Anthrax

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Overview

- History, etiology, pathogenesis
- Burden of natural disease
- Disease forms
- Recognition and diagnosis
- Differential diagnosis
- Treatment
- Prevention
History

- Malignant Pustule, Malignant Edema, Siberian plague, Black Baine, Ragpicker's disease, Woolsorter's disease

- Described since ancient times

- Medieval Period - multiple pandemics

- 1876 - The first microbial etiology (Koch)

- 1881 - The first live bacterial vaccine (Pasteur)
Etiology

- *Bacillus anthracis*

- Gram positive, spore forming, non-motile bacillus
**Bacillus anthracis**: Microbiology

- Tacky (egg white)
- Non-hemolytic
- Penicillin susceptible (97%)
- Tails (medusa head) colony morphology
- Phage susceptible
Anthrax Binary Toxins

Lethal Factor
(LF, 90kDa)
Endopeptidase

Protective Antigen
(PA, 83kDa)
Receptor binding & toxin internalisation

Edema Factor
(EF, 89kDa)
Adenylyl cyclase

Lethal Toxin
MAPKK cleavage
MØ lysis
Cytokine modulation
Fatal toxic shock

Edema Toxin
ATP --> cAMP
Cytokine modulation
Edema

CDC
Anthrax Toxin - Mode of Action
(from Leppla, 1999)

- PA83
- Furin
- PA20
- PA63
- CaM
- ATP
- cAMP
- MEK-1
- EF or LF
- Translocation
- Endocytosis
- H+
Pathogenesis of Anthrax

**Spores**

**Cutaneous**
- Low-level germination and growth at one site lead to local edema and necrotic lesion.
- Macrophage
- Bacillus
- Bacterial virulence factors
- Capsule
- Exotoxins
- Other factors
- Regional lymph node
- Regional hemorrhagic lymphadenitis
- Meningitis
- Death
- Septicemia, toxemia
- Death

**Intestinal**
- Low-level germination at one site leads to massive effusion, mucosal edema, and necrotic lesion.
- Spore
- Edema toxin
- Lethal toxin
- ATP
- MAPKK (or others)
- cAMP
- $\text{O}_2^\cdot + \text{H}_2\text{O}_2^\cdot$ (reactive oxygen intermediates)
- TNF-α + interleukin-1β + other cytokines
- Shock
- Death

**Pulmonary**
- Pulmonary edema
- Death
- Pulmonary lymphatic blockage
- Death

*NEJM 1999; 341: 815-826*

Centers for Disease Control and Prevention
Anthrax in Animals

Rapid progression from febrile illness to death with hemorrhage

Dogs and pigs get a pharyngeal form – more resistant
Epidemiology and Transmission in Humans

Spores live in the soil for many yrs: at least 60 yrs

Animals ingest spores

Humans become infected from animal products

- Cutaneous: direct contact
- Gastrointestinal: ingestion of infected meat
- Inhalation: inhalation of aerosolized spores

Generally, not transmissible person-to-person
Why is Anthrax a Threat Agent?

- Persistence of endospore in environment
- Pathogenicity
- Delayed onset of recognizable symptoms renders treatment ineffective
- Can be manufactured using standard laboratory equipment
- No recognizable color, taste, or odor
2001 Anthrax Threat Letters
Examples of Sources

- Animals with anthrax - veterinarians
- Contaminated hair, hides - mill workers, hobbyists
- Contaminated meat (not in milk) - Africa
- Biological warfare-related - 1979 Sverdlosk, Russia
- Bioterrorism-related – US anthrax letters, 2001
Burden of Natural Disease

- Disease absent/sporadic in Northern Europe
- More common in Greece, Italy, Spain, Turkey, Yugoslavia
- U.S. - South Dakota, Nebraska, Oklahoma, Texas
- Enzootic in Central America, Peru, Bolivia, Venezuela
- Hyperendemic in Middle Eastern and adjoining countries of former USSR republics

- Largest recent epidemic: Zimbabwe, 1978-80 - 10,000 human cases

- Reporting deficiencies due to decreasing veterinary experience in case recognition and civil unrest
Cases of Anthrax in the United States 1951-2001

Animal (Sterne strain) vaccine started in 1957, after Oklahoma enzootic; recommended in endemic areas thereafter

