Overview of Bioterrorism Agents

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Objectives

- Identify the major biological threat agents
- Describe the natural transmission of Category A biological agents
- Describe clinical presentations of Category A biological agents
- Describe available treatments and prophylaxis options

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Ideal Qualities for a Biologic Terrorist Agent

- High rate of illness among those exposed
  - High attack rate
- High rate of death among those who get ill
  - High case fatality rate
- Short time between onset of illness and death
  - Small window to start treatment
- Low level of immunity in the population

Ideal Qualities for a Biologic Terrorist Agent (cont)

- No effective or available treatment
- Can be transmitted person to person
- Easy to produce and disseminate
- Difficult to diagnosis either clinically or diagnostically (i.e. laboratory identification)

Epidemiological Clues

What we look for...

- Large outbreak with high illness and death rate
- Single case of uncommon disease (e.g., Smallpox)
- Unusual symptoms or severity of illness
- Infection is non-endemic to region
- Unusual seasonal distribution
- Multiple simultaneous outbreaks in non-contiguous areas
- Sick or dying animals
Bioterrorism Threats: Priority Biological Agents

- Bacterial
  - Anthrax
  - Plague
  - Tularemia
  - Brucellosis
  - Q fever
  - Other
    - food borne pathogens
    - waterborne pathogens

- Viral
  - Smallpox
  - Viral Hemorrhagic Fevers
  - Viral Encephalitis

- Toxins
  - Botulism
  - Staph Enterotoxin B
  - Ricin toxin
  - Trichothecane mycotoxins

Anthrax
- Gram positive spore forming bacterium Bacillus anthracis
- Primarily disease of herbivores which are infected by ingesting spores in soil
- Natural transmission to humans by contact with infected animals or contaminated animal products
  - “Woolsorter’s disease”
- Three forms of disease
  - Cutaneous
  - Inhalational
  - Gastrointestinal (GI)

CDC: Gram stain of B. anthracis

Epidemiology of Transmission

- Direct contact
- Ingestion
- Inhalation

Infected herbivores and soil are reservoir

Cutaneous anthrax

Gastrointestinal anthrax

Pulmonary/mediastinal anthrax
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**Anthrax:**

**Cutaneous**
- Accounts for 80% of naturally occurring Anthrax cases
- Enters through openings in skin from abrasions, lacerations
- 20% progress to systemic form if untreated
- Most cases recover

**Inhalational**
- Inhalation of spores
- Incubation, 2-3 days (range up to 60 days)
- Spores engulfed by macrophages and transported to mediastinal and peribronchial lymph nodes
- Insidious onset: malaise, low grade fever, nonproductive cough
- Abrupt development of respiratory distress
- Hemorrhagic mediastinitis
- Hematogenous spread
- Meningitis in 50%, usually fatal

**Pulmonary/Mediastinal**
- Mediastinal widening from anthrax
- Normal chest x-ray
Ciprofloxacin
400 mg intravenous every 12 hours for adults
10-15 mg/kg intravenous every 12 hours for children

Doxycycline
100 mg intravenous every 12 hours for adults and children > 8 yr and > 45 kg
2.2 mg/kg every 12 hours for children < 8 yr (up to 200 mg/day)

PLUS
- One or two additional anti-microbial agents effective against anthrax (e.g. imipenem, clindamycin, rifampin, macrolides)

Additional issues
- Penicillin should never be used as a monotherapy
- If meningitis is suspected, an antibiotic with good CSF penetration should also be administered (e.g. rifampin or chloramphenicol)
- Supportive therapy for shock, fluid volume deficit and airway management may be needed.
- Drainage of pleural effusions may improve clinical outcome

Anthrax Immune Globulin (AIG) can be used to neutralize anthrax toxin.

Patient Care Inhalational Anthrax

Anthrax: Post-Exposure Prophylaxis
- Start 60 days of oral antibiotics ASAP after exposure
  - Ciprofloxacin or Levofloxacin
  - OR
  - Doxycycline
  - OR
  - Amoxicillin or Penicillin (if known PCN sensitive)
- Vaccine
  - Can be given post-exposure in conjunction with antibiotics

Smallpox
- Variola virus, two forms of the disease: minor and major
- Spread via respiratory droplets or aerosols expelled from the oropharynx
- May also spread via direct contact
- Patients are most contagious during the time at which the skin rash is present
- Approx. 30% of patients exposed go on to develop the disease
- Approx. 30% mortality with ordinary smallpox
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Smallpox Characteristics
- Febrile Syndrome – occurring 1–4 days prior to rash.
- Classic Smallpox lesion – deep-seated, firm/hard, round, well-circumscribed; lesion may become umbilicated or confluent.
- Lesion in Same Stage of Development – Evolve from macules → papules → pustules at the same time.
- Centrifugal distribution – First lesion on oral mucosa, face, or forearms.

