Anthrax

Investigative Guidelines
March 2019

1. DISEASE REPORTING

1.1 Purpose of Surveillance and Reporting

Rapid detection of anthrax-related illness to allow expeditious treatment of those who are ill, prompt identification of the source of infection, including identification of intentional release of anthrax in the context of a terrorist attack, and rapid implementation of control measures.

1.2 Laboratory and Physician Reporting Requirements

Healthcare providers and laboratory personnel should report suspected anthrax infection immediately, day or night.

1.3 Local Public Health Authority (LPHA) Reporting and Follow-Up Responsibilities

Notify Oregon Public Health Division (OPHD), Acute and Communicable Disease Prevention Section (ACDP) at 971-673-1111 immediately of any suspected anthrax infection. Coordinate with ACDP and other agencies as necessary to determine source of infection as well as to carry out contact investigation and prophylaxis for others who appear to have been exposed. (Realistically, if we have an event, the place is going to be swarming with Centers for Disease Control and Prevention (CDC) and other federal folks. We won't have to do this on our own.)

2. THE DISEASE AND ITS EPIDEMIOLOGY

2.1 Etiologic Agent

Bacillus anthracis: an aerobic, non-motile, spore-forming, encapsulated, Gram positive, rod-shaped bacterium.

While this isn't likely to come up often, there are sub-species of another related organism, *Bacillus cereus*, that can cause anthrax-like illness. This probably won't make much of a practical difference for you. Any time clinicians call up and say they think they've got an anthrax case, no need to quibble over the specific bacteria responsible; give us a call. See Section 3.4, *Services Available at the Oregon State Public Health Laboratory (OSPHL),* for further details.

2.2 Description of Illness

Anthrax typically presents as one of three clinical syndromes, depending on the route of exposure.

1. Cutaneous Anthrax

Cutaneous disease is characterized by development of one or more painless, itchy papules on the skin, typically on exposed areas such as the face, neck, forearms, or hands. Within 24 hours, the papule enlarges to form a skin ulcer. This subsequently crusts over, forming the painless black eschar that is the hallmark of the cutaneous form of the disease. Localized swelling, inflammation of the lymph channels, painful regional lymph node swelling, and systemic symptoms also occur. The untreated case fatality rate is 20%; with appropriate therapy, death is rare. More severe cutaneous and systemic infections associated with IV drug use have been reported. These may present with soft tissue involvement and no eschar formation.

2. Inhalational Anthrax

Inhalational disease typically progresses through two distinct stages. The first, lasting from several hours to several days, involves influenza-like symptoms such as fever, cough, shortness of breath, headache, chills, and at times, abdominal or chest discomfort. The second stage involves abrupt onset of sweats, spiking fever, severe respiratory distress, and shock. Of 11 people who developed inhalational disease during the 2001 anthrax attacks, five (45%) died. Therapy must be started early in the course of illness to be effective.

3. Ingestion-related Anthrax

This form of the disease is rarely seen in the U.S. When it affects the oropharynx, it is associated with sore throat, trouble swallowing, and neck swelling. In the gut, it presents with nausea, vomiting, and malaise, then progresses to bloody diarrhea, acute abdomen, and sepsis. The case fatality rate may approach 60%, although lower rates have been reported in some outbreaks. Early antibiotic use appears to decrease mortality.

2.3 Reservoirs

Historically, anthrax has come from contact with:

- Herbivores (cattle, sheep, goats, etc.) ill with the disease.
- Contaminated products (wool, goat hair, meat, hides, etc.) from ill herbivores.

While dormant anthrax spores are found in the soil of many areas in the U.S. and other parts of the world, infection resulting from direct inhalation of natural spores in soil appears to be very rare.

From a bioterrorism (BT) perspective, the main concern is specially processed spores which, when released, would have a higher potential for causing infection. The extent of stockpiling of such weapons by nations and terrorist groups is unknown.

2.4 Sources and Routes of Transmission

- Spore contact with the skin or, rarely, through injection.
- Inhalation of spores.
- Eating contaminated food, typically meat from an infected animal.

2.5 Incubation Period

- Inhalational: 2–60 days.
- Cutaneous: 1–12 days.
- Ingestion-related: 1–7 days.

2.6 Period of Communicability

Anthrax is not known to spread person-to-person.

2.7 Treatment

ACDP will get up-to-date information on prophylaxis to you as needed. See Tables 1–3 on pages 9–11. Raxibacumab, a monoclonal antibody, has been approved for treatment of inhalational anthrax, when used in combination with appropriate antibiotics.