Formalin treatment of imported hides

Vaccine for humans approved in 1970

2001

23
Cutaneous Anthrax

- 95% of human cases
- 1 - 2 days post exposure, papule develops (2 - 19 days)
- 2 - 4 days, ulcer surrounded by vesicles
- Black eschar forms - painless with edema
- Most common site is head, forearm, hands
- Untreated: 5-20% case-fatality rate
Anthrax: Cutaneous

- Vesicle development Day 2
- Day 4
- Eschar formation
- Day 6
- Day 10
Anthrax: Cutaneous

Ulcer and vesicle ring

Black eschar. Redness remains
Cutaneous Anthrax Resulting from Bioterrorism, NYC, October, 2001
Diagnosis of Cutaneous Anthrax

- Eschar formation
- Culture of vesicular fluid or exudate
- Blood culture
- Biopsy
- Polymerase chain reaction
- Immunofluorescence and immunohistochemistry
Differential Diagnosis of Cutaneous Anthrax

- Spider bite
- Rickettsialpox
- Varicella zoster
- Herpes simplex
- Staphylococcal or streptococcal cellulitis
- Ecthyma gangrenosum
- Ulceroglandular tularemia
- Plague
Gastrointestinal Anthrax

• Ingestion
  – Rare natural incidence
    • Undercooked, ground beef
  – Most simple, high-consequence application method
    • Possible route of choice for criminals and non-state sponsored terrorists
  – Symptoms
    • Nausea 2-5 days after ingestion
  – Mortality
    • Up to 50% without treatment

Intestinal lesion of GI anthrax
Inhalation Anthrax

- 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%
- Case fatality rate before 2001 – 90%
Inhalation Anthrax
Inhalation Anthrax: Diagnosis

- Chest radiographs - widened mediastinum, pleural effusions
- Blood or cerebrospinal fluid culture and Gram stain
- Polymerase chain reaction (PCR)
- Immunofluorescence and immunohistochemistry
Differential Diagnosis of Inhalation Anthrax

- Mycoplasmal pneumonia
- Legionnaires’ disease
- Psittacosis
- Tularemia

- Q fever
- Viral pneumonia
- Histoplasmosis (fibrous mediastinitis)
- Coccidioidomycosis
Distinguishing Anthrax from Influenza-like Illness (ILI)

• ILI:
  – Nasal congestion and rhinorrhea
  – ILI not usually associated with radiographic findings of pneumonia
  – Person-to-person spread
  – Rapid influenza testing and viral culture useful to indicate whether viruses are circulating among specific populations

• Anthrax:
  – Abnormal chest radiographs
  – No person-to-person spread
Treatment of Inhalation or Complicated Cutaneous Anthrax

Assumptions:
• Rapid progression / systemic
• Beta-lactamases were present in isolates from FL, NY, DC (2001)
• Toxin – mediated
• High fatality

Strategy:
• Early treatment
• Combination therapy
• Avoid penicillins, at least early
• ? Antitoxin (not available)
• ? Steroids
• Treat for 60 days total
## Recommended Initial* Anthrax Treatment

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cutaneous</strong></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>14 days</td>
</tr>
<tr>
<td>500mg BID PO</td>
<td></td>
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<tr>
<td>OR</td>
<td></td>
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<tr>
<td>Doxycycline</td>
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<tr>
<td>100 mg BID PO</td>
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<tr>
<td><strong>Inhalation</strong></td>
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<tr>
<td>Ciprofloxacin</td>
<td>14 days, may switch to PO</td>
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<tr>
<td>400 mg IV BID</td>
<td>when clinically appropriate</td>
</tr>
<tr>
<td>OR</td>
<td></td>
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<tr>
<td>Doxycycline</td>
<td></td>
</tr>
<tr>
<td>100 mg BID IV</td>
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Ciprofloxacin or doxycycline also recommended as initial therapy for children in appropriate doses

*Until antibiotic susceptibility test results available
**Recommended Postexposure Antibiotic Prophylaxis for Prevention of Inhalation Anthrax**

<table>
<thead>
<tr>
<th>Adult Group</th>
<th>Initial Therapy</th>
<th>Duration</th>
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</thead>
<tbody>
<tr>
<td>Adults (including pregnant women and immunocompromised)</td>
<td>Ciprofloxacin 500 mg PO BID OR Doxycycline 100 mg PO BID</td>
<td>60 days</td>
</tr>
<tr>
<td>Children</td>
<td>Ciprofloxacin 10-15 mg/kg PO Q 12 hrs OR Doxycycline:</td>
<td>60 days</td>
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<tr>
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<td>&gt;8 yrs and &gt;45 kg: 100 mg PO BID</td>
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<tr>
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<td>&gt;8 yrs and ≤45 kg: 2.2 mg/kg PO BID</td>
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<tr>
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<td>&lt;8 yrs: 2.2 mg/kg PO BID</td>
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Control / Prevention

Human disease is controlled by:

- Reducing infection in livestock
- Supervised slaughter and meat inspection
- Reducing exposure through import restriction, biosafety precautions, education
- Vaccination of high-risk human populations
- Treatment and post-exposure prophylaxis
Anthrax Vaccine

US Vaccine: BioThrax or Anthrax Vaccine Adsorbed

- Cell-free filtrate of a nonencapsulated, toxigenic strain of B. anthracis
- Produces humoral response against protective antigen
- Preexposure vaccination schedule: 6 doses SQ at 0, 2, 4 weeks, 6, 12, 18 months will yearly booster
- Postexposure vaccination schedule: 3 doses SQ at 0, 2, 4 weeks + 60 days of antibiotics
- Precautionary use in immunosuppressed individuals
- Contraindicated for pregnant women
Human Anthrax Vaccine Trial


- Randomized adjuvant control trial using alum vaccine
- 4 mills processing goat hair
- 379 vaccinated and 870 controls
  - 3 cases (cutaneous) in vaccinated group: 2 had not completed series
  - 23 cases in unvaccinated group, 5 inhalation
  - 93% efficacy (95%CI = 65% to 95%)
Animal Studies of Post-exposure Prophylaxis


  Methods: 5 days of penicillin compared to penicillin with postexposure vaccination

  Results: 9 of the 10 receiving only penicillin died, while all of the macaques receiving penicillin and vaccine survived

- Friedlander et al (1993): Aluminum hydroxide PA filtrate vaccine

  Methods: 30 days of various antibiotics compared to 30 days of doxycycline with postexposure vaccination

  Results: 9 of the 10 animals in the doxycycline-alone arm survived, while all receiving doxycycline and vaccine survived
Anthrax Vaccine Safety

- Mild local reactions (tenderness, swelling, nodule formation) occur in 30% - 60% of recipients
- Large local reactions occur in ≤ 1% of vaccinees
- Systemic reactions: 5%-35% experience muscle ache, joint ache, headache, malaise, fever
- Serious side effect profile similar to other vaccines given to adults (influenza and hepatitis)
Deaths with and without post-exposure prophylaxis following an anthrax release

Case Study 1

• It is 5pm on a Friday afternoon in December and you are getting ready to go a Christmas party with your family. Your last appointment of the day is a 53 year old male office worker with the following complaints:
  – Headache, malaise, muscle ache, feels feverish and having some difficulty breathing

• Your exam findings: absence of breath sounds on the right side of the thorax, crackles on the left side, body temperature 37.5° C
Chest X-Ray Results

What is on your list of differential diagnoses?
• You hospitalize the patient; his condition worsens rapidly with dyspnea, cyanosis, and hemoptysis

• What samples should you consider collecting?
Specimen Selection is Important

Anthrax

- Blood or cerebrospinal fluid – gram stain
- Pleural fluid – request immunohistochemical staining

Tularemia

- Serum for antibody titer
- Pharyngeal wash or sputum specimen for culture, direct florescent antibody, organism gram stains poorly

Pneumonic Plague

- Sputum/throat or bronchial washings- request Wayson stain to see bipolar organism, or direct florescent antibody of smear
Case Study 2: A US tourist comes to see you with this lesion on her arm. What questions would you ask this patient?
Seven days after her first visit, she comes to see you again. The lesion now looks like this – what is on your list of differential diagnoses?
DO NOT PANIC!

• Individuals must be exposed to *B. Anthracis* spores
• To cause disease, *B. anthracis* spores must enter the skin, be swallowed, or inhaled
• Disease can be prevented after exposure to anthrax spores by early treatment with appropriate antibiotics
• Anthrax is NOT spread from person to person
Anthrax Information

- www.aad.org/BioInfo/Biomessage2
- www.who.int/emc-documents/zoonoses/docs
- www.bt.cdc.gov
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