Smallpox Rash
Chickenpox Rash
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Smallpox vs. Chickenpox: Distribution

Smallpox Characteristics
- Febrile Syndrome - occurring 1-4 days prior to rash.
- Classic Smallpox lesion – deep-seated, firm/hard, round, well-circumscribed; lesion may become umbilicated or confluent.
- Lesion in Same Stage of Development – Evolve from macules → papules → pustules at the same time.
- Centrifugal distribution – First lesion on oral mucosa, face, or forearms.
- Lesion on palms and soles

Clinical Timeline for Smallpox

Exposure
- Early Rash Phase
  - Mucous membrane lesions
  - Small red spots on the tongue and throat
  - Lesions enlarge, ulcerate, then shed virus infectious 24 hours before visible skin rash

Prodrome phase (2 - 4 days)
- Abrupt onset of fever >38.3°C
- Malaise/myalgia
- Headache
- Nausea/vomiting
- Backache

Rash Phase
- (21 days)
  1) macules
  2) papules
  3) vesicles
  4) pustules
  5) scabs

Infectious until all scabs fall off

Usually NOT Infectious
Smallpox Progression

Day 4
- Papules

Day 6
- Vesicles
- "pocks"

Day 13
- Pustules
- Scabs

Smallpox: Medical Management
- Strict respiratory/contact isolation of patient
  - Patient infectious until all scabs have separated
- Treatment is supportive care only
- Antivirals are under evaluation
  - Cidofovir
  - ST246

Smallpox: Prevention and Control
- Immediate vaccination of ALL close contacts (<6 ft) and ALL contacts of patients contacts (Ring vaccination)
- Vaccination within 4 days of exposure may prevent or lessen disease
- Mass vaccination may be necessary and/or everyone may want to be vaccinated
Smallpox: Current Vaccine

- Live vaccinia virus
- Because it is a live virus, there can be adverse events from vaccination
  - Occurs mostly in immunologically suppressed persons
- Immunity is not life-long, but having been vaccinated in the past may reduce morbidity and mortality

Plague

- Plague is a severe bacterial disease of humans and animals produced by the gram negative nonsporulating bacillus *Yersina pestis*
  - Bite of a rodent flea that is carrying the plague bacterium, or by handling an infected animal
  - Hundreds of millions of people died when human dwellings were inhabited by flea-infested rats
  - Modern antibiotics are effective, but without prompt treatment the disease can likely cause illness or death

Types of Plague

- Three types:
  - Bubonic
  - Septicemic
  - Pneumonic
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Plague: Epidemiology of Natural Transmission

Animal Reservoirs

Secondary plague cases
Primary bubonic plague
Primary septicemic plague
Primary pneumonic plague

Routes of Plague Transmission
A: Bite of flea
B: Contact with animal or carcass
C: Inhalation of respiratory droplets
D: Contact with sputum or fluid

Plague: Clinical Presentation of Pneumonic Plague

Exposure
Incubation period 1-6 days

Early Presentation
- Abrupt onset of fever, malaise, headache, myalgia
- Chest pain and dyspnea
- Tachypnea (particularly in young children)
- Productive cough (sputum may be purulent or watery, frothy, blood-tinged)
- Hemoptysis

Late Presentation
- Rapid progression to pulmonary disease/ARDS
- Pulmonary edema, dyspnea, cyanosis
- Meningitis may be a complication
- Hypotension, DIC, septicemia, and death
- Lab findings—bacterial infection and sepsis
- Organism usually seen on sputum gram stain
- Mortality approaches 100% if untreated in 24 hours

Antibiotic therapy in the first 24 hours can prevent septicemia, cardiorespiratory failure, shock, and death!

Plague: Patient Care

Early antibiotic treatment* is paramount to patient survival

Adults:
- Streptomycin 1 gm IM b.i.d. for 10 days
- Chloramphenicol 25 mg/kg IM or IV 4 times daily for 10 days
- Gentamicin 5 mg/kg IM or IV once daily for 10 days
- Doxycycline 100 mg IV b.i.d. or 200 mg IV once daily for 10 days
- Ciprofloxacin 400 mg IV b.i.d. for 10 days

Children:
- Streptomycin 15 mg/kg IM twice daily for 10 days (max 2 gm/day)
- Chloramphenicol 25 mg/kg IV 4 times daily for 10 days (max 4 gm/day)
- Gentamicin 2.5 mg/kg IM or IV 3 times daily for 10 days
- Doxycycline 2.2 mg/kg IV twice daily for 10 days (max dose 200 mg/day)
- Ciprofloxacin 15 mg/kg IV twice daily for 10 days (max 1 gm/day)

*CDC recommends initiating treatment with two drugs believed effective against Y. pestis until antimicrobial susceptibility data is available.

