In the name of **God**

ANTHRAX AS AN AGENT OF BIOTERRORISM

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- When bioterrorism became a reality in the autumn of 2001, worldwide interest became focused on *B. anthracis,* With a few grams of anthrax spores dispersed in letters, the recognition of the threat of bioterrorism prompted a dramatic increase in research, training, public health preparedness, countermeasures.

- Anthrax remains the agent of greatest concern for future use as a bioterrorist's weapon. With naturally occurring cases not uncommon in much of the world, *B. anthracis* is readily accessible to terrorists; easy to grow in even a rudimentary laboratory; and, in the spore form, stable, easily stored, and portable in small quantities that can wreak havoc when dispersed.

History of *Bacillus anthracis* as a Bioterrorist Agent

- The history of anthrax being spread intentionally to infect others is relatively recent (compared with plague and smallpox), extending only as far back as World War I, when Germans were reported to have
  shipped infected horses and cattle with *B. anthracis* to be used by the Allies.
- During World War II, both the Axis and the Allies had biological warfare programs that involved anthrax.

- The Soviet Union maintained an active anthrax program well into the 1990s. The widely studied accidental release of anthrax spores in 1979 from a Soviet military microbiology facility in Sverdlovsk, Russia, was responsible for approximately 70 human cases of inhalational anthrax. It remains the largest outbreak of inhalational anthrax known.

- During the reign of Saddam Hussein, Iraq was known to have an active biological warfare program. At the close of the first Gulf War, Iraqi authorities admitted to having produced anthrax and placed into munitions but denied ever having used them.

- Far more widely known is the use of the US Postal Service in 2001 to mail anthrax spore–laden letters, after which 22 people developed anthrax, 11 with inhalational infections and 11 with cutaneous infections. There were five deaths among the inhalational cases.

Dissemination of Anthrax as a Bioterrorist Agent

- History has already presented a number of methods in which anthrax can be weaponized. Anthrax has proven itself to be a versatile agent for a terrorist to use. Spores can be dispersed or sprayed as a powder or liquid, or animals can be infected and released with the intent to spread infection among others. Anthrax can be delivered by an aerosol in bombs, sprayed from a plane, or sent in the mail.

- It is generally believed that an intentional release of anthrax would most likely be associated with aerosols and subsequent inhalational infections.
- Determinations of the number of inhaled spores per hour raise questions about the infective dose (ID) and lethal dose (LD) of anthrax
  spores. Obviously, controlled studies cannot be performed on humans; therefore we must rely on extrapolation of data from estimates of known inhalational cases and from studies in nonhuman primates

- the LD_{50} for humans is generally considered to range from approximately 4000 to 55,000 spores based on studies in nonhuman primates.
- Data from nonhuman primates suggest that inhaled doses of 1000 to 5500 spores results in mortalities from 10% to 25%.

Outbreak Characteristics After Use of Anthrax as a Bioterrorist Agent

- spores could be introduced into food supplies or water, the cutaneous, oropharyngeal, and gastrointestinal disease that would result is far less fatal than inhalational anthrax.
- Knowledge of the number of spores needed to infect humans via ingestion is not available.
- It is generally understood that significantly more are needed than via inhalation, and experiments in nonhuman primates suggest it is very difficult to deliberately cause infection by the oral route

- An aerosol release, whether from an envelope, a sprayer on the ground, or on a larger scale from a plane, is considered the most likely
terrorist scenario.
- particles larger than 5 µm typically cannot reach the terminal bronchioles and alveoli; they are captured in the respiratory tract mucus, removed by the mucociliary elevator to the mouth, and swallowed

- This is likely why inhalational anthrax has been uncommon in natural settings but was more common in factories where wool, hair, or hides were dried and manipulated by machinery, resulting in particle sizes of 1 to 5 µm.
- It can be assumed that a sophisticated terrorist using anthrax spores would consider the following:
  1. Engineering of spores a Enhancement of stability and infectivity

- 2. Use of high concentrations of spores to overcome any degree of innate immunity
  3. Selection of a strain demonstrating antimicrobial resistance
  4. Genetic modifications to decrease protection from vaccination or increase toxin production
- The incubation period in natural inhalational anthrax is generally considered to be 2 to 10 days, but with large inocula it may be as short as 1 day.

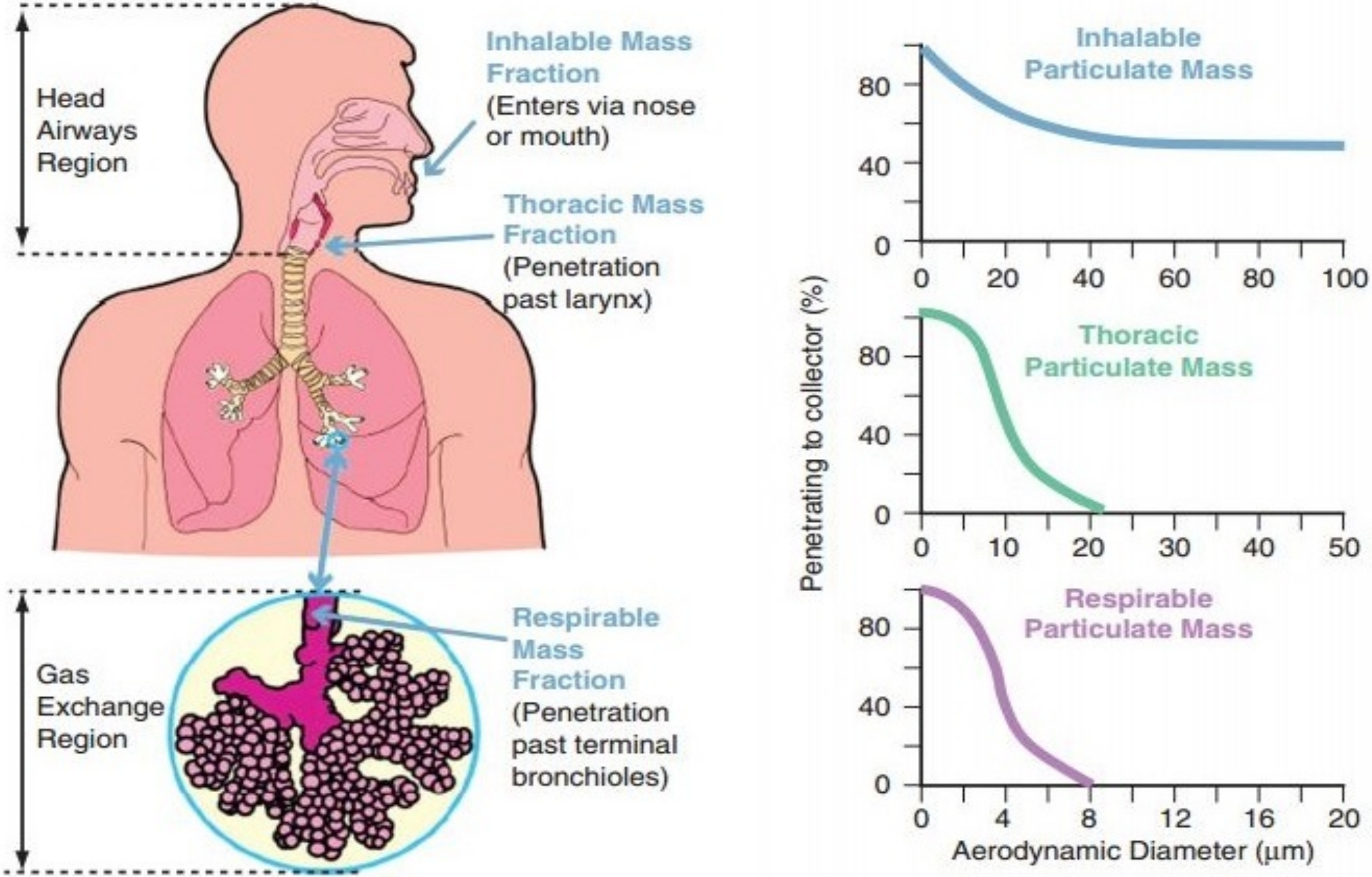


FIG. 207.9 Deposition of anthrax spores in the human respiratory tract depends on the size of spore aggregates. Indiv

- In a series of 58 nonhuman primates, noticed the time to death after exposure to spores varied from 2 to 9 days. However, there are reports of three infected and untreated animals with possible times to death of 20, 28, and 98 days after exposure.
- it is likely that the first evidence of anthrax bioterrorism, as in 2001, will be a critically ill patient discovered to have *B. anthracis* in a blood culture.

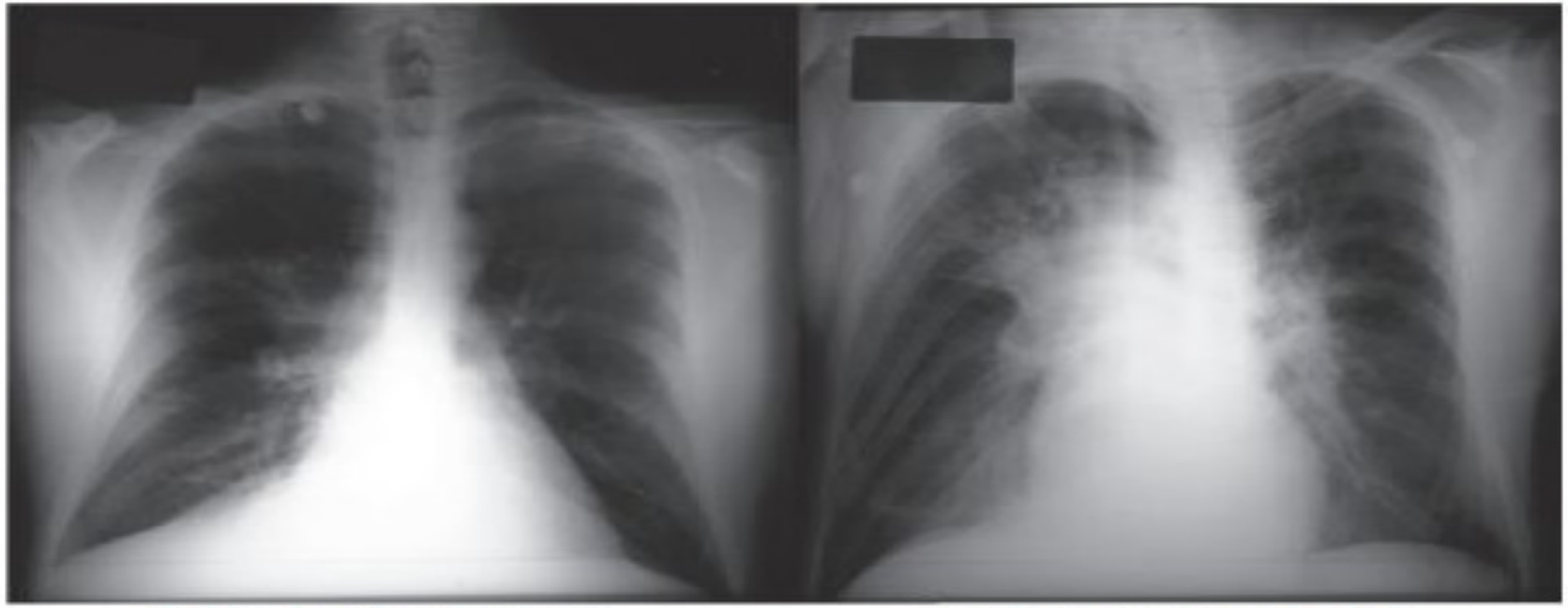
- it can be expected that some patients will present with cutaneous disease (because aerosolized spores deposited on the body can be introduced into the skin) or gastrointestinal disease and others will present with inhalational disease or meningitis.

- The early symptoms of inhalational anthrax are nonspecific and similar to those of influenza. It is important to rapidly determine who has inhalational anthrax, influenza or influenza-like illness, or community acquired pneumonia so that appropriate therapy can be initiated.
- patients who had inhalational anthrax were more likely to have tachycardia, high hematocrit, low albumin, and low sodium levels and were less likely to have myalgia, headache, sore throat, and nasal symptoms.

- Compared with patients who had community-acquired pneumonia, patients with inhalational anthrax were more likely to have nausea or vomiting, tachycardia, high aminotransferase levels, low sodium levels, and normal white blood cell counts
- Patients with fever and spore exposure should also have blood cultures obtained; all seven patients with inhalational anthrax in 2001 who were not taking antibiotics had positive blood cultures.

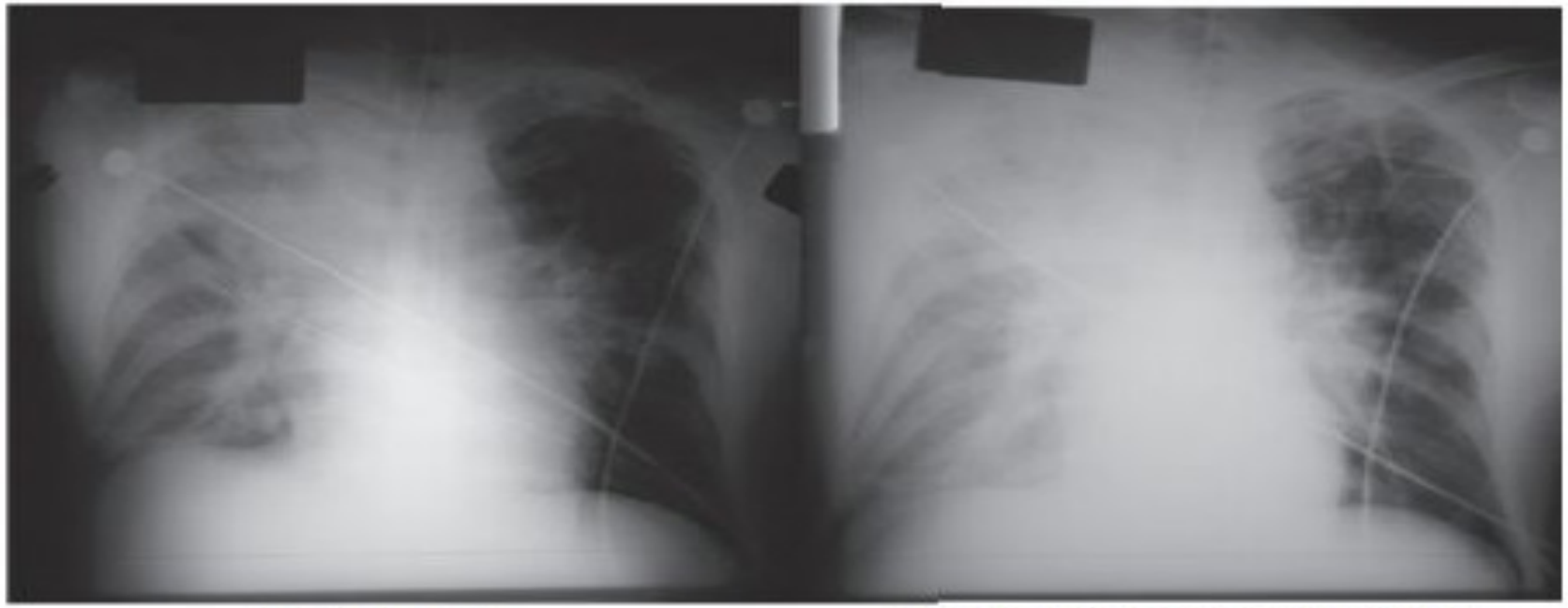
- the most accurate predictor of anthrax was a chest radiograph demonstrating mediastinal widening or pleural effusion.
- This is consistent with our ideas of pathogenesis in that the lymph nodes draining the site where the spores are introduced are those anticipated to become infected and enlarged.

- Thus mediastinal widening on a radiograph should alert the physician to suspect inhalational anthrax from an aerosol exposure and a bioterrorist event until proved otherwise.



10/21/01 0300 (intital ER visit)

10/22/01 0530 (hospital admit)



10/22/01 0900

10/22/01 1100 (shortly before death)

