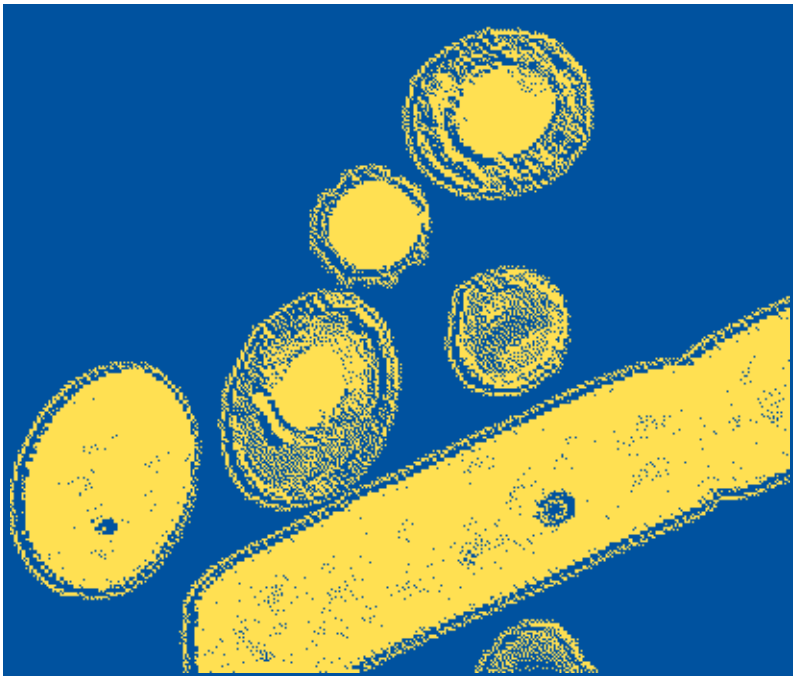
Preparing for and Responding to Bioterrorism

Information for Primary Care Clinicians



Anthrax

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*This manual and the accompanying MS Powerpoint® slides are current as of July 2002. Please refer to **http://nwcphp.org/bttrain/** for updates to the material.

Last Revised July 2002

Acknowledgements

This manual and the accompanying MS PowerPoint® slides were prepared for the purpose of educating primary care clinicians in relevant aspects of bioterrorism preparedness and response. Instructors are encouraged to freely use all or portions of the material for its intended purpose. The following people and organizations provided information and support in the development of this curriculum.

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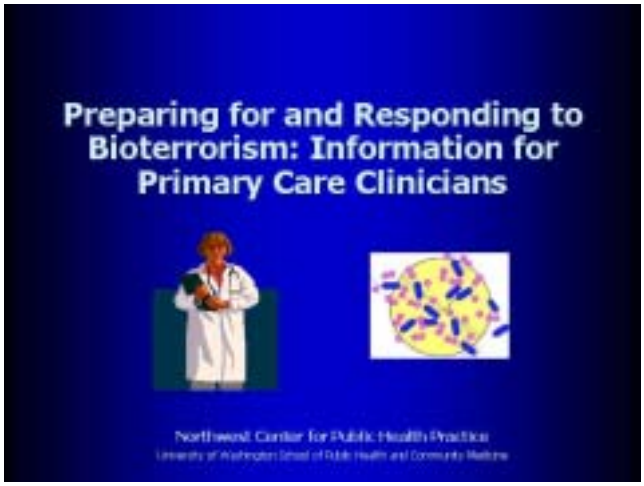
About This Course



"Preparing for and Responding to Bioterrorism: Information for Primary Care Clinicians" is intended to provide primary care clinicians with a basic understanding of bioterrorism preparedness and response, how the clinician fits into the overall process, and the clinical presentation and management of diseases produced by agents most likely to be used in a biological attack. The course was designed by the Northwest Center for Public Health Practice in Seattle, Washington, and Public Health – Seattle & King County.

The course incorporates information from a variety of sources, including the Centers for Disease Control and Prevention, the United States Army Medical Research Institute in Infectious Disease (USAMRIID), the Working Group on Civilian Biodefense, Public Health – Seattle & King County, and the Washington State Department of Health, among others (a complete list of references is given at the end of the manual). The course is not copyrighted and may be used freely for the education of primary care clinicians.

Course materials will be updated on an as-needed basis with new information (e.g., research study results, consensus statements) as it becomes available. For the most current version of the curriculum, please refer to: http://nwcphp.org/bttrain/.

How to Use This Manual

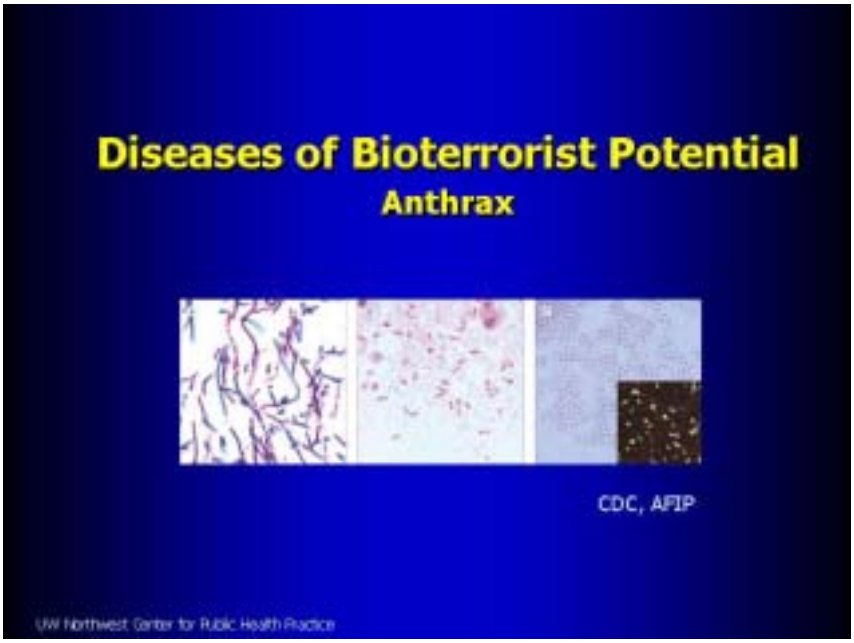
This manual provides the instructor with additional useful information related to the accompanying MS PowerPoint® slides. The manual and slides are divided into four major sections: Introduction to Bioterrorism, Bioterrorism Preparedness and Response, Diseases of Bioterrorist Potential, and Psychological Aftermath of Crisis. Learning objectives precede each section, and a list of resources is given at the end of each section. Four slide sets comprise the section on the diseases of bioterrorist potential: Anthrax, Smallpox, Plague and Botulism, and Tularemia and Viral Hemorrhagic Fevers. Each disease slide set contains the same introductory material on the critical agents at the beginning and the same list of resources at the end. Instructors who want to skip this introductory material can use the navigation pages provided in the Plague and Botulism and Tularemia and Viral Hemorrhagic Fever modules (click the section to which you want to go), or the custom show option in the Anthrax and Smallpox modules (go to "Custom Shows" under the "Slide Show" option on the MS PowerPoint® toolbar; select "Anthrax/Smallpox, skip intro").

Links to Web sites of interest are included in the lower right-hand corner of some slides and can be accessed by clicking the link while in the "Slide Show" view. Blocks of material in the manual are summarized in the "Key Point" sections to assist the instructor in deciding what material to include in a particular presentation. A Summary of Key Points is indicated in bold, at the beginning of each section.

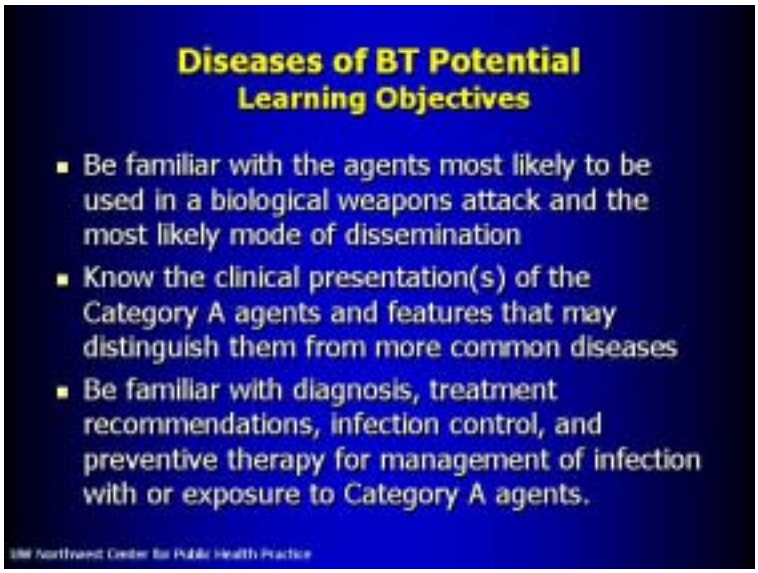
The slide set can be presented in its entirety, in subsections, or as an overview, depending on the level of detail included. The entire course was intended to be presented in a six- to seven-hour block of time, divided into one- to three-hour blocks according to instructor/audience preference. For instructors who want to present a less detailed "overview" course, suggestions for more abbreviated presentations are incorporated into the modules. These latter options are built into the slide set and can be accessed by going to "Custom Shows" (under the "Slide Show" option on the MS PowerPoint® task bar).

Diseases of Bioterrorist Potential

The photo shows, from left to right, gram stains of *Bacillus anthracis* (anthrax), *Yersinia pestis* (plague), and *Francisella tularensis* (tularemia). The source for the first two photos is the CDC, and for the gram stain of *F. tularensis*, the Armed Forces Institute of Pathology



Learning Objectives (Slide 4)



The learning objectives for this session are:

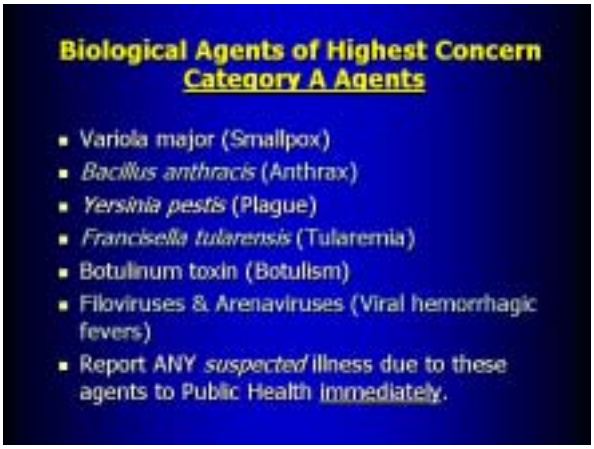
1. Be familiar with the agents most likely to be used in a biological weapons attack and the most likely mode of dissemination
2. Know the clinical presentation(s) of the Category A agents and features that may distinguish them from more common diseases
3. Be familiar with diagnosis, treatment recommendations, infection control, and preventive therapy for management of infection with or exposure to Category A agents

Section 1: Biological Agents of Highest Concern

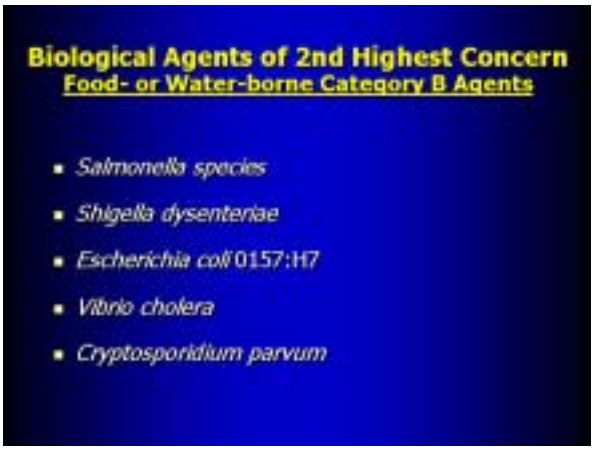
(Slides 6-10)

CDC has designated "**critical agents**" with potential for use as biological weapons and grouped them according to level of concern (Rotz et al., Emerging Infect Dis 2002; 8(2):225-230). Several factors determine the classification of these agents, including previous use or development as a biological weapon, ease of dissemination, ability to cause significant mortality or morbidity, and infectious nature.

Category A agents, designated as agents of highest concern, will be the focus of this session; they are listed in slide 7. Category A agents include variola major (smallpox), *bacillus anthracis* (anthrax), *yersinia pestis* (plague), *francisella tularensis* (tularemia), *clostridium botulinum* toxin (botulism), and the filoviruses and arenaviruses (hemorrhagic fever viruses).



Category B agents are of the next highest level of concern and are listed in slides 8 and 9. These agents are moderately easy to disseminate and produce lower mortality and moderate morbidity.



A subset of the Category B agents includes food- and water-borne agents. These agents more commonly produce disease outbreaks from a non-deliberate source and may also be employed in a biological attack.

The final category of agents – **Category C** – includes emerging pathogens with potential for mass dissemination based on availability, ease of production and dissemination, and potential for high morbidity and mortality. They are listed in slide 10.

The Laboratory Response Network

The CDC has established a multi-level **Laboratory Response Network (LRN)** for bioterrorism. Labs are identified by increasing levels of proficiency to respond to bioterrorism, from Level A to Level D; these categories take into consideration the bio-safety level capacity of the labs, as well as other resource and capacity issues.

Level A – Most clinical labs are Level A and include public health and hospital labs with a certified biological safety cabinet as a minimum.

Level B – State and local public health labs with BSL-2 facilities that incorporate BSL-3 practices

Level C – BSL-3 facilities with the capability to perform nucleic acid amplification, molecular typing, toxicity testing (Washington Public Health Laboratories, for example)

Level D – Possess BSL-3 and BSL-4 biocontainment facilities and include CDC and USAMRIID labs. Level B/C labs can register for the LRN and then have password-protected access to information over the Web.

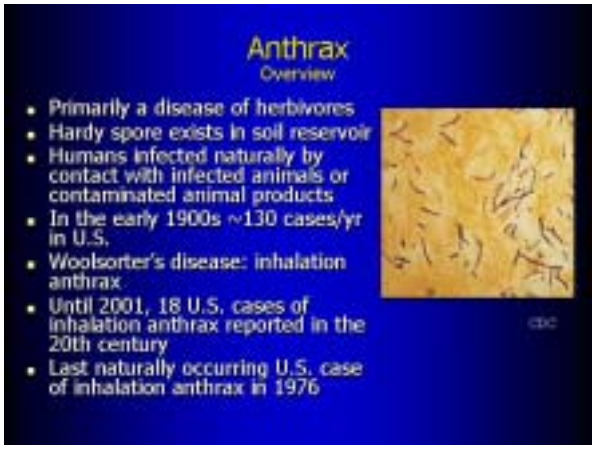
Section 2: Anthrax (Slides 10-54)

Summary of Key Points:

(Listed in slides 51-53)

1. The most likely presentation of anthrax in a BT attack is inhalational disease; cutaneous disease is also possible.
2. Early in the course of illness, inhalational anthrax is not easily distinguished from an influenza-like illness due to other causes.
3. Symptoms suggestive of inhalational anthrax include a febrile respiratory illness with profound fatigue, drenching sweats, GI involvement, or chest pressure or pain.
4. There are no specific chest x-ray findings for inhalational anthrax. CXR is usually abnormal and may demonstrate mediastinal widening/hilar adenopathy, infiltrates/consolidation, or pleural effusions.
5. CT scan of the chest is a more sensitive test and may show these abnormalities before they appear on CXR. Hyperdense lymphadenopathy on a non-enhanced CT of the chest is suggestive of anthrax.
6. Antibiotic prophylaxis and possibly anthrax vaccine can be used to prevent development of disease in infected persons.
7. Anthrax is not transmitted person to person.

Overview (Slide 10)



The causative agent of anthrax is *Bacillus anthracis*, a gram positive, spore-forming bacteria. Anthrax is primarily a disease of herbivores (e.g., sheep, cows), which acquire infection via exposure to *B. anthracis* spores in soil. Humans acquire infection through contact with infected animals or contaminated animal products; hence hunters and textile workers ("woolsorter's disease") have historically been high-risk groups. The last U.S. case of inhalational anthrax, prior to the 2001 outbreak, occurred in a home craftsman and was acquired from imported animal-origin yarn (Suffin et al., Hum Pathol 1978 Sep;9(5):594-7).

Animal vaccination programs have dramatically decreased the number of animal deaths due to anthrax. Industrial hygiene practices and restrictions on imported animal products helped to decrease the incidence of anthrax among humans in the United States.

Cutaneous anthrax is the most common natural form of the disease (gastrointestinal anthrax is very rare), but inhalational anthrax is the most likely presentation in a BT attack.

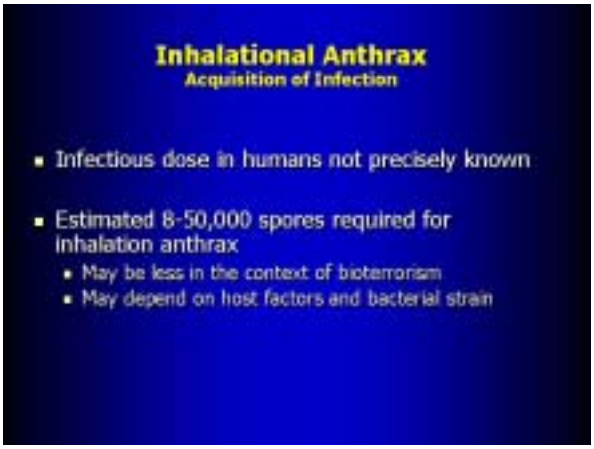
Inhalational Anthrax (Slides 11-30)

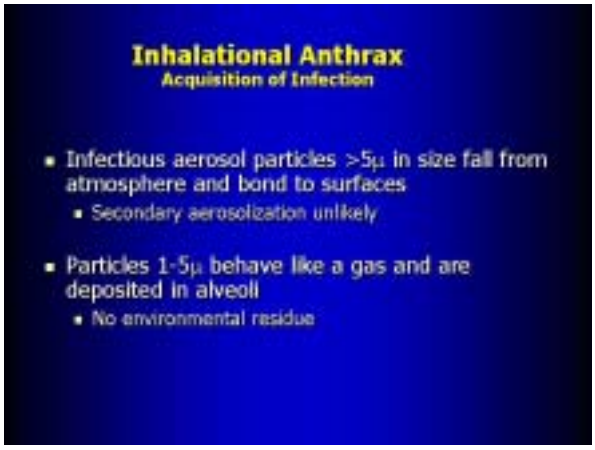
Key Points

1. The clinical features of anthrax are the result of toxin-produced edema, tissue necrosis, and systemic effects.
2. Inhalational anthrax begins with a non-specific "flu-like" prodrome followed within two to five days by a rapid progression to respiratory failure, shock, and possibly death.
3. Although historically most cases were fatal, early and aggressive treatment can improve patient outcome.

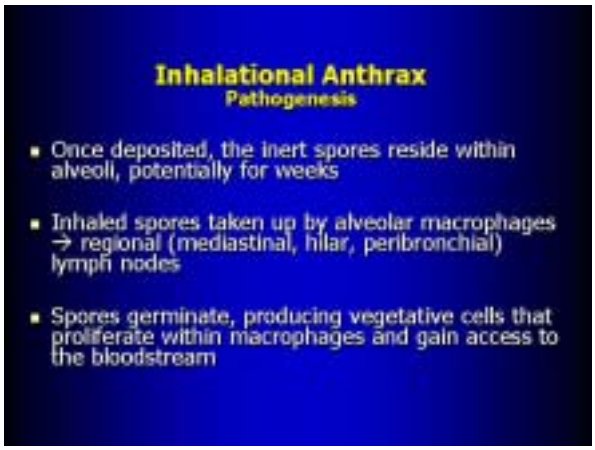
Acquisition of Infection and Pathogenesis (Slides 11-14)

The infectious dose of anthrax for humans is not precisely known. The anthrax outbreak of 2001 and historical data suggest that the infectious dose may vary, with increasing patient age and underlying medical conditions corresponding to increased susceptibility to infection. In addition, infection rates would also be expected to vary according to the ability of a particular preparation of anthrax spores to remain aerosolized in respirable particles. Because anthrax prepared for use as a weapon may employ particularly virulent organisms, the infectious dose may be lower than in naturally occurring infection.



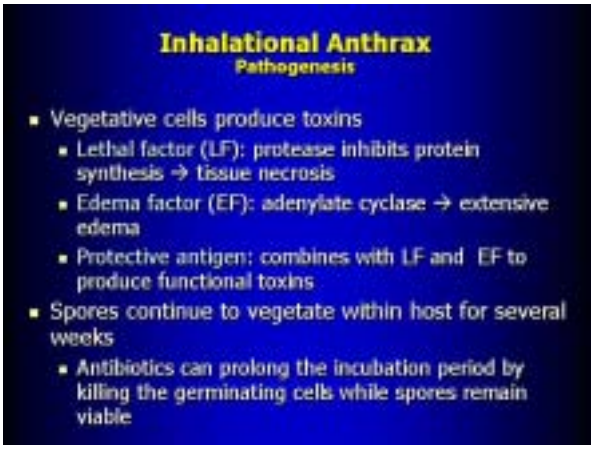


Inhalational anthrax follows the deposition of 1-5 μm spore-bearing particles into alveolar spaces. The greatest risk for contracting inhalational anthrax after an aerosol attack occurs after primary aerosolization (i.e., before particles hit the ground, probably within one day, depending on environmental conditions and the chemical properties of the aerosol). Secondary aerosolization is thought to be unlikely, since these particles will be primarily large in size (> 5μm) and require much energy to be re-suspended.



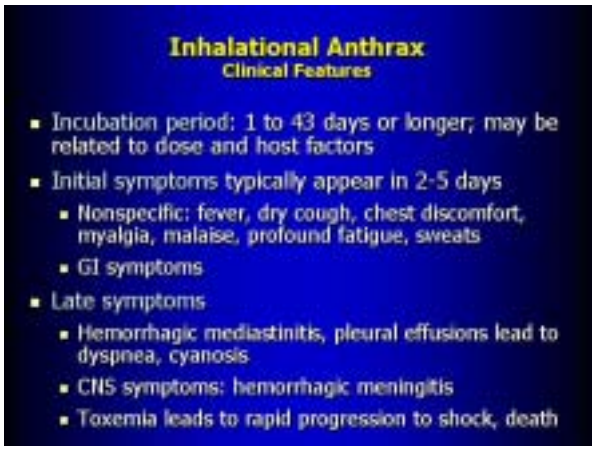
Inhaled spores are taken up by alveolar macrophages, and those not lysed by the macrophages are deposited in mediastinal lymph nodes, where they may sit dormant for up to 100 days. Germination of spores results in vegetative cells that produce toxin and gain access to the bloodstream, and may occur up to 60 days post-exposure.

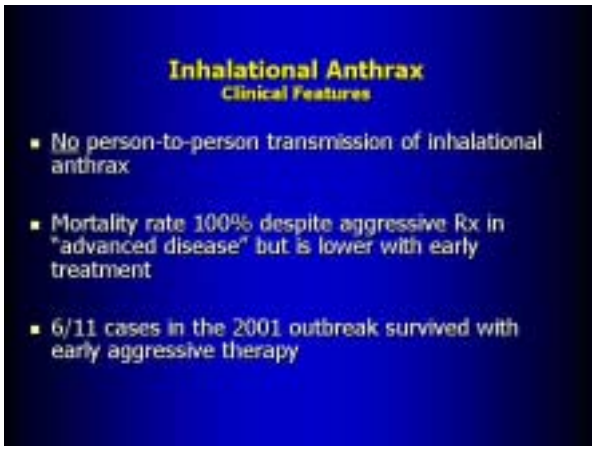
The clinical manifestations of anthrax are mediated by three proteins that combine to form two toxins. Lethal factor plus protective antigen produces a toxin causing tissue necrosis, resulting in the hemorrhagic lymphadenitis of inhalational anthrax and the characteristic black eschar of cutaneous anthrax. Edema factor plus protective antigen produces a toxin causing extensive edema, most readily appreciated in the significant rim of edema observed around the eschar of cutaneous anthrax lesions.



Spores continue to germinate within the host for several weeks. Because antibiotics do not destroy spores, administration of antibiotics may prolong the incubation period if discontinued prematurely. On the other hand, prophylactic antibiotics are effective in preventing disease in infected persons by killing spores as they germinate.

Clinical features (Slides 15-24)

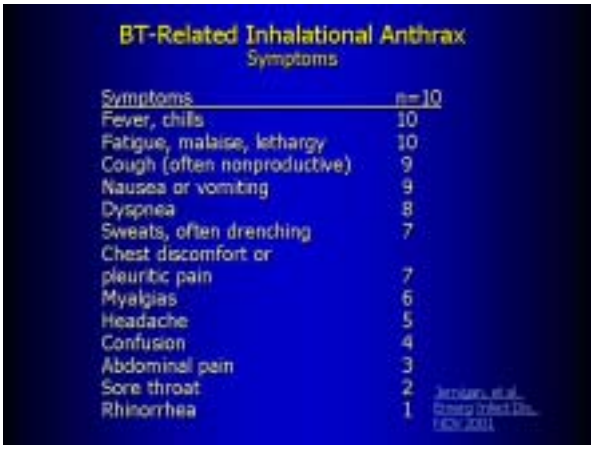


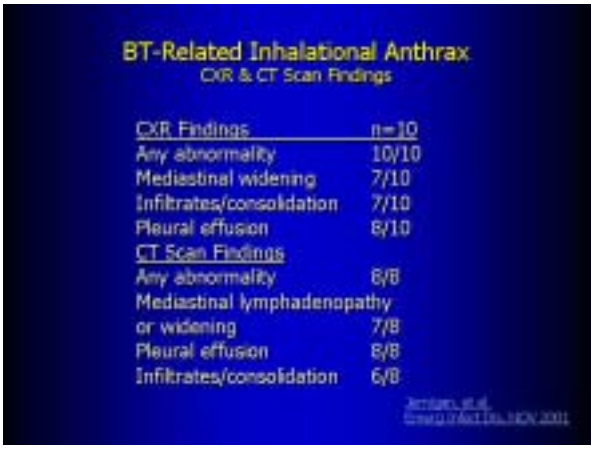


The next seven slides list and illustrate the clinical features of inhalational anthrax. The incubation period ranges from 1-43 days and may be relatively short if the inhaled dose is very high, or greater than a month under some circumstances, such as low inoculum or premature discontinuation of treatment. Typically, symptoms appear two to five days after exposure.

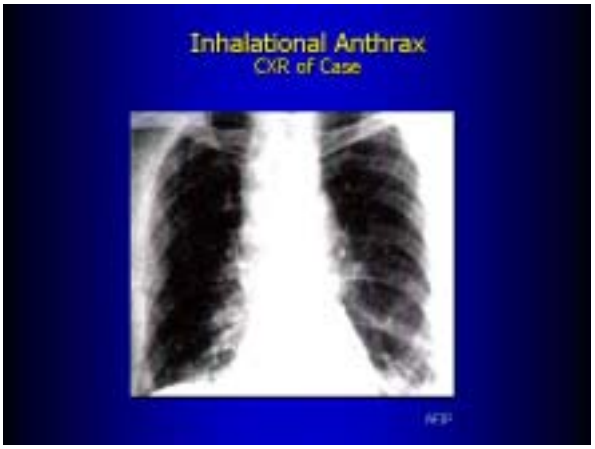
The first stage of illness consists of nonspecific flu-like symptoms and lasts hours to a few days. The second stage comes on abruptly and progresses quickly. Historically, cases were nearly always fatal. Outcome in the 2001 anthrax outbreak was better than previously observed with a 45% case fatality rate (5 deaths/11 cases) (slide 24). Several possible reasons exist for the improved survival rate observed, including differences in host resistance (most cases were middle-aged and relatively healthy), early recognition and initiation of treatment, the use of a combination of antibiotics effective against anthrax, and better supportive care.

Slides 17 and 18 list the symptoms and radiological findings of the first 10 inhalational anthrax letter cases. All presented with the nonspecific findings of fever and fatigue, and all but one had a cough. All cases had an abnormal chest x-ray, but only 7/10 had the classic mediastinal widening associated with anthrax.

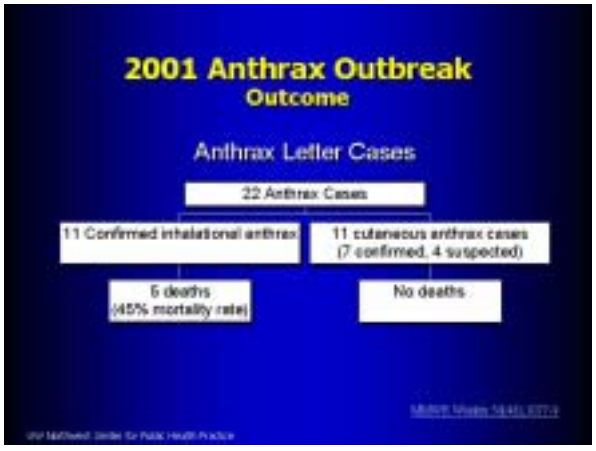




Slide 19 shows a widened mediastinum representing hemorrhagic mediastinitis, which is pathognomonic for inhalational anthrax. Computed tomography proved to be a more sensitive test for detecting pulmonary pathology during the recent 2001 anthrax outbreak.

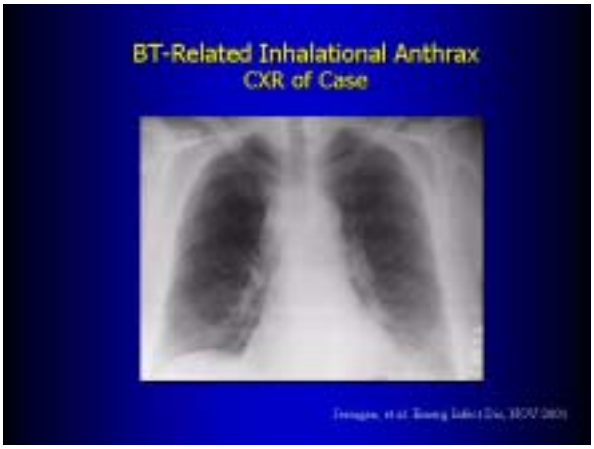


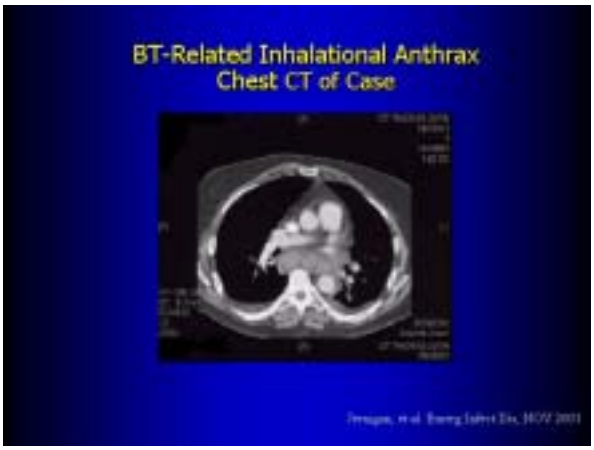
Slide 20, also a patient with inhalational anthrax, shows diffuse consolidation but no mediastinal widening. A computed tomography of the chest for the same patient (slide 21) shows bilateral pulmonary consolidation and pleural effusions.



Outcome in the 2001 anthrax outbreak was better than previously observed with a 45% case fatality rate (5 deaths/11 cases) (slide 24).

Slides 22 and 23 show a chest x-ray (mediastinal widening and a small left pleural effusion) and chest CT (mediastinal adenopathy and small bilateral pleural effusions) for a third patient with inhalational anthrax.

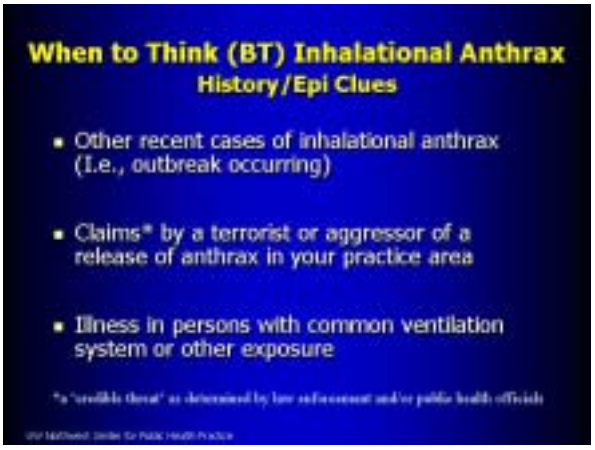


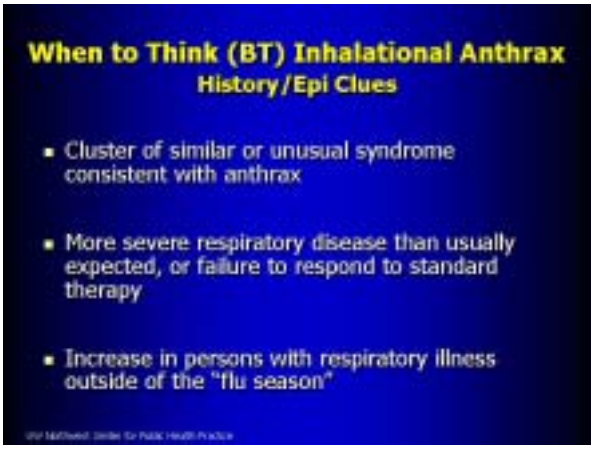


Key Points, Slides 25-31

1. The differential diagnosis for inhalational anthrax includes influenza, other community-acquired respiratory tract illnesses, and pneumonia.
2. Symptoms, signs, and epidemiologic clues can assist the physician in determining the likelihood of anthrax in a patient with flu-like illness.
3. An abnormal chest x-ray or CT scan supports, and positive blood cultures confirm, the diagnosis of inhalational anthrax. Immunohistochemistry and PCR are also potentially useful.
4. There are no clinically useful tests to confirm anthrax exposure in the absence of disease.

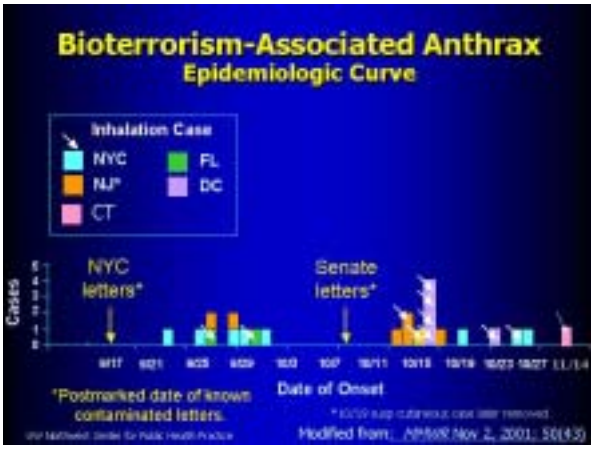
When to Think Inhalational Anthrax? (Slides 25-27)





Slides 25-27 highlight epidemiological and clinical factors that can assist the clinician in determining when to suspect inhalational anthrax and how to prioritize the medical evaluation. Most important in determining if a disease is the result of a bioterrorist incident are epidemiologic clues (covered in session 1) and the patient history. A few of these clues applicable to inhalational anthrax are listed in slides 25-26. The presence of these clues may lead the clinician to look for a critical agent (agent of bioterrorism) as a potential source of disease in his/her patient.

Slide 27 shows the epidemiological curve (graph of cases by date of onset and location) for the 2001 bioterrorism-associated anthrax cases. The y-axis indicates the number of cases (cutaneous and inhalational), the x-axis, the date of illness onset for each case (September 17-November 14), the colored blocks denote the location of the cases (New York City, District of Columbia, New Jersey, Florida, Connecticut), and the white arrows denote inhalational anthrax cases.



The curve illustrates several epidemiological clues of a BT incident:

Claims* by a terrorist or aggressor of a release of anthrax (The letters contained a threat of anthrax exposure.)

Illness in persons with a common ventilation system or other exposure (All but two of the cases were postal workers, mail handlers, or sorters or individuals who processed, handled, or received letters containing *B. anthracis* spores.)

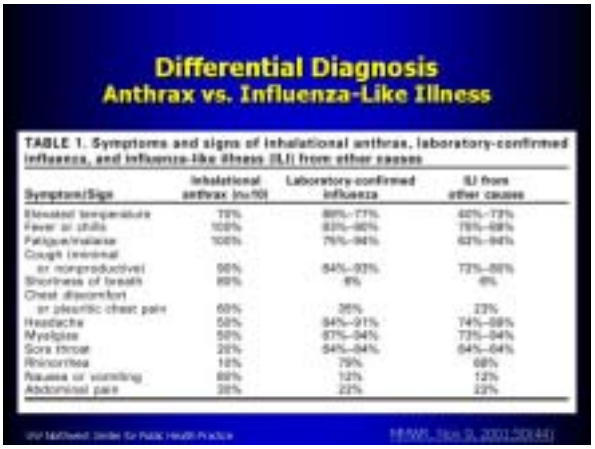
Cluster of cases with a similar or unusual syndrome

Severe disease

Atypical route of transmission (inhalational vs. cutaneous)

*A credible threat, as determined by law enforcement or public health officials

Differential Diagnosis (Slide 28)



The differential diagnosis for inhalational anthrax includes influenza and other influenza-like illnesses and other causes of severe community-acquired pneumonia. Slide 28 compares signs and symptoms of the first 10 inhalational anthrax letter cases with laboratory-confirmed influenza and influenza-like illness (ILI) from other causes [MMWR. November 9, 2001; 50(44)].

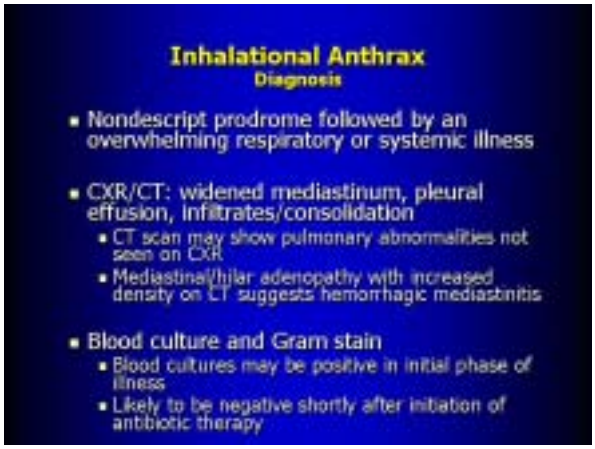
There are no specific clinical signs or symptoms that differentiate inhalational anthrax from influenza-like illness, but some patterns can be observed.

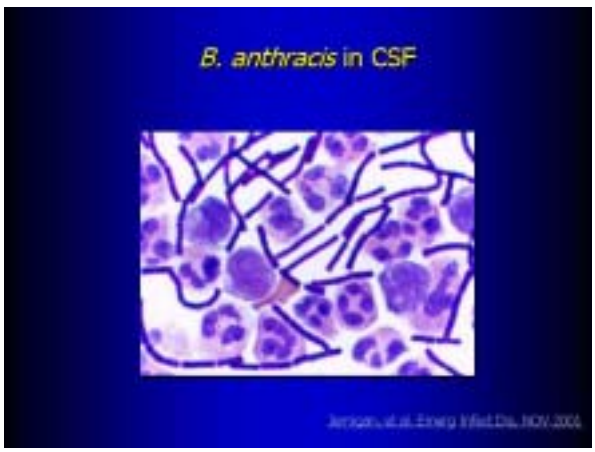
Sore throat and rhinorrhea were relatively uncommon in the 10 inhalational anthrax cases, but are fairly common in ILI from other causes.

On the other hand, nausea/vomiting, shortness of breath, and chest discomfort were fairly common among the inhalational anthrax cases, but are uncommon in ILI due to other causes.

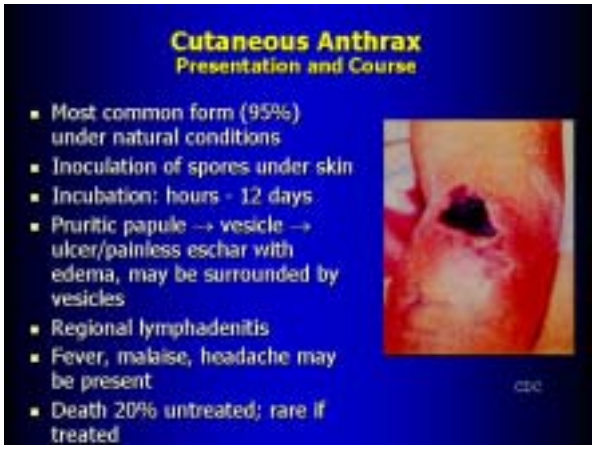
Diagnosis (Slides 29-31)

The diagnostic evaluation of inhalational anthrax is described in slides 29-31. Blood cultures are most useful when obtained before the administration of antibiotics. Cerebrospinal fluid (CSF) culture and gram stain is useful for those with central nervous system symptoms. Nasal swabs are neither sensitive nor specific for anthrax infection and are not useful in clinical case management. They are of limited utility in epidemiologic investigations for defining the extent and patterns of exposure among populations, but do not provide information useful in the clinical management of patients. Slide 31 is a gram stain of CSF illustrating the gram positive bacilli of *B. anthracis*. Confirmatory testing for anthrax should be performed under bio-safety level 2 (BSL-2) conditions (in WA: DOH Public Health Labs or Spokane Regional Health District Lab).

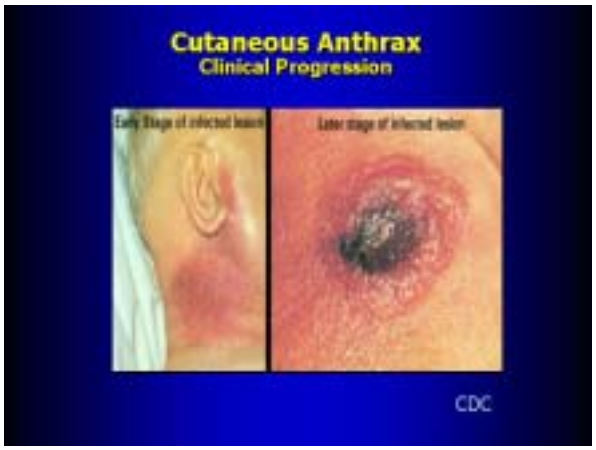




Cutaneous anthrax (Slides 32-40)



Cutaneous anthrax is the most common naturally occurring form of anthrax and may occur in a BT attack (as was seen in the 2001 "anthrax letter" cases). The clinical presentation and diagnosis are detailed in slides 32-40.

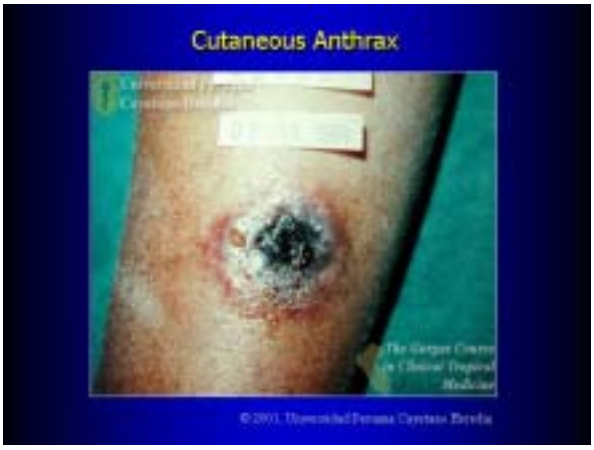


Note the edema surrounding the eschar in slide 33.

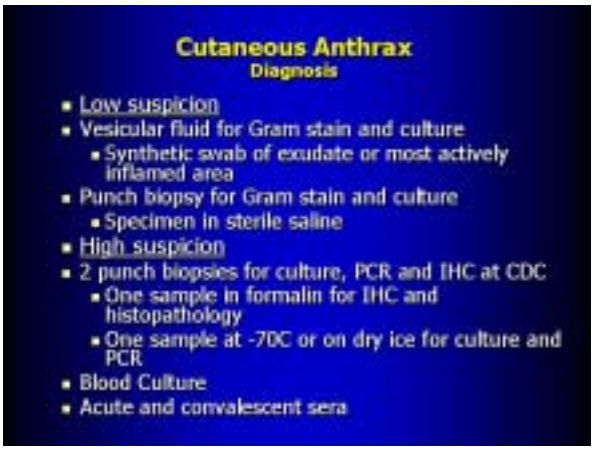
Slide 34 shows four stages of a cutaneous anthrax lesion.

On day 7, there is a depressed black eschar with minimal erythema and swelling. By day 10-12, the eschar is drying, and the edema and erythema have disappeared. The photo in the lower right corner of the slide shows another anthrax lesion on day 15; there is an area of hard necrosis that is beginning to separate from the surrounding tissue.

Slides 35-39 are additional pictures of eschars secondary to anthrax. Slide 37 shows an area of significant necrosis.



Diagnosis of Cutaneous Anthrax (Slide 40)



The diagnosis of cutaneous anthrax is outlined in slide 40. Gram stain and culture of vesicular fluid, with or without punch biopsy, are sufficient for a case with low clinical suspicion for anthrax. If clinical suspicion for anthrax is high, obtain two punch biopsies for culture, PCR and IHC. In addition, draw blood for culture and acute and convalescent (two to four weeks after onset of symptoms) sera. Coordinate specimen collection, packaging, and transport with the public health authorities.

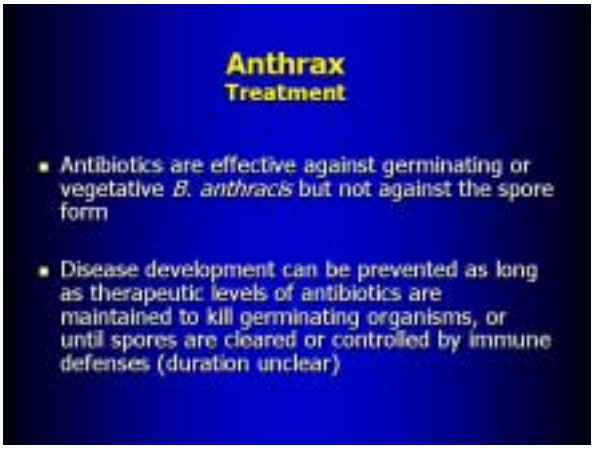
Anthrax Treatment and Prophylaxis (Slides 41-50)

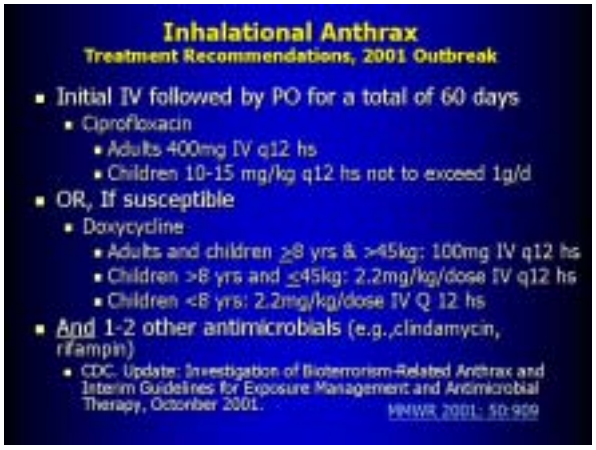
Key Points

1. Ciprofloxacin or doxycycline (if susceptible), plus one to two other antibiotics is the currently recommended initial empiric treatment for bioterrorism-produced anthrax.
2. Treatment can be adjusted after antibiotic susceptibility results are known.
3. Antibiotic treatment and prophylaxis for anthrax should be continued for at least 60 days to prevent the development of disease from germinating spores.
4. Inhalational anthrax is not transmitted person to person, and thus only standard precautions are necessary.

Treatment

Treatment of inhalational and cutaneous anthrax is outlined in slides 41-44. The clinician should be aware of current recommendations and advisories from CDC and state and local public health agencies (http://www.bt.cdc.gov).

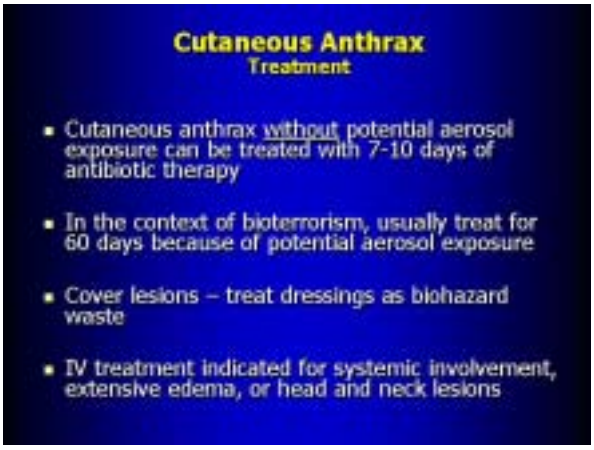




Engineered resistance to more common antibiotics is possible in agents used for bioterrorism purposes, hence the Civilian Working Group on Biodefense has recommended the use of ciprofloxacin as first-line for treatment or prophylaxis of anthrax in a BT attack. Combination therapy is recommended for treatment of inhalational anthrax. It is recommended that under routine circumstances, children under age 16-18 not receive ciprofloxacin and those under age 9 not receive doxycycline, due to the risk of adverse effects associated with use of these antibiotics. There are also concerns with using these antibiotics in pregnant women. Treatment recommendations for antibiotic use in the context of a bioterrorist attack may differ from FDA-approved indications. In the setting of a bioterrorist attack, ciprofloxacin and doxycycline have been recommended for use in both children and pregnant women by expert advisory groups. Isolation of inhalational anthrax cases is not necessary, due to the lack of person-person transmission.

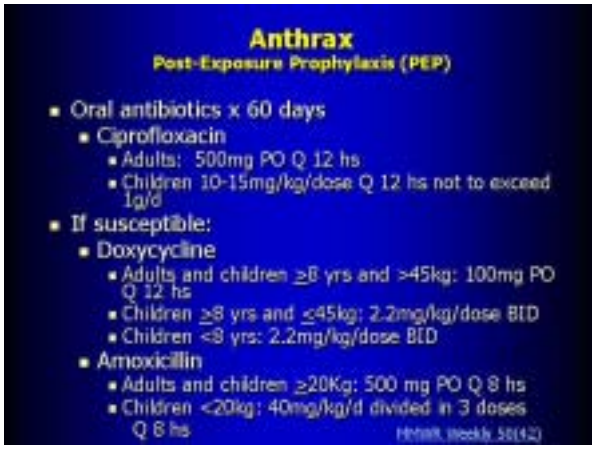
There is a theoretical possibility of transmission of infection from cutaneous anthrax lesions, therefore covering the area with a dressing that is then disposed of as biohazard waste is recommended.

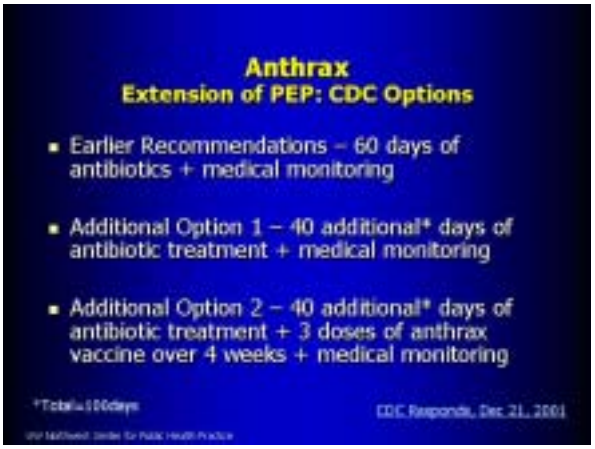
A shorter course of antibiotic therapy (7-10 days) can be given in cases of naturally occurring cutaneous anthrax without potential aerosol exposure. In the context of bioterrorism, however, an unrecognized aerosol exposure is possible, and thus treatment is recommended for the entire 60 days. Intravenous antibiotics are indicated for more extensive disease, head and neck lesions, and symptoms and signs of systemic infection.



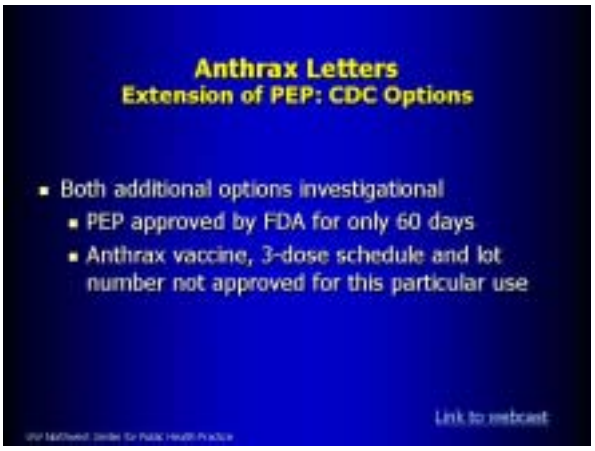
Post-Exposure Prophylaxis

Post-exposure prophylaxis (PEP) is outlined in slides 45-48. The Civilian Working Group on Biodefense has recommended the use of ciprofloxacin as first-line for treatment or prophylaxis of anthrax in a BT attack. Doxycycline or amoxicillin are potential alternative antibiotics for prophylaxis if the infecting strain of *B. anthracis* is susceptible. Antibiotic prophylaxis should be continued for at least 60 days. Animal studies have demonstrated viable spores in mediastinal lymph nodes as far out as 100 days post-exposure.



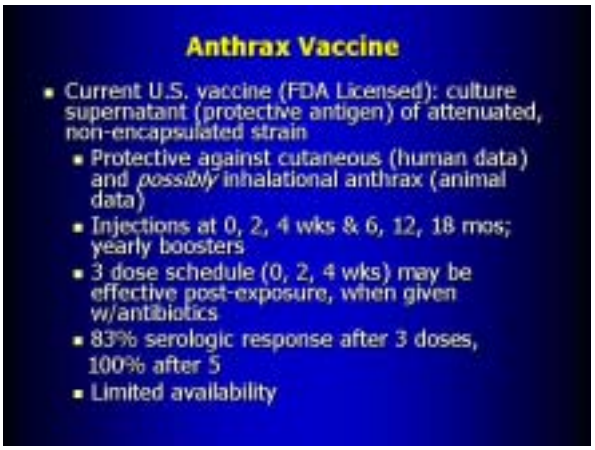


The limited data available to assess the magnitude of risk beyond 60 days, led CDC to offer an additional 40 days of PEP to those exposed during the 2001 anthrax outbreak.

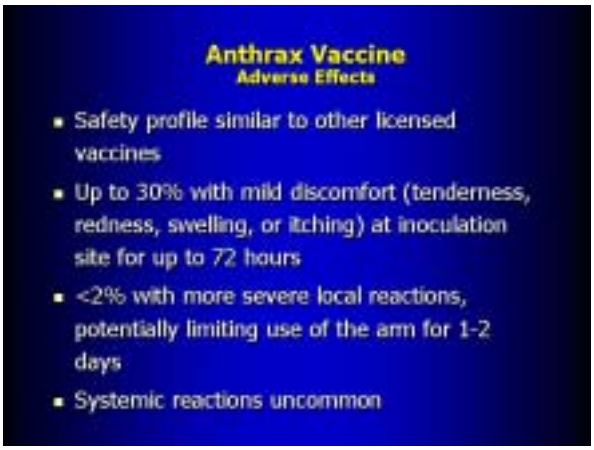


The CDC program for use of the anthrax vaccine as additional prophylaxis in individuals exposed during the 2001 outbreak is outlined in slides 19-21. Both of the additional options are considered investigational.

Anthrax Vaccine (Slides 49-50)

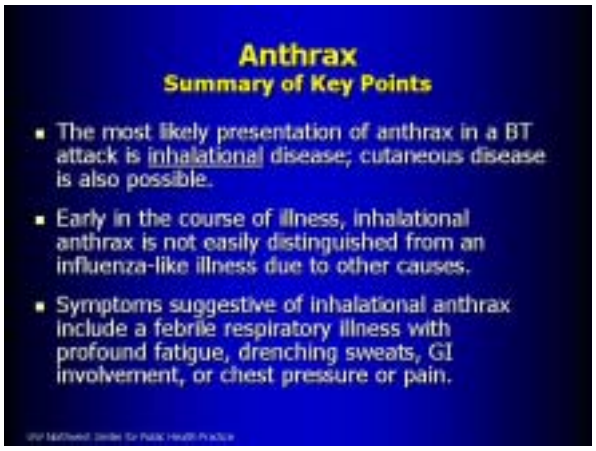


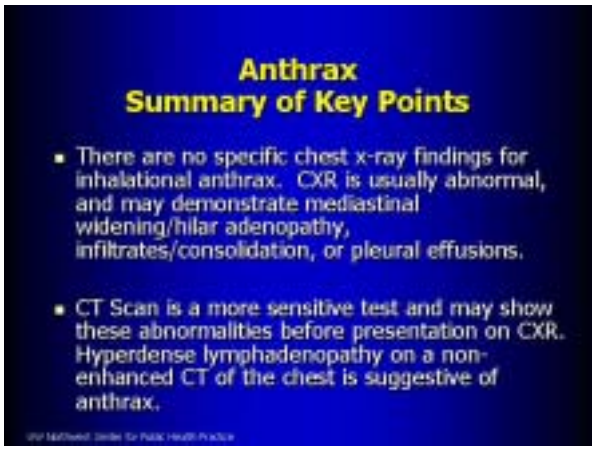
An anthrax vaccine is available through CDC under investigational new drug protocol (although in limited supply) for the post-exposure prophylaxis of persons exposed to anthrax in the setting of a biological attack. The vaccine is routinely recommended for persons processing *B. anthracis* cultures or other workers engaged in activities with high potential for *B. anthracis* aerosol production. The human vaccine is created from a cell-free filtrate of *B. anthracis* culture and is different from the live-virus animal vaccine, not considered sufficiently safe for humans.



Side effects of the vaccine are usually mild and self-limited. The anthrax vaccine was suggested as a possible cause of illness in Persian Gulf War veterans, but a CDC evaluation did not find a specific association between anthrax vaccination and self-reported illness. An Institute of Medicine Report (*Gulf War and Health: Volume 1. Depleted Uranium, Pyridostigmine Bromide, Sarin, and Vaccines*, 2000) concluded that there is "inadequate/insufficient evidence to determine whether an association does or does not exist between anthrax vaccination and long-term adverse health effects."

Summary of Key Points

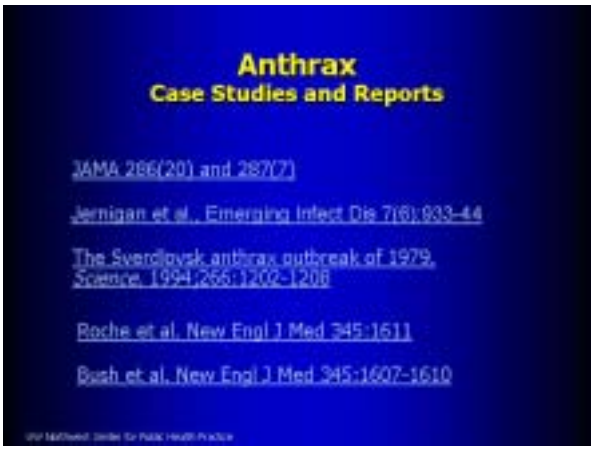




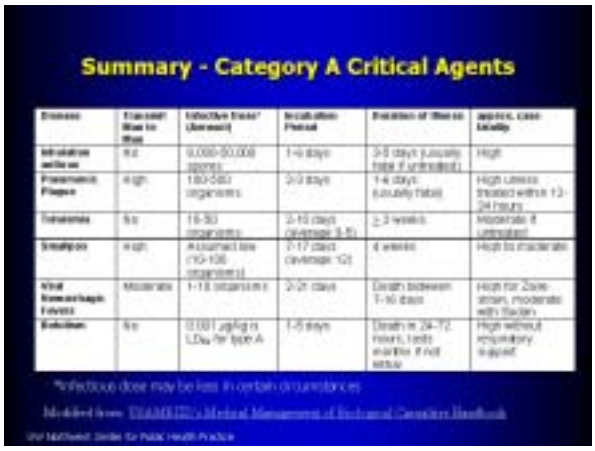
Slides 51-53 summarize the key points in this module.

Case Studies & Reports

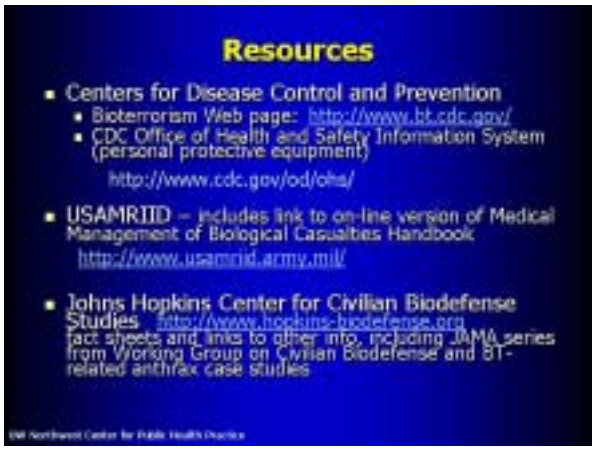
This slide contains links to case studies and reports on anthrax.

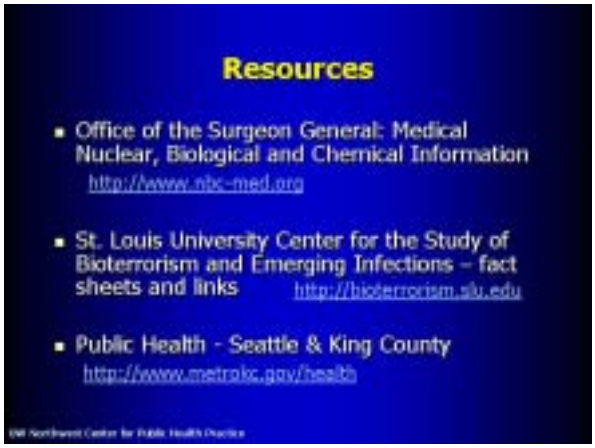


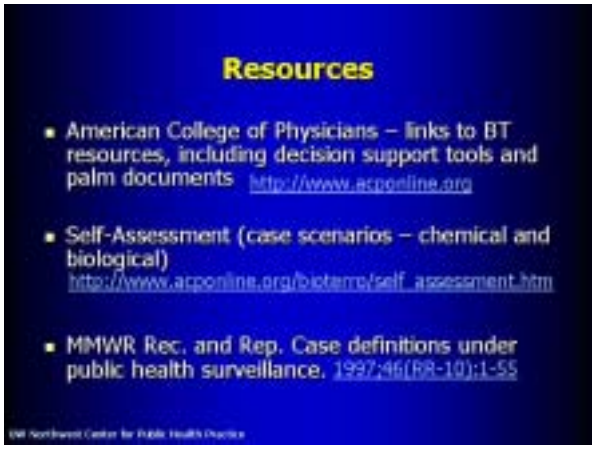
Summary: Category A Critical Agents



Resources


Resources
Centers for Disease Control and Prevention
Bioterrorism Web page: http://www.bt.cdc.gov/
CDC Office of Health and Safety Information System (personal protective equipment)
http://www.cdc.gov/od/ohs/
USAMRIID – includes link to on-line version of Medical Management of Biological Casualties Handbook
http://www.usamriid.army.mil/
Johns Hopkins Center for Civilian Biodefense Studies http://www.hopkins-biodefense.org
fact sheets and links to other info, including JAMA series from Working Group on Civilian Biodefense and BT-related anthrax case studies


Resources
Office of the Surgeon General: Medical Nuclear, Biological and Chemical Information
http://www.nbc-med.org
St. Louis University Center for the Study of Bioterrorism and Emerging Infections – fact sheets and links http://bioterrorism.slu.edu
Public Health - Seattle & King County
http://www.metrokc.gov/health


Resources
American College of Physicians – links to BT resources, including decision support tools and palm documents http://www.acponline.org
Self-Assessment (case scenarios – chemical and biological)
http://www.acponline.org/bioterro/self_assessment.htm
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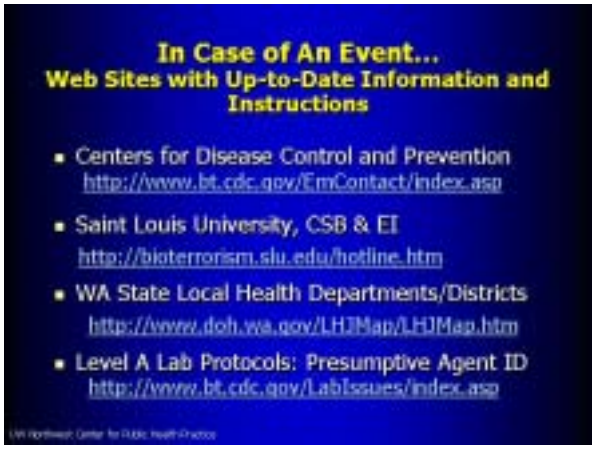
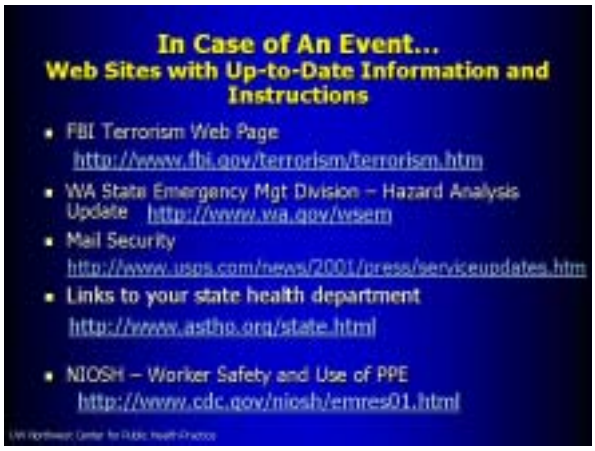
In Case of An Event…





The next two slides highlight Web-based resources valuable to clinicians during a BT event. Most of the links have been presented previously in the resources following the different sections of this curriculum. They are included here again because they contain answers to questions clinicians may have during the course of an event – updates on disease investigations and threats, current testing, treatment and prophylaxis recommendations, and contact numbers for additional information and reporting.

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