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Plague: Prophylaxis

- Pneumonic plague contacts (transmitted via droplets)
  - Oral Doxycycline or Ciprofloxacin
  - For 7 days after last exposure
- Vaccine no longer manufactured

Botulism

Caused by toxin from Clostridium botulinum

- Colorless, odorless and tasteless
- Lethal dose for 70kg human is 1ng/kg
  - Botulinum toxin is the most lethal neurotoxin known to man
  - Dispersal of aerosolized toxin, 1 gm of aerosolized toxin could kill up to 1.5 million people
- Seven toxin types
  - Human disease: A, B, E, and F
  - Animal disease: C, D, and G

Botulism: Epidemiology of Natural Transmission

- Food prepared in house, prepared or stored at ambient temperature
- Ingestion and toxin production in an open wound
- Nervous system and toxin production in susceptible infants and adults
- C. botulinum in the soil, flora, and fauna
Clinical Presentation of Botulism

Exposure
- Incubation Period
- Botulism is 24-72 hours
- Foodborne
- Inhatalional

Cranial Nerve Palsies
- Cranial Nerves III, IV, VI, VII, IX
- Blurred vision
- Diplopia
- Paralysis
- Expressiveness
- Regurgitation
- Dysarthria/Dysphagia

Descending Flaccid Paralysis
- Symmetric Paralysis Voluntary Muscles
- Neck
- Shoulders
- Upper extremities
- Lower extremities
- BP often normal; Mental status normal

Cranial Nerve Palsies

Botulism: Medical Management
- Early administration of antitoxin
- Supportive care
  - Monitoring respiratory function
  - Providing mechanical ventilation
  - May be needed for weeks or months

Botulism: Antitoxin
- Preferably within 24 hours of symptom onset
- Type of antitoxin based on type of botulism
  - Bivalent antitoxin specific to serotype A and B
  - Monovalent antitoxin specific to serotype E
  - Heptavalent antitoxin specific to serotypes A, B, C, D, E, F, and G
- 1 vial per person
- Acts by binding free systemic toxin
  - Does not reverse paralysis already present
Viral Hemorrhagic Fevers (VHF)
- Hemorrhagic fever viruses (RNA) belong to four taxonomic families:
  - Filoviridae (Ebola/Marburg)
  - Arenaviridae (Bolivian HF)
  - Bunyaviridae (Congo-Crimean HF)
  - Flaviviridae (Dengue)
- Natural vectors – virus dependent
  - Rodents, mosquitoes, ticks
- No natural occurrences in U.S.

VHF as a Biological Weapon
- These viruses are considered suitable weapons because:
  - They have a low infectious dose
  - They cause high morbidity and mortality
  - They cause fear and panic in the general public
  - Effective vaccines are either not available, or supplies are limited

Clinical Timeline for VHF

**Exposure**

**Pre-Event**

**Early Manifestations**
- In general:
  - High fever
  - Headache
  - Myalgia
  - Arthralgia
  - Anorexia
  - Varying degrees of nausea, vomiting and diarrhea

**Later Manifestations**
- External/Intravascular Hemorrhage
  - Ecchymosis
  - Petechiae
  - Bleeding from puncture site
  - Bleeding from nose and gums
  - Hemorrhagic conjunctivitis
  - Gastrointestinal bleeding
  - Severe vaginal bleeding
  - Pleural effusion
  - Renal failure
  - Shock

**Laboratory Findings**
- Leukopenia or leucocytosis
- Thrombocytopenia
- Elevated Liver Function Tests
- Anemia or hemococoncentration
- Prolonged PT, PTT
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**Clinical Presentation of VHF**
- Ecchymosis
- Petechiae
- Melena

**VHF Clinical Management**
- Aggressive supportive care with intravenous fluids, colloids, blood products as needed
- Specific therapy (ribavirin) may be helpful in bunyaviruses and arenaviruses
- Avoid IM injections or invasive procedures (due to bleeding)
- Strict aerosol precautions (i.e. respiratory isolation)

**Sources of Information**
- Centers for Disease Control (CDC)
  - www.cdc.gov
- CDC Emergency Preparedness
  - www.emergency.cdc.gov
- CDC Quarantine and Isolation
  - www.cdc.gov/niddod/dp/index.htm
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