3. CASE DEFINITIONS, DIAGNOSIS AND LABORATORY SERVICES

3.1 Confirmed Case Definition

A clinically compatible illness with one of the following:

- Culture and identification of *B. anthracis* from clinical specimens or isolates, using Laboratory Response Network (LRN) reference procedures (available at OSPHL).
- Demonstration of *B. anthracis* antigens in tissues by immunohistochemical staining using both *B. anthracis* cell wall and capsule monoclonal antibodies.
- Evidence of a four-fold rise in antibodies to protective antigen between acute and convalescent sera or a four-fold change in antibodies to protective antigen in paired convalescent sera using CDC quantitative anti-PA IgG ELISA testing.
- Detection of *B. anthracis* or anthrax toxin genes by LRN-validated polymerase chain reaction (PCR) or sequencing in clinical specimens collected from a normally sterile site (such as blood or CSF) or lesion of other affected tissue (skin, pulmonary, reticuloendothelial, or gastrointestinal).
- Detection of lethal factor (LF) in clinical serum specimens by LF mass spectrometry.

3.2 Probable Case Definition

A clinically compatible illness that does not meet the confirmed case definition, but with one of the following:

- A case that meets clinical criteria and has epidemiologic evidence relating the illness to anthrax or

- A case that meets clinical criteria and has either:
  - A Gram stain demonstrating square-ended, Gram-positive rods in pairs or short chains, or
  - A positive result for *B. anthracis* on a test with established performance in a CLIA-accredited laboratory.

3.3 Suspect Case Definition

Clinically compatible illness in a patient for whom anthrax testing has been ordered, but with no epidemiologic evidence relating it to anthrax. This would also include someone who died of an unknown cause and who has organ involvement consistent with anthrax.

3.4 Services Available at Oregon State Public Health Laboratory (OSPHL)

OSPHL offers rapid, rule-out PCR testing and LRN Reference Laboratory confirmatory culture testing. For complete specimen submission instructions, please visit the OSPHL Lab Test Menu at www.healthoregon.org/labtests. Notify the OSPHL prior to shipping specimens at 503-693-4100.

Note: Subtypes of *Bacillus cereus* have caused anthrax-like illness in gorillas and chimpanzees in West Africa, and isolated human cases. We're not likely to see this around here, but if we get a call about anthrax-like illness and it's associated with a *Bacillus cereus* isolate, there is more lab work to be done. In this situation, call us and have the isolate forwarded to OSPHL for further testing.

4. CASE INVESTIGATION

4.1 Identify the Source of the Infection

Treat any case of anthrax as a potential bioterrorism incident (until this can be ruled out). Any resulting investigation is potentially both a public health and a criminal investigation. Immediately interview all cases, suspect or confirmed, to identify the route and venue of exposure. Consider directed environmental sampling of a suspect venue to localize the exposure.

4.2 Identify Potentially Exposed Persons (Contacts)

Once the route and venue of exposure have been established:

1. Determine the time and spatial extent of the exposure.
2. In circumscribed exposures, develop a list of persons with suspected exposure, using:
   - interviews with those known to be exposed,
   - review of attendee lists of any functions where exposure is suspected to have occurred,
   - credit card receipts from such events, and
   - any other evidence available.

3. Contact all persons on list to assess for illness and to discuss possible prophylaxis.
4. When broad, outdoor dissemination and resultant widespread exposure are suspected, collect information about activities and areas visited preceding symptom onset in those who are ill. For gastrointestinal anthrax, explore the seven (7) days prior to onset. For cutaneous disease, go back 14 days. For inhalational disease (at least for initial cases), go back 60 days prior to onset.

In coordination with ACDP, CDC, and other potentially affected nearby jurisdictions, make a best estimate of the area of exposure to guide prophylaxis efforts for the population at risk.

5. CONTROLLING FURTHER SPREAD

5.1 Education

When contacting potentially exposed persons, educate them about possible symptoms of anthrax disease, including specific conditions that should prompt immediate medical evaluation, such as:

- fever,
- cough or shortness of breath,
- vomiting,
- diarrhea, or
- appearance of a painless sore on the skin.

Describe possible adverse reactions to any medicine given for prophylaxis, and reinforce the possibility of spore germination and resultant disease if medications are not continued for the full course.

5.2 Isolation and School or Day Care Restrictions

Decontamination of buildings containing weaponized *B. anthracis* spores would not be easy. Expert advice would be required. The decision to decontaminate potentially exposed individuals is based upon the credibility of the threat, as established by the FBI, and the potential for exposure of those at the scene. In general, personal decontamination should consist of soap and water on exposed skin and removal of possibly contaminated outer garments and shoes. Once home, a shower to wash off any lingering spores could also be worthwhile.

Depending upon the situation, clothing may be collected as evidence (and the individual supplied with an over-garment), may be removed and bagged for decontamination at home or a commercial facility (and the individual supplied with an over-garment), or may be worn home and laundered or dry cleaned. If more extensive exposure to anthrax is suspected, all potentially contaminated garments should be removed, bagged and laundered, and exposed person should take a full shower, washing thoroughly with soap and warm water.

5.3 Isolation

Not indicated.

5.4 Prophylaxis

1. Post-exposure

   Although not currently licensed for use in the post-exposure setting, anthrax vaccine was used under an investigational new drug protocol in response to the 2001 attacks. Several antimicrobials can be used for prophylaxis in those who have been exposed to anthrax. If this becomes necessary, ACDP will provide up-to-date guidelines. See post-exposure anthrax prophylaxis protocol at: www.oregon.gov/oha/PH/PREVENTIONWELLNESS/VACCINESIMMUNIZATION/IMMUNIZATIONPROVIDERRESOURCES/Documents/SOanthraxPHEP.pdf

2. Pre-exposure

   An inactivated cell-free vaccine exists and can be given as a six-dose series with annual boosters. It is currently recommended only for those with regular occupational exposure to *B. anthracis* and is also used by the U.S. military. It is not recommended for public health workers or the general public.

6. MANAGING SPECIAL SITUATIONS

6.1 Response Following Discovery of a Suspicious Substance in a Community

Evaluation by law enforcement

Upon discovery of a suspicious substance (white powder or otherwise), 911 should be contacted immediately. If there is evidence of explosion or illness or injury, the 911 dispatcher should immediately call both local law enforcement and fire/paramedical services. If there is no evidence of explosion or acute illness, 911 dispatcher should call local law enforcement. Local law enforcement should then assess whether or not a "credible threat" exists. They may then call in a hazardous material (haz-mat) team to aid in a safety assessment, but the initial key step in the "response cascade" is a threat assessment by law enforcement. **If this has not occurred, refer the person contacting you to local law enforcement (or 911) to begin this process.** After this evaluation, there are two possible situations in which public health might be involved:

1. Law enforcement concludes that there is no credible threat.
   - In this case, the local public health authority (LPHA) could be contacted to help in explaining risk (or the lack of it), providing information about the incident, etc.
   - Provide information/explanation of situation if requested.
   - Consult ACDP/Preparedness Surveillance Epidemiology Team (PSET) as needed to draft statements.
2. Law enforcement concludes that there is a credible threat.
   - Law enforcement will retain custody of the suspicious substance.
   - FBI will arrange for further evaluation through OSPHL or CDC.

6.2 Public Health Response in the Setting of Credible Threat

- Communicate periodically with ACDP/PSET to review available information.
- ACDP should contact OSPHL, give them information about the incident, and let them know that FBI may be contacting them about specimen testing, if this has not happened already.
- Consider developing a press release outlining the steps being taken to investigate the event, reviewing that all such events are taken seriously, and that any threat or intentional release of a suspicious substance, even as a hoax is a crime.
- There are two principal situations that might arise from completion of laboratory analysis to detect bioterrorism agents.

  1. The analysis is negative (no biological agent is detected).
     - Develop press release outlining the findings of the investigation and negative results of the laboratory analysis.
  2. The analysis is positive (a biological agent is detected).
     - OSPHL will notify the State Epidemiologist, FBI, and the CDC Emergency Operations Center of the findings.
     - OPHD will inform the LPHA.
     - Press release will be developed (for presentation by people higher up the ladder than us) outlining the findings of the investigation so far and their implications.
     - Pursue case investigation to identify people who have been exposed to the substance as outlined in Section 4, "Case Investigation".

6.3 Positive Signal at a U.S. Postal Service Biohazard Detection System (BDS) Program Facility

1. Three counties (Jackson, Lane, and Multnomah) have postal facilities that conduct on-going, real-time PCR testing for anthrax.
2. In 2006, CDC issued guidance that, due to the high specificity of this BDS testing, a positive signal should trigger decontamination and prophylaxis of those potentially exposed, rather than waiting for the confirmatory testing that will follow.
3. BDS-specific response plans have been developed by U.S. Postal Service, the participating facilities, and the counties where these facilities are located. These plans can be used to guide response in the setting of a positive BDS signal.

