Overview of Category A Bioterrorism Agents

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Learning Objectives

• List properties of each agent
• Describe recommended response measures for each agent
• Explain agent-specific special considerations
• Identify additional resources
Category A Bioterrorism Agents

- **Anthrax**- *Bacillus anthracis*
- **Botulism**- *Clostridium botulinum*
- **Plague**- *Yersinia pestis*
- **Smallpox**- *Variola virus*
- **Tularemia**- *Francisella tularensis*
- **Viral Hemorrhagic Fever Viruses**
Properties of Category A Agents

- Can be easily disseminated or transmitted from person to person
- Result in high mortality with major public health impact
- Would cause panic and social disruption
- Require special action for public health preparedness
Categories B and C Agents

• Cat B Agents
  – Moderately easy to disseminate
  – Moderate morbidity, low mortality
  – Require enhancement of current diagnostic/laboratory capabilities and enhanced surveillance

• Cat C Agents
  – Emerging pathogens thought to have potential
Category B Examples

• Bacterial/rickettsial/protozoal agents
  – Brucellosis, Glanders, Melioidosis, Q Fever, Psittacosis, Typhus Fever
  – Cholera, Cryptosporidiosis (water threats)

• Toxins
  – Staphylococcus enterotoxin B, C. perfringens epsilon toxin, ricin toxin

• Viral agents
  – Viral encephalitides – Venezuelan, Western, and Eastern Equine Encephalitis
Category C Examples

• Emerging viral pathogens
  – Nipah virus
  – Hantavirus
    • Hantavirus pulmonary syndrome
    • Hantavirus hemorrhagic fever syndrome

• Currently not as well-developed as Cat B
• Higher mortality than Cat B Agents
Detection of BT Release

• Claims by those who released the agent
• Observation of suspicious activity
• BioWatch alarm
• Clinical diagnosis by front-line health care providers – emergency depts. and doctors, school nurses, community health practitioners, pharmacists, veterinarians
“When you hear hoofbeats….”
“...consider some zebras.”
Important Points to Remember

• BT agents often behave differently from their naturally occurring counterparts.
• There is little epidemiological data on impact of BT agents in humans.
• Early diagnosis is critical.
• Rapid reporting is essential to containment.
• Response to contained and mass casualties will vary.
Prophylaxis/Treatment

- Oral antibiotics – tablet, capsule, liquid
  - doxycycline, ciprofloxacin
- Vaccines to be given intramuscularly
  - Biothrax; Nuthrax (anthrax vaccine)
- Vaccines to be given percutaneously
  - ACAM 2000 (replicating live vaccinia vaccine)
  - Imvamune (nonreplicating live vaccinia vaccine)
- Antitoxins to be given intravenously
  - HBAT (Heptavalent Botulinum Antitoxin, eq.)
- Antivirals to be given by mouth, IM, IV
Anthrax ~ Bacillus anthracis

• Spore-forming bacteria; found naturally in soil worldwide

3 Types of disease:

• Cutaneous
  – most common naturally occurring form
  – skin inoculation with spores from infected animals, hides, wool, etc.

• Gastrointestinal
  – ingestion of undercooked, contaminated meat

• Inhalational
  – inhalation of spores in 1-5 micron particles
  – most deadly form and most likely in BT
  – odorless and invisible
Cutaneous Anthrax

- Incubation period 1-10 days; (usually 5 days)
- Small macule or papule forms ulcer – (day 2)
- Vesicle appears and ruptures – (5-7 days)
- Ulcer dries into black eschar – (1-2 weeks)
- Malaise, low grade fever, lymphadenopathy
- Complications: toxic shock and death within 36 hours in 20% of untreated patients
Inhalational Anthrax

- Incubation period: 1-5 days (up to 60+)
- Inhalation of spores (1-5 microns)
- Infective dose may be quite low
- Fever, fatigue, cough, headache, and chest discomfort
- Severe dyspnea, chest pain, abdominal pain, nausea, vomiting, diaphoresis
- Hemorrhagic meningitis – 50%
- Toxic shock and death within 24-36 hrs
Pathophysiology of Inhalational Anthrax

• Spores are inhaled – taken up by alveolar macrophages which then move to lymph nodes
• Spores germinate, producing edema factor and lethal factor toxins
• Toxins produce local hemorrhagic lymphadenitis and necrosis in the chest (mediastinum)
• Septicemia can result, leading to sepsis and multi-organ failure
• Even with full ICU treatment, mortality is very high once symptoms develop
Inhalational Anthrax

Normal chest x-ray

Mediastinal widening with inhalation anthrax (*JAMA* 1999:281:1735-1745)
Diagnosing Inhalational Anthrax

• Possible history of exposure
• Differential diagnosis: tularemia, staph/strep
• Widened mediastinum/possible pleural effusion on chest xray
• Hemorrhagic mediastinal nodes on scan
• Gram positive bacteria (rods) on peripheral smear
• ELISA test – IgG for Protective Antigen -- rapid results
• Call your state epidemiologist for assistance with collection of specimens and diagnosis
Treatment for Inhalational Anthrax

- For symptomatic patients – IV therapy with two or more antibiotics, depending on sensitivity
- Supportive care (ICU – ventilator)
- Draw labs to confirm diagnosis and initiate therapy immediately – delayed treatment results in worse prognosis
Anthrax ~ Post-Exposure Prophylaxis (PEP)

CDC recommends combined therapy:

- 3 doses of vaccine - investigational new drug (IND)
- Oral antibiotics for 60 days:
  - ciprofloxacin
  - doxycycline
  - amoxicillin or penicillin (if susceptibility testing is supportive)
- Oral antibiotics – before symptom onset
- Vaccine alone is not protective for PEP
- PEP may depend on numbers of people exposed
Special Considerations - Anthrax

• Not spread person to person
  – No risk of spreading disease among clinic attendees
  – Minimal PPE needed to protect clinic staff
• Incubation period 1 to 60+ days
  – PEP must be started very early
• Inhaled spores may stay viable inside body for >60 days
  – PEP must be continued for at least 60 days
Special Considerations, Anthrax (cont.)

• Inhalation anthrax is a DEADLY disease
  – If PEP isn’t begun before symptoms arise, prognosis is grave (“worst-case scenario”)
  – Need great risk communication to target pop.

• CDC recommendation: oral antibiotics x 60 days + series of 3 vaccinations

• Logistical challenges of delivering materiel on this scale
Botulism ~ Clostridium botulinum

• Spore-forming bacteria; found naturally in soil
• Produces most poisonous substance known
• Toxins are colorless, odorless, tasteless
• Inactivated by heat (≥ 85°C for 5 min)
Botulism ~ Types

- **Infant (3–30 days)**
  - toxin produced by organisms in intestinal tract

- **Wound (4-14 days)**
  - toxin produced by organisms contaminating wound

- **Foodborne (12-36 hrs)**
  - ingestion of pre-formed toxin from improperly processed or canned, low-acid foods

- **Inhalation botulism (12-72 hrs)**
  - inhalation of toxin, not natural occurrence, BT threat only
Pathophysiology of Botulism

• Toxin binds permanently to neuromuscular junction, preventing the release of neurotransmitter (acetylcholine)
• Muscles controlled by affected nerves are completely paralyzed
• Branches will grow around affected nerve axons, creating new pathways for neural impulses. Slowly, paralysis resolves… although this takes weeks to months
Infant Botulism ("floppy baby")
Diagnosing Botulism

- History of possible exposure
- Sudden onset descending, bilateral, symmetrical, floppy paralysis, starting at top of head
- Double vision, drooping of eyelids, mumbling, hoarseness, difficulty swallowing, dry mouth/pharynx; increasing difficulty with secretions; also nausea and diarrhea; progresses downward
- Awake, alert, aware, oriented; no fever
- Diagnosis is primarily clinical. Lab tests can help confirm diagnosis, but they take time
Diagnosing Botulism (cont.)

- Differential diagnosis:
  - Myasthenia gravis ( + Tensilon® test)
  - Guillain-Barre syndrome (+ CSF protein; EMGs; ascending paralysis)
  - Paralytic shellfish poisoning (paresthesias)
  - Stroke (unilateral s/s, + findings on scans)
  - Other toxins or drugs ( + tox screens)
  - In New England, also consider tick paralysis (ascending paralysis; exposure to and presence of tick)
Botulism ~ Treatment

- Combined supportive care and antitoxin
- Consult with state public health officials to obtain antitoxin
- Botulinum antitoxin
  - New heptavalent product from CDC (HBAT, equine)
  - BabyBIG – human antitoxin for infant botulism, available from CA Health Dept.
- Recovery may be prolonged (many months)
- Monitor exposed persons for signs of illness
Special Considerations - Botulism

• Antibiotics won’t help – toxin is preformed substance
• Antitoxin will stop but not reverse progression
• Antitoxin usually given IV as treatment
• Antitoxin = equine origin = ALLERGENIC
• Mass casualty prophylaxis/treatment will be determined by local, state, and federal public health officials at the time of the event.
Tularemia ~ Francisella tularensis

- Small, non-spore-forming bacteria
- Survives for weeks at low temps in water, soil, hay, straw and animal carcasses
- Extremely infectious; as few as 10 organisms can cause disease
- Small mammals (rabbits) – reservoirs
- Occurs in North America, Europe, Russia, China and Japan
Tularemia ~ Transmission & Types

• Diverse transmission routes:
  – Insect bite, mammal bite, contact with infectious tissue, ingestion of contaminated food or water, and inhalation

• Diverse clinical presentations, dependent on route of transmission

• Incubation period
  1-21 days (ave. 3-5 days)
Tularemia ~ Symptoms

- All forms - rapid onset of fever and inflamed lymph nodes
  - “Influenza-like illness”
- Pneumonic - resembles plague
  - Inhalational tularemia is characterized by inflammation of upper and/or lower airways, including in some cases destruction of the air sacs in the lungs
- Typhoidal – rare, septicemia, abdominal pain, diarrhea, vomiting, gastrointestinal bleeding
- Other forms include: glandular and cutaneous
Tularemia Lesions

CDC Public Health Image Library
Pneumonic Tularemia -- Pathophysiology

• Organism hides, survives and replicates inside macrophages

• Pneumonic tularemia can develop secondarily after ulceroglandular or glandular disease
Diagnosing Pneumonic Tularemia

• Difficult to diagnose because of nonspecific signs and symptoms
• Diagnosis may rely on epidemiologic evidence (e.g., history of mowing lawn in endemic area)
• Some laboratory studies may be useful depending on stage of disease
• A large number of cases of pneumonic tularemia (or disease in a nonendemic area) would raise the level of concern for a BT release
Treating Tularemia

• Antibiotics -- mainstay of therapy
• Genetically engineered resistant strains may be used as BT weapons
• Contact your state health department for treatment guidance and protocols
Tularemia ~ Post Exposure Prophylaxis

- Mass casualty - oral antibiotics for 14 days
  - doxycycline or ciprofloxacin
- Potential exposure – place on fever watch and administer antibiotics if needed
- Vaccination – not recommended as PEP
  - Short incubation period
  - Incomplete protection for inhalational tularemia
Special Considerations -- Tularemia

• Not spread person to person
  – Antibiotic dispensing clinics do not pose risk of transmission to healthy staff or community members

• Incubation period variable, as short as 1 day

• Tularemia can usually be treated successfully after symptoms arise
  – Mass casualty response will probably include “fever watch” and treatment of those who develop symptoms if release is not detected immediately
Plague ~ Yersinia pestis

- Naturally occurring zoonotic infection
- Bacterial reservoir – small rodents, other mammals
- Transmitted by bite of an infected flea
- Occurs worldwide - 1,700 cases/yr
- Occurs in southwestern US; 12-14 cases/yr
Plague ~ Types

- **Bubonic** – most common type; painful swelling of lymph nodes
- **Pneumonic** – primary or secondary; inhalation of aerosolized bacilli into lungs or infection of lungs from bacteria
- **Septicemic** – primary or secondary; less common
- Meningitis or pharyngitis – less common
- Pneumonic and septicemic – approaching 100% fatal if untreated
**Pathophysiology of Plague**

- After a flea bite, bacteria travel to regional nodes, producing suppurative adenitis (buboes)
- Bacteremia can develop, seeding the lungs and/or resulting in sepsis
- Plague also spread in droplets expelled while coughing
Inguinal/Femoral and Axillary Buboes

Source: All photos from CDC Image Library
“The Black Death”

All photos taken from CDC Image Library
Pneumonic Plague Symptoms

- Incubation period 1-6 days (usually 2-4 days)
- Malaise, fever, chills, headache, muscle ache
- Cough, chest pain, difficulty breathing
- Rapidly progressing, severe pneumonia
- Copious bloody, watery, or purulent sputum presenting transmission danger
- Prominent gastrointestinal symptoms
- Death in 2-6 days after exposure without treatment – prognosis grim if treatment delayed
Diagnosing Pneumonic Plague

• History of exposure/endemic areas
• Chest x-ray – usually bilateral alveolar infiltrates
• Extensive, fulminant pneumonia with bloody sputum in an otherwise healthy, immunocompetent host, with Gram neg “safety-pin” rods in sputum
• DFA (direct fluorescent antibody) useful
Pneumonic Plague ~ Treatment and Post-Exposure Prophylaxis

- Treatment – IV antibiotic therapy for 10 days with supportive treatment, as needed
- Mass casualty PEP – oral antibiotics for 7 days (doxycycline)
- Mass casualty – treatment instituted for fevers, new cough
Special Considerations – Plague

• Plague transmissible from person to person
  – Pneumonic plague is highly contagious
    • Precautions until 72 hrs after institution of effective antibiotic therapy
  – Bubonic plague also contagious
    • Precautions until 48 hrs after institution of effective antibiotic therapy
    • Pneumonic plague can develop secondarily
  – Clinic setting will pose risk to staff and community members
  – Pre-clinic screening and PPE necessary
  – Alternatives to “pull” clinic setting preferable
• Plague requires PEP before symptoms begin
Smallpox- Variola

• Variola Virus
  o Variola Major (30% case fatality rate)
  o Variola Minor (variant with milder disease)
  o Hemorrhagic Smallpox (immunocompromised pts; approaching 100% mortality)

• Transmission:
  - Via respiratory droplets of the patient (airborne transmission)
  - Direct contact
  - Indirect contact with contaminated linens

• Small infectious dose

• Incubation period: 7-17 days (10-14 days)

• Aerosol release – virus inactive after 2 days
Smallpox

• **No** natural host outside of humans; does not currently exist in nature
• Last case in the US 1949
• Ceased routine vaccination in US 1972
  • Immunity wanes in 3-5 years
  • Immunity probably absent after 10 years
  • Most of US population = UNPROTECTED
• Last naturally occurring case 1977
• WHO declares eradicated 1980
• Virus destroyed except for two depots:
  • Atlanta
  • Moscow
Smallpox - Symptoms

- High fever, malaise, headache, backache
- Rash (about 15 days after exposure):
  - maculopapules, day 1-2 of rash
  - vesicles, day 4-5 of rash
  - pustules - round, firm, embedded in dermis, day 7
- Infectious from onset of fever – virus is shed from oral lesions preceding rash onset.
- Death from toxemia – 2\textsuperscript{nd} week of illness
- Hemorrhagic and malignant smallpox – more severe, less common forms of smallpox
Smallpox rash progression

Source: www.cdc.gov
Diagnosing Smallpox

Rule out smallpox for any febrile rash illness
Smallpox vs. Chickenpox

**Smallpox**
- Centrifugal Rash
- Pox over 1-2 day period, all evolve at same rate
- All pox at same stage
- **Rash on palms and soles**
- Lesions extend into dermis
- Pronounced prodrome and fever

**Chickenpox**
- Centripetal Rash
- Crops of lesions at different stages of development
- Adjacent lesions at different stages
- Never on palms or soles
- Lesions not as deep
- Mild or no prodrome/fever
Smallpox vs. Chickenpox

Source: CDC
Smallpox Rash

Source: CDC
Smallpox Rash

Photo: CDC Image Library
Smallpox- Treatment and Post Exposure Prophylaxis

• Supportive therapy for patients
• Afebrile contacts – under fever surveillance for 18 days (14 days, if vaccinated)
• Febrile contacts – isolated for 5 days
• General public: vaccination within 3 days
• VIG – to counter adverse reactions and for immunocompromised people
Special Considerations – Smallpox

• Smallpox is highly contagious – staff and clients may be at risk in clinic settings
  – Pre-screening and PPE may be needed
  – Alternate vaccine distribution may be preferable, but difficult
• It takes time to build immunity after vaccination
  – Those not vaccinated within a few days after exposure will get sick
  – Vaccination after a few days may mitigate if not prevent disease
Special Considerations – Smallpox (cont.)

• Smallpox mortality rate: 30% (may be much higher among immunocompromised)
• Vaccination technique requires training
• Live vaccine (vaccinia) requires “cold chain” and careful handling
• Vaccination site requires about 4 weeks of special care until scab falls off
  – Clients must be trained to care for vaccination site
Special Considerations – Smallpox (cont.)

• Vaccination site must be evaluated in 6 to 8 days after vaccination to check for a successful reaction called a “take”
• Standard vaccine has risk of adverse events
  – Limited amounts of nonreplicating vaccine soon available
Vaccination Site Evaluation

Development of a major cutaneous reaction at the site

- Lesion evolves gradually
  - papule after 2-5 days
  - papule becomes vesicular, then pustular, and reaches its maximum size at 8-10 days after vaccination
  - pustule dries and forms a scab, which usually separates within 14-21 days, leaving a pitted scar.

Source: ACAM 2000 “Highlights of Prescribing Information”
Examples of Major Reactions ("Takes") vs. Equivocal Reactions

Source: CDC Image Library
Viral Hemorrhagic Fevers (VHFs)

- Severe multisystem syndrome - 4 virus families
- Arenaviruses and filoviruses are Cat A agents
  - Ex: Lassa, Argentine (Junin), Bolivian (Machupo), Ebola, Marburg
- Animals and insects – natural reservoir
- Geographically restricted to host environment
- Zoonotic with human to human transmission
- Outbreaks occur sporadically; not predictable
- Limited treatment options for all VHFs
- VHFs successfully aerosolized as bioweapons
Each virus has its own routes of transmission....

- **Vectorborne:**
  - mosquitoes or ticks (dengue hemorrhagic fever)
- **Rapid spread via contact with:**
  - Rodents (Junin, Machupo)
  - Rodents’ urine or feces (hantaviruses)
  - Infected animal, person, blood or body fluids (Ebola, Marburg) including contaminated bedding or medical equipment
- **Some airborne spread possible** (e.g. aerosolized Ebola, arenaviruses)
VHF Symptoms

• Incubation period: 1-21 days; ave. 3-10 days
• Initial symptoms:
  – ILI
  – Filoviruses – characteristic red rash
• Severe symptoms:
  – Coagulation abnormalities
  – bleeding under the skin, in internal organs, or from body orifices
  – shock, nervous system malfunction, coma, delirium, and seizures, renal failure
• Duration of symptoms: few days to couple of weeks
• Fatality rates range 10% to 90%
Bolivian Hemorrhagic Fever
(source: JAMA 2002)

Marburg Rash
(source: JAMA 2002)

Hemorrhagic Fever
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VHFs Treatment & Infection Control

• No vaccines except for Argentine HF and yellow fever. Others in pipeline
• Don’t transport patients; don’t do unnecessary venipunctures
• Supportive care, careful IV fluid maintenance
• No cure or established drug treatment (? steroids, ribavirin, other antivirals, ? immune plasma? Treat coagulopathies if diagnosed. Dialysis if indicated )
• Standard, contact, droplet, and airborne precautions, patient isolation.
• Bedding and medical equipment - cleaned and sterilized
• Personal surveillance for close contacts
Special Considerations – Viral Hemorrhagic Fevers

- Antibiotics, antitoxins of no use
- Vaccines of very limited use (e.g., Junin)
- Oral antivirals probably of no use; IV antivirals may be helpful for some VHF; in very short supply
Reporting Suspect BT Incidents

• Report all suspect cases of BT immediately to your state health department

• Find out now what the reporting protocols are in your jurisdiction or state
Resources


Resources

• CDC website:  http://www.bt.cdc.gov/bioterrorism/training.asp

• Special Pathogens:  www.cdc.gov/ncidod/dvrd/spb

• MA Dept of Public Health. Guide to Surveillance, Reporting and Control. 2006; available online at www.mass.gov/dph; on left side of page, under Key Resources, click on Infectious Disease Reporting and Requirements. See following for updates.
Resources


Resources


Resources


• Iowa State University Center for Food Security and Public Health (veterinary pages): [http://www.cfsph.iastate.edu/DiseaseInfo/](http://www.cfsph.iastate.edu/DiseaseInfo/)

Resources


• Preston, Richard.
  – *The Demon in the Freezer*. NY, Random House, 2002 (smallpox and bioweapons)
Acknowledgements

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