 years)
 - Immunologically intact
 - No underlying illness
 - No recent international travel or other exposure to potential source of infection
2. Serious, unexpected, acute illness
 - Abrupt onset
 - Prostration
 - Cardiovascular collapse
 - Respiratory distress
 - Obtundation/change in mental status
 - Disseminated intravascular coagulation
3. Multiple similarly presenting cases, especially if
 - Geographically associated, or
 - Closely clustered in time
4. Increases in common syndromes occurring out of season
 - Influenza-like-illness in the summer

Please call the Public Health Department, Disease Prevention and Control immediately. We would like to hear from you even if you only have some suspicion that something isn't quite right.

- During business hours (M-F, 8 am – 5 pm) **(408) 885-4214**
- Email: healthofficer@hhs.co.santa-clara.ca.us
- After hours, call county communications and ask to speak with the Health Officer or Disease Control Officer **(408) 299-2501**
- Public Health Laboratory (specimen submission, routing info) **(408) 885-4272**

Selected Biowarfare Agent Characteristics

Disease	Symptoms	Person-to-Person transmission	Infective Dose (Aerosol)	Incubation Period	Duration of Illness	Lethality	Persistence of Organism	Treatment
Inhalation anthrax	Fever, malaise, cough, respiratory distress	No	8,000-50,000 spores	1-6 days	3-5 days (usually fatal if untreated)	High	spores remain viable in soil for > 40 yrs	Ciprofloxacin Doxycycline
Pneumonic Plague	High fever, chills, headache, productive cough – watery then bloody	High	<100 organisms	2-3 days	1-6 days (usually fatal)	High unless treated within 12-24 hours	For up to 1 year in soil; 270 days in live tissue	Streptomycin Gentamycin or Chloramphenicol
Botulism	Dry throat, blurred vision, slurred speech, difficulty swallowing, progressive descending symmetrical paralysis	No	0.001 µg/kg is LD ₅₀ for type A	12-36 hours (range up to several days)	Death in 24-72 hours; lasts months if not lethal	High without respiratory support	For weeks in non-moving water and food	Antitoxin Supportive care
Smallpox	Non-specific flu-like prodrome (malaise, fever, headache) then synchronously evolving maculopapular rash progressing to vesicles then pustules	High	Assumed low (10-100 organisms)	12-14 days (range 7-17 days)	4 weeks	High to moderate	Very stable	?Cidofovir
Brucellosis	Irregular fever, chills, headache, malaise, cough and chest pain in 20%, osteoarticular disease	No	10–100 organisms	5-60 days (average 1-2 months)	Weeks to months	≤5% untreated	6 weeks in dust and 10 weeks in soil or water	Doxycycline + Rifampin
Tularemia	Fever, headache, malaise, weight loss, nonproductive cough	No	10-50 organisms	3-6 days (range 1-21 days)	≥ 2 weeks	Moderate if untreated	For months in moist soil or other media	Streptomycin Gentamycin
Q Fever	Fever, chills, headache, diaphoresis, malaise, fatigue, anorexia, and weight loss	Rare	1-10 organisms	7 days (range 2-14 days)	Weeks	Very low	Able to withstand heat and drying; persists in environment for weeks to months	Tetracycline Doxycycline
Viral Encephalitides	Fever, rigors, severe headache, photophobia, malaise, nausea, vomiting, diarrhea may follow	Low	10-100 organisms	1-5 days	Days to weeks	Variable	Relatively unstable in the environment	Supportive care
Viral Hemorrhagic Fevers	Fever, malaise, myalgia, prostration; vascular permeability may present as conjunctival injection and petechial hemorrhage and progress to mucous membrane hemorrhage and shock	Moderate	1-10 organisms	4-21 days	Days to weeks	5 – 90 % case fatality rate depending on virus	Relatively unstable in the environment	Ribavirin Supportive care
Staph Enterotoxin B	Sudden onset fever, chills, headache, myalgias, non-productive cough	No	30 ng/person incapacitation	3-12 hours after inhalation	Days	<1%	Resistant to freezing	Supportive care
Ricin	Depends on route of exposure. Aerosol route: fever, chest tightness, cough, hypothermia. Oral route: gastrointestinal hemorrhage	No	3-5µg/kg is LD ₅₀	18-24 hours	Days. Death within 10-12 days for ingestion	High	Stable	Inhalation: supportive GI: lavage, charcoal, cathartics
T-2 Mycotoxins	Skin pain, redness, necrosis, sloughing of epidermis, wheezing, chest pain, hemoptysis	No	Moderate	Minutes to hours	Variable. Death may occur in min., hrs. or days	Moderate	For years at room temperature	Supportive care

LD₅₀ = Lethal Dose µg/kg
 Ricin and botulinum are lethal at all levels.
 ? = may be effective
 1998

Source: Adapted from Medical Management of Biological Casualties – USAMRIID



ANTHRAX

ALL SUSPECT CASES OF ANTHRAX MUST BE REPORTED IMMEDIATELY TO THE PUBLIC HEALTH DEPARTMENT COMMUNICABLE DISEASE CONTROL:

During business hours: 408-885-4214
After hours (County Communications): 408-299-2501

Epidemiology:

- Anthrax can be transmitted by inhalation, ingestion, or inoculation (inhalation is the most likely during a bioterrorist attack)
- The spore form of anthrax is highly resistant to physical and chemical agents; spores can persist in the environment for years
- Anthrax is **not** transmitted from person to person

Clinical:

- Incubation period is 1-5 days (range up to 43 days)
- Inhalation anthrax presents as acute hemorrhagic mediastinitis
- Biphasic illness, with initial phase characterized by nonspecific flu-like illness followed by acute phase characterized by acute respiratory distress and toxemia (sepsis)
- Chest x-ray findings: **Mediastinal widening in a previously healthy patient in the absence of trauma is pathognomonic for anthrax**
- Mortality rate for inhalation anthrax approaches 90%, even with treatment. Shock and death within 24 – 36 hours

Laboratory Diagnosis:

- Laboratory specimens should be handled in a Biosafety Level 2 facility (e.g. California state Microbial Diseases Laboratory)
- Gram stain shows gram positive bacilli, occurring singly or in short chains, often with squared off ends (safety pin appearance). In advanced disease, a gram stain of unspun blood may be positive
- Distinguishing characteristics on culture include: non-hemolytic, non-motile, capsulated bacteria that are susceptible to gamma phage lysis
- ELISA and PCR tests are available at national reference laboratories

Patient Isolation:

- Standard barrier isolation precautions. Patients do **not** require isolation rooms
- Anthrax is **not** transmitted person to person

Treatment:

- Prompt initiation of antibiotic therapy is essential
- Antibiotic susceptibility testing is KEY to guiding treatment
- Ciprofloxacin (400 mg IV q 12 hr) is the antibiotic of choice for penicillin-resistant anthrax or for empiric therapy while awaiting susceptibility results
- All patients should be treated with anthrax vaccine if available; antibiotic treatment should be continued until 3 doses of vaccine have been administered (day 0, 14 and 28). If vaccine is unavailable, antibiotic treatment should be continued for 60 days.

Prophylaxis:

- If vaccine is available, all exposed persons (as determined by local and state health depts) should be vaccinated with 3 doses of anthrax vaccine (days 0, 14 and 28)
- Start antibiotic prophylaxis immediately after exposure with ciprofloxacin (500 mg po q 12 hrs) or doxycycline (100 mg po q 12 hrs). (If strain is penicillin-susceptible, therapy can be modified to penicillin or amoxicillin.)
- Antibiotic prophylaxis should be continued until 3 doses of vaccine have been administered; if vaccine is unavailable, antibiotics should be continued for 60 days.





PLAGUE

ALL SUSPECT CASES OF PLAGUE MUST BE REPORTED IMMEDIATELY TO THE PUBLIC HEALTH DEPARTMENT COMMUNICABLE DISEASE CONTROL:

During business hours: 408-885-4214
After hours (County Communications): 408-299-2501

Epidemiology:

- Highly infectious after aerosolization
- Person-to-person and animal-to-human transmission can occur with pneumonic plague via respiratory droplet

Clinical:

- Incubation period is 1-3 days (ranges up to 7 days)
- Aerosolization would most likely result in pneumonic plague
- Pneumonic plague presents with acute onset of high fevers, chills, headache, malaise and a productive cough, that is initially watery before becoming bloody

Laboratory Diagnosis:

- Bacterial cultures (blood, sputum, or lymph node aspirate specimens) should be handled in a Biosafety Level 2 facility
- Wright, Giemsa, or Wayson stain shows gram negative coccobacilli with bipolar “safety-pin” appearance
- Organism grows slowly (48 hrs for observable growth) on standard blood and MacConkey agar
- Immunofluorescent staining for capsule (F1 antigen) is diagnostic

Patient Isolation:

- Strict respiratory isolation with droplet precautions (gown, gloves, and eye protection) until the patient has received at least 48 hours of antibiotic therapy and shows clinical improvement

Treatment:

- Streptomycin (1 g IM bid) or gentamicin (5 mg/kg IM or IV qd) are the preferred antibiotics
- Tetracyclines or fluoroquinolones are alternative choices
- Co-trimoxazole is recommended for pregnant women and children between the ages of 2 months and 8 years
- Chloramphenicol should be used for plague meningitis

Prophylaxis:

- Antibiotic prophylaxis is recommended for all persons exposed to the aerosol or persons in close physical contact with a confirmed case
- Tetracyclines or fluoroquinolones are recommended for 7 days from last exposure to a case





SMALLPOX

ALL SUSPECT CASES OF SMALLPOX MUST BE REPORTED IMMEDIATELY TO THE PUBLIC HEALTH DEPARTMENT COMMUNICABLE DISEASE CONTROL:

During business hours: 408-885-4214
After hours (County Communications): 408-299-2501

Epidemiology:

- Highly infectious after aerosolization
- Person-to-person transmission can occur via droplet nuclei or aerosols expelled from the oropharynx and by direct contact
- Contaminated clothing or bed linens can also spread the virus
- About 30% of susceptible contacts will become infected

Clinical:

- Incubation period is 12-14 days (ranges 7-17 days)
- Characteristic rash appears 2-3 days after nonspecific, flu-like prodrome (fever and headache)
- Maculopapular rash begins on mucosa of mouth and pharynx, face, hands, forearms and spreads to legs and centrally to trunk; lesions are more predominant on the face and extremities than on the trunk.
- Lesions progress synchronously on any given part of the body from macules to papules to vesicles to pustules to crusty scabs

Laboratory Diagnosis:

- Mask and gloves should be worn by person obtaining specimen, preferably a person who has been recently vaccinated
- Vesicular fluid is obtained by opening lesions with the blunt edge of a scalpel, harvesting fluid with a cotton swab; scabs can be removed by forceps. Swabs and scabs should be placed in a vacutainer, sealed with tape, and placed in a second, durable, watertight container
- Laboratory specimens must be handled in a Biosafety Level 4 facility (e.g. CDC) and will be evaluated with electron microscopy and cell culture


Patient Isolation:

- Strict isolation in negative pressure room (high efficiency particulate air filtration ideal) from onset of rash until all scabs separate
- Laundry and waste should be autoclaved before being laundered or incinerated

Treatment:

- Supportive care is the mainstay of therapy
- In-vitro antiviral activity against poxviruses has been shown with adefovir, cidofovir, dipivoxil, and ribavirin. (Animal studies suggest that cidofovir may be most effective).

Prophylaxis:

- Smallpox vaccine would be required for all persons exposed at the time of the bioterrorist attack or anyone with close personal contact with a smallpox case
 - Vaccine is most effective if given before or within 3 days of exposure
 - Ideally, all exposed persons should be placed in strict quarantine for 17 days after last contact with a smallpox case
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TULAREMIA

ALL SUSPECT CASES OF TULAREMIA MUST BE REPORTED IMMEDIATELY TO THE PUBLIC HEALTH DEPARTMENT COMMUNICABLE DISEASE CONTROL:

During business hours: 408-885-4214

After hours (County Communications): 408-299-2501

Epidemiology:

- Highly infectious after aerosolization
- Infectious dose can be as low as 10-15 organisms
- Person-to-person transmission does not occur

Clinical:

- Incubation period is 3-6 days (ranges 1-21 days)
- Aerosolization would most likely result in typhoidal tularemia, with pneumonic involvement
- Typhoidal tularemia is a nonspecific illness, with fever, headache, malaise and non-productive cough (mortality rates can be as high as 30-60%)
- Diagnosis requires high index of suspicion given nonspecific presentation

Laboratory Diagnosis:

- Bacterial cultures should be handled in a Biosafety Level 3 facility; isolation of organism can otherwise put laboratory workers at risk
- Organism is difficult to culture and grows poorly on standard media; cysteine-enriched media is required
- Serology is most commonly used for diagnosis


Patient Isolation:

- Standard precautions. Respiratory isolation not required.

Treatment:

- Streptomycin (7.5 mg/kg IM q 12 hours x 10-14 days) or gentamicin (3-5 mg/kg/day IV or IM qd in 3 divided doses x 10-14 days) are the preferred antibiotics
- Tetracyclines are alternative choices, although they are bacteriostatic and associated with higher relapse rates and must be continued for at least 14 days

Prophylaxis:

- Antibiotic prophylaxis is most effective if begun within 24 hours after exposure to aerosol
 - Tetracyclines are recommended for 14 days
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VIRAL HEMMORHAGIC FEVERS

ALL SUSPECT CASES OF VIRAL HEMMORHAGIC FEVERS MUST BE REPORTED IMMEDIATELY TO THE PUBLIC HEALTH DEPARTMENT COMMUNICABLE DISEASE CONTROL:

During business hours: 408-885-4214
After hours (County Communications): 408-299-2501

Etiologic Agents: Arenaviridae (Lassa, Junin, Machupo, Guanarito, and Sabia), Filoviridae (Marburg and Ebola), Bunyaviridae (Congo-Crimean hemorrhagic fever virus and hantaviruses) and Flaviridae (yellow fever and Dengue) can all cause viral hemorrhagic fever (VHF)

Epidemiology:

- Highly infectious after aerosolization
- Infectious dose can be as low as 1-10 organisms
- Risk of person-to-person transmission depends on virus

Clinical:

- Incubation period is 4 – 21 days, depending on virus
- Clinical presentation would vary by viral agent; however, dominant clinical features of all are a consequence of microvascular damage and changes in vascular permeability. Fever, myalgia, and prostration may evolve to shock, generalized mucous membrane hemorrhage, and neurologic, hematopoietic, or pulmonary involvement.

Laboratory Diagnosis:

- Viral isolation should be handled in a Biosafety Level 3 or 4 facility and may take 3 – 10 days
- ELISA or reverse transcriptase PCR available for most VHF viruses


Patient Isolation:

- Isolation room with contact precautions.

Treatment:

- Ribavirin (30 mg/kg IV x 1, then 15 mg/kg IV q 6 h x 4 days, 7.5 mg/kg IV q 8 x 6 days) may be helpful for Congo-Crimean hemorrhagic fever or arenaviruses

Prophylaxis:

- Licensed vaccine available only for yellow fever
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BOTULISM

ALL SUSPECT CASES OF BOTULISM MUST BE REPORTED IMMEDIATELY TO THE PUBLIC HEALTH DEPARTMENT COMMUNICABLE DISEASE CONTROL:

During business hours: 408-885-4214

After hours (County Communications): 408-299-2501

Epidemiology:

- Botulism neurotoxins (A-F) could be transmitted by aerosol or contamination of food and water supplies
- Botulism is not transmitted from person to person

Clinical:

- Incubation period is 12-36 hours (can be several days)
- Early symptoms include blurred vision, diplopia, and dry mouth
- Later symptoms include dysarthria, dysphagia, dysphonia, ptosis and the development of a symmetrical, descending progressive paralysis and respiratory failure
- Patients are usually alert and afebrile

Laboratory Diagnosis:

- Diagnosis is primarily based on a compatible clinical presentation
- Spinal protein is normal and characteristic findings are seen on EMG (facilitation of the compound muscle action potential on repetitive nerve stimulation)
- Toxin can be detected in serum (collect 30 cc in red top) and stool (foodborne botulism) by mouse neutralization bioassay performed at California Microbial Diseases Laboratory

Patient Isolation:

- Standard precautions. Patients do not require isolation rooms.

Treatment:

- Supportive care is the mainstay of therapy; prolonged ventilatory support is often required in severe cases
- Botulism anti-toxin (for A, B and E toxins) is in limited supply and is available only from the Division of Communicable Disease Control, California Dept of Health Services

Prophylaxis:

- Currently, there is no available post-exposure prophylaxis
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