UPDATE LOG

February 2019. Updated sections on clinical presentation (added oropharyngeal and injection forms of illness), case definition, and treatment. Updated information about anthrax-like illness associated with *Bacillus cereus*, and about Biohazard Detection System activities in Oregon postal facilities. Added link to post-exposure prophylaxis standing order. Minor edits for clarity. (Leman)

July 2017. Added information about *Bacillus cereus* biovar *anthracis* and recommendation to have any *Bacillus* isolate associated with anthrax-like illness sent to OSPHL for further testing. (Leman)

February 2014. House-keeping with correction of typos; minor revisions to treatment tables. (R. Leman)

January 2013. Updated treatment recommendations based on CDC guidance. Added case investigation (Sec 4) outlining strategies when broad outdoor dissemination suspected. Added information to Decontamination Section (See 5.2) Added info on response to positive signal from Postal Service Biohazard Detection System Program facility to "Managing Special Situations" (Sec 6). (R. Leman)

April 2011. Info on use of vaccine in post-exposure setting, background information under “Description of Illness," and information on managing special situations were revised. (R. Leman)

2003. Original guideline released.

Table 1. Recommended therapy for inhalational anthrax infection in the contained casualty setting[ab]

Category	Initial IV therapy[c,d]	Duration
Adults	Ciprofloxacin 400 mg every 12 hours (recommended unless contraindicated) or Doxycycline 100 mg every 12 hours[f] and 1 or 2 additional antimicrobials[d]	IV treatment initially[e] before switching to oral antimicrobial therapy when clinically appropriate: Ciprofloxacin 500 mg twice daily or Doxycycline 100 mg twice daily Continue oral and IV treatment for 60 days[j]
Children	Ciprofloxacin 10-15 mg every 12 hours[g,h] (recommended unless contraindicated) or Doxycycline[f,i] for those aged: >8 y and weight ≥45 kg: 100 mg every 12 hours >8 y and weight ≤45 kg: 2.2 mg/kg every 12 hours ≤8 y: 2.2 mg/kg every 12 hours and 1 or 2 additional antimicrobials[f]	IV treatment initially[e] before switching to oral antimicrobial therapy when clinically appropriate. Ciprofloxacin 10-15 mg every 12 hours[h] (recommended unless contraindicated) or Doxycycline[i] for those aged: >8 y and weight ≥45 kg: 100 mg twice daily >8 y and weight 2.2 mg/kg twice daily ≤8 y: 2.2 mg/kg twice daily Continue oral and IV treatment for 60 days[1]
Pregnant women	Same as for nonpregnant adults Ciprofloxacin recommended in pregnancy prior to third trimester	IV treatment initially[e] before switching to oral antimicrobial therapy when clinically appropriate, oral therapy regimens are the same as for non pregnant adults
Immunocompromised persons	Same as for non-immunocompromised adults and children	

a. This table is adapted with permission from *Morbidity and Mortality Weekly Report*. For gastrointestinal and oropharyngeal anthrax, use regimens recommended for inhalational anthrax.
b. Raxibacumab, a monoclonal antibody, is now approved for treatment of inhalational anthrax.
c. Steroids may be considered as an adjunct therapy for patients with severe edema and for meningitis based in experience with bacterial meningitis of other etiologies. Early aggressive drainage of pleural effusions recommended for inhalational anthrax.
d. Other agents with in vitro activity include rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, and clarithromycin. Because of concerns of constitutive and inducible β lactamases in *Bacillus anthracis*, penicillin and ampicillin should not be used alone. Consultation with an infectious disease specialist is advised. Given risk of meningeal involvement with systemic anthrax, choose agents with adequate CNS penetration.
e. Initial therapy may be altered based on the clinical course of the patient; 1 or 2 antimicrobial agents may be adequate as patient improves.
f. If meningitis is suspected, doxycycline may be less optimal because of poor central nervous system penetration.
g. If intravenous (IV) ciprofloxacin is not available, oral ciprofloxacin may be acceptable because it is rapidly and well absorbed from the gastrointestinal tract with no substantial loss by the first-pass metabolism. Maximum serum concentrations are attained 1 to 2 hours after oral dosing but may not be achieved if vomiting or ileus is present.
h. In children, ciprofloxacin dosage should not exceed 1 g/d.
i. The American Academy of Pediatrics recommends treatment of young children with tetracyclines for serious infections (i.e., Rocky Mountain spotted fever).
j. Because of potential persistence of spores after an aerosol exposure, antimicrobial therapy should be continued for 60 days.

