

# BIOTERRORISM AGENTS

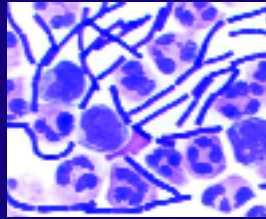
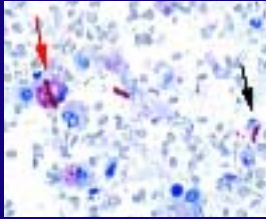


## PRACTICAL INFORMATION ABOUT ANTHRAX

AMERICA'S PHARMACEUTICAL COMPANIES

[www.homelandhealth.com](http://www.homelandhealth.com)

## B. anthracis



Gram positive, spore forming, non-motile bacillus

## BASICS

- Caused by the spore-forming bacterium *Bacillus anthracis*. Anthrax spores have been documented in soil samples throughout the world.
- Natural human anthrax infections are acquired through cutaneous contact with infected animals and animal products (most common) or by ingestion or inhalation of spores.
- Natural anthrax is rare in the United States; 236 reported cases (most cutaneous) between 1955-1999; all were occupational.
- Bioterrorism anthrax cases first detected in October 2001; related to distribution of *B. anthracis* spores via letters in the U.S. postal system.

## CLINICAL FORMS

### Cutaneous Anthrax

- **Acquired via:** direct cutaneous contact with *B. anthracis* spores; often but not always at a site of prior injury
- **Incubation period:** 1-12 days after exposure; may be longer
- Onset as macule or papule similar in appearance to a spider bite; progresses through a vesicular phase; and then evolves to a painless, depressed, black, necrotic eschar 1-3 cm in diameter; edema, erythema, and/or necrosis without ulceration, and regional lymphadenopathy also occur.
- Lesions may expand with marked local edema and erythema that resembles a more aggressive cellulitis with systemic symptoms and signs.
- Systemic symptoms and signs may include fever, headache, and malaise.
- **Differential diagnosis:** spider bite; ecthyma gangrenosum; ulceroglandular tularemia; plague; staphylococcal cellulitis; streptococcal cellulitis; other bacterial cellulitis
- **Fatality rate:** low (<20% with no treatment; less than 1% with appropriate antimicrobial therapy)

## Anthrax: Cutaneous



Typical Lesions



Day 2



Day 4



Day 6



Day 8

## Inhalational Anthrax

- **Acquired via:** inhalation of *B. anthracis* spores; spores deposited in alveolar space are trafficked in macrophages to hilar and mediastinal lymph nodes
- **Incubation period:** usually short; 1-7 days; may be prolonged - up to 48 days or longer
- Influenza-like illness (fever, myalgia, profound fatigue; conspicuous diaphoresis, headache, vomiting, abdominal pain, significant chest pain, non-productive cough); progresses to severe dyspnea, diaphoresis, hypoxemia, and shock; meningitis also common; nasal congestion not common.
- Illness is toxin-mediated and may progress even when cultures are sterilized with antimicrobial therapy; hemorrhagic mediastinitis with bilateral hemorrhagic pleural effusions characteristic findings.
- **Differential diagnosis:** influenza, other influenza-like respiratory illnesses; acute histoplasmosis; tuberculosis; coccidiomycosis; overwhelming bacterial sepsis syndrome; toxic shock syndromes; bacterial meningitis; myocardial infarction
- **Fatality rate:** high once symptoms appear; 45% even with appropriate antimicrobials and supportive care in late 2001 bioterrorism attacks

## Gastrointestinal Anthrax

- **Acquired via:** ingestion of contaminated foods
- **Incubation period:** 1-7 days; sometimes longer
- Oropharyngeal syndrome characterized by sore throat, dysphagia, cervical lymphadenopathy, local/regional edema, fever, can progress to sepsis syndrome.
- Abdominal syndrome characterized by abdominal pain, bloody emesis, bloody diarrhea; can progress to sepsis syndrome with massive ascites.
- **Fatality rate:** high once symptoms appear even with appropriate antimicrobials and supportive care

## Anthrax: Inhalational



Mediastinal Widening and Pleural Effusion on Chest X-Ray in Inhalational Anthrax

## GENERAL DIAGNOSTIC RECOMMENDATIONS

- **Report** any patient with an illness suggestive of anthrax to local and/or state public health authorities and appropriate infection control personnel in the involved facility.
- **Culture** appropriate sites (blood, spinal fluid, affected skin) **BEFORE** antimicrobial treatment is initiated; if the patient is stable and evaluation can proceed quickly, cultures of other affected sites (e.g. pleural fluid) should also be obtained before antimicrobial therapy is started.
- **Initiate empiric treatment** once cultures are obtained.
- If the patient has been treated with antimicrobials, a negative culture does not exclude the diagnosis of anthrax.
- Special diagnostic studies including immunohistochemical stains, polymerase chain reaction to detect *B. anthracis*, serologic tests, etc. may be obtained if indicated through public health laboratories and/or CDC.
- A CXR is indicated when inhalational anthrax is suspected; if not diagnostic, a chest CT should be obtained.
- Cultures obtained by nasal swabbing are not recommended as a diagnostic test for anthrax. Nasal swabs may be indicated to aid in assessment of the extent of environmental contamination during an acute anthrax spore exposure event if recommended by public health authorities; otherwise their use should be discouraged.

## GENERAL TREATMENT RECOMMENDATIONS

- Current treatment guidelines for cases of anthrax associated with 2001 bioterrorist attacks are based on known antimicrobial susceptibility data for these isolates. Updated guidance should be sought from <http://www.cdc.gov>.

The following table represents summaries of current U.S. Centers for Disease Control and Prevention treatment guidelines. These guidelines contain information that has not been approved by the Food and Drug Administration and do not necessarily represent FDA approved information about drug indications, dosing and administration, side effects, contraindications, precautions, and warnings. These guidelines are not intended to replace information contained in each product's approved labeling. Each product's approved package insert should be consulted prior to initiation of drug therapy.

**Table 1. Inhalational anthrax treatment protocol\*,+ for cases associated with this bioterrorism attack**

Category	Initial therapy (intravenous)§,¶	Duration
Adults	Ciprofloxacin 400 mg every 12 hrs* <b>OR</b> Doxycycline 100 mg every 12 hrs++ <b>AND</b> One or two additional antimicrobials¶	IV treatment initially**. Switch to oral antimicrobial therapy when clinically appropriate:  Ciprofloxacin 500 mg po BID <b>OR</b> Doxycycline 100 mg po BID  Continue for 60 days (IV and po combined)§§
Children	Ciprofloxacin 10 mg/kg IV every 12 hrs¶¶*** <b>OR</b> Doxycycline:+++ >8 yrs and >45kg: 100 mg every 12 hrs >8 yrs and ≤45kg: 2.2 mg/kg every 12 hrs ≤8 yrs: 2.2 mg/kg every 12 hrs <b>AND</b> One or two additional antimicrobials¶	IV treatment initially** Switch to oral antimicrobial therapy when clinically appropriate:  Ciprofloxacin 10/15 mg/kg po every 12 hrs*** <b>OR</b> Doxycycline:+++ >8 yrs and >45 kg: 100mg po BID >8 yrs and ≤45 kg: 2.2 mg/kg po BID ≤8 yrs: 2.2 mg/kg po BID  Continue for 60 days (IV and po combined)§§
Pregnant women§§§	Same for nonpregnant adults (the high death rate from the infection outweighs the risk posed by the antimicrobial agent)	IV treatment initially. Switch to oral antimicrobial therapy when clinically appropriate.+ Oral therapy regimens same for nonpregnant adults
Immunocompromised Persons	Same for nonimmunocompromised persons and children	Same for nonimmunocompromised persons and children

\* For gastrointestinal and oropharyngeal anthrax, use regimens recommended for inhalational anthrax.  
 + Ciprofloxacin or doxycycline should be considered an essential part of first-line therapy for inhalational anthrax.  
 § Steroids may be considered as an adjunct therapy for patients with severe edema and for meningitis based on experience with bacterial meningitis of other etiologies.  
 ¶ Other agents with *in vitro* activity include rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, and clarithromycin. Because of concerns of constitutive and inducible beta-lactamases in *Bacillus anthracis*, penicillin and ampicillin should not be used alone. Consultation with an infectious disease specialist is advised.  
 \*\* Initial therapy may be altered based on clinical course of the patient; one or two antimicrobial agents (e.g., ciprofloxacin or doxycycline) may be adequate as the patient improves.  
 ++ If meningitis is suspected, doxycycline may be less optimal because of poor central nervous system penetration.  
 §§ Because of the potential persistence of spores after an aerosol exposure, antimicrobial therapy should be continued for 60 days.  
 ¶¶ If intravenous 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 first-pass metabolism. Maximum serum concentrations are attained 1-2 hours after oral dosing but may not be achieved if vomiting or ileus are present.  
 \*\*\* In children, ciprofloxacin dosage should not exceed 1 g/day for oral; 800mg/day for IV.  
 +++ The American Academy of Pediatrics recommends treatment of young children with tetracyclines for serious infections (e.g., Rocky Mountain Spotted Fever).  
 §§§ Although tetracyclines are not recommended during pregnancy, their use may be indicated for life-threatening illness. Adverse effects on developing teeth and bones are dose-related; therefore, doxycycline might be used for a short time (7-14 days) before 6 months of gestation.

The following table represents summaries of current U.S. Centers for Disease Control and Prevention treatment guidelines. These guidelines contain information that has not been approved by the Food and Drug Administration and do not necessarily represent FDA approved information about drug indications, dosing and administration, side effects, contraindications, precautions, and warnings. These guidelines are not intended to replace information contained in each product's approved labeling. Each product's approved package insert should be consulted prior to initiation of drug therapy.

**Table 2. Cutaneous anthrax treatment protocol\* for cases associated with this bioterrorism attack**

Category	Initial therapy (oral)+	Duration
Adults*	Ciprofloxacin 500 mg BID <b>OR</b> Doxycycline 100 mg BID	60 days§
Children*	Ciprofloxacin 15 mg/kg every 12 hrs (not to exceed 1g/day)+ <b>OR</b> Doxycycline: ¶ >8 yrs and >45 kg: 100 mg every 12 hrs >8 yrs and ≤45 kg: 2.2 mg/kg every 12 hrs ≤8 yrs: 2.2 mg/kg every 12 hrs	60 days§
Pregnant women*,**	Ciprofloxacin 500 mg BID <b>OR</b> Doxycycline 100 mg BID	60 days§
Immunocompromised Persons*	Same for nonimmunocompromised persons and children	60 days§

\* 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. Table 1.  
 + Ciprofloxacin or doxycycline should be considered first-line therapy. Amoxicillin 500 mg po TID for adults or 80 mg/kg/day divided every 8 hours for children 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.  
 § Previous guidelines have suggested treating cutaneous anthrax for 7-10 days, but 60 days is recommended in the setting of this attack, given the likelihood of exposure to aerosolized *B. anthracis* (6).  
 ¶ The American Academy of Pediatrics recommends treatment of young children with tetracyclines for serious infections (e.g., Rocky Mountain Spotted Fever).  
 \*\* Although tetracyclines or ciprofloxacin are not recommended during pregnancy, their use may be indicated for life-threatening illness. Adverse effects on developing teeth and bones are dose-related; therefore, doxycycline might be used for a short time (7-14 days) before 6 months of gestation.

## GENERAL PROPHYLAXIS RECOMMENDATIONS

- Current treatment guidelines for cases of anthrax associated with 2001 bioterrorist attacks are based on known antimicrobial susceptibility data for these isolates. Updated guidance should be sought during future events.
- Prophylactic antimicrobial therapy to prevent inhalational anthrax is indicated for those exposed to *B. anthracis* spores by the airborne route.
- The optimal duration of prophylactic treatment is not known.
- Currently, 60 days of antimicrobial therapy is recommended by CDC; the option for an additional 40 days of therapy under a treatment IND is also available.
- Ampicillin/amoxicillin can be used as post exposure anthrax prophylactic treatment among children and pregnant/breastfeeding women if the isolate is not resistant.

See <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5045a5.htm> on special considerations for children and pregnant and breastfeeding women.

## GENERAL VACCINATION RECOMMENDATIONS

- Pre-exposure vaccination is recommended only for persons at ongoing risk of *B. anthracis* spore exposure (e.g. anthrax research laboratory personnel and certain military personnel). Use of the vaccine is not recommended for the general public.
- Early post-exposure vaccination after *B. anthracis* exposures was not available during the late 2001 bioterrorism attacks. Efforts are in progress to make vaccine available to prevent infection after exposure in the future. Consult with local public health authorities or CDC.
- Late post-exposure vaccination (i.e. after 60 days of antimicrobial therapy) was an option made available to persons at risk for inhalation anthrax in the 2001 bioterrorist attacks.
- Post-exposure vaccination (3 doses of vaccine over 4 weeks) does not provide long-term immunity. Antimicrobial treatment is necessary until protective immunity is achieved.
- Post-exposure anthrax vaccination is investigational and requires informed consent.
- Known adverse events associated with anthrax vaccine include mild local reactions, subcutaneous nodules at the injection site that can be associated with significant erythema and edema (confused with cellulitis), and very rarely, more serious systemic inflammatory or allergic reactions.

**This material is provided by the U.S. Centers for Disease Control and Prevention (CDC) and distributed by the Pharmaceutical Research and Manufacturers of America (PhRMA). For updated or more specific information go to <http://www.cdc.gov>.**