Table 2. Recommended therapy for inhalational anthrax infection in the mass casualty setting[a]

Category	Initial oral therapy[b]	Alternative therapy if strain is proved susceptible	Duration after exposure
Adults	Ciprofloxacin 500 mg twice daily	Doxycycline 100 mg every 12 hours[c], or Amoxicillin 500 mg orally every 8 hours[d]	60 days
Children	Ciprofloxacin 20-30 mg/kg per day orally taken in 2 daily doses, not to exceed 1 g/d[e]	Doxycycline[f] for those aged: >8 y and weight >45 kg: 100 mg every 12 hours >8 y and weight ≤45 kg: 2.2 mg/kg every 12 hours ≤8 y: 2.2 mg/kg every 12 hours, or Amoxicillin: >20 kg: 500 mg orally every 8 hours[d] <20 kg: 40 mg/kg orally in	60 days
Pregnant women	Ciprofloxacin 500 mg orally every 12 hours	Doxycycline[f] 100 mg every 12 hours, or Amoxicillin 500 mg orally every 8 hours[d]	60 days
Immunocompromised persons	Same as for non-immunocompromised adults and children		

a. Some of these recommendations are based on animal studies or *in vitro* studies and are not approved by the U.S. Food and Drug Administration. (Table adapted from Inglesby, et al. JAMA 2002;287[17]:2236–52.)
b. *In vitro* studies suggest ofloxacin (400 mg orally every 12 hours), or levofloxacin, 500 mg orally every 24 hours could be substituted for ciprofloxacin.
c. *In vitro* studies suggest that 500 mg of tetracycline orally every 6 hours could be substituted for doxycycline. In addition, 400 mg of gatifloxacin or moxifloxacin, both fluoroquinolones with mechanisms of action consistent with ciprofloxacin, taken orally could be substituted.
d. According to the Centers for Disease Control and Prevention recommendations, amoxicillin is suitable for completion of therapy only after 10 to 14 days of fluoroquinolones or doxycycline treatment and then only if there are contraindications to these 2 classes of medications (e.g., pregnancy, lactating mother, aged >18 years or intolerance of other antibiotics).
e. Doxycycline could also be used if antibiotic susceptibility testing, exhaustion of drug supplies, or adverse reactions preclude use of ciprofloxacin. If meningitis is suspected, doxycycline may be less optimal because of poor central nervous system penetration.
f. Ciprofloxacin is preferred. If there is a contraindication to fluoroquinolone use, doxycycline can be substituted.

Table 3. Recommended therapy for cutaneous anthrax infection associated with a bioterrorism attack[a]

Category	Initial oral therapy[b]	Duration[c]
Adults	Ciprofloxacin 500 mg twice daily[b] or Doxycycline 100 mg twice daily[b]	60 days
Children	Ciprofloxacin 10-15 mg/kg every 12 hours (not to exceed 1 g/d)[b] or Doxycycline for those aged: >8 y and weight >45 kg: 100 mg every 12 hours >8 y and weight ≤45 kg: 2.2 mg/kg every 12 hours ≤8 y: 2.2 mg/kg every 12 hours	60 days
Pregnant women[e]	Ciprofloxacin 500 mg twice daily or Doxycycline 100 mg twice daily	60 days
Immunocompromised persons	Same as for non-immunocompromised adults and children	

a. This table is adapted with permission from *Morbidity and Mortality Weekly Report.* Cutaneous anthrax with signs of systemic involvement, extensive edema, or lesions on the head or neck require intravenous therapy, and a multidrug approach is recommended.
b. Ciprofloxacin or doxycycline should be considered first-line therapy. Amoxicillin can be substituted if a patient cannot take a fluoroquinolone or tetracycline class drug. Adults are recommended to take the 500 mg of amoxicillin orally 3 times a day. For children, 80 kg/mg of amoxicillin divided into 3 doses in 8-hour increments is an option for completion of therapy after clinical improvement. Oral amoxicillin dose is based on the need to achieve appropriate minimum inhibitory concentration levels.
c. Previous guidelines have suggested treating cutaneous anthrax for 7 to 10 days, but 60 days is recommended for bioterrorism attacks, given the likelihood of exposure to aerosolized *Bacillus anthracis*.
d. The American Academy of Pediatrics recommends treatment of young children with tetracycline for serious infections (e.g., Rocky Mountain spotted fever).
e. Although tetracyclines or ciprofloxacin are not recommended during pregnancy, their use may be indicated for life-threatening illnesses. In this setting, barring contraindications, ciprofloxacin would be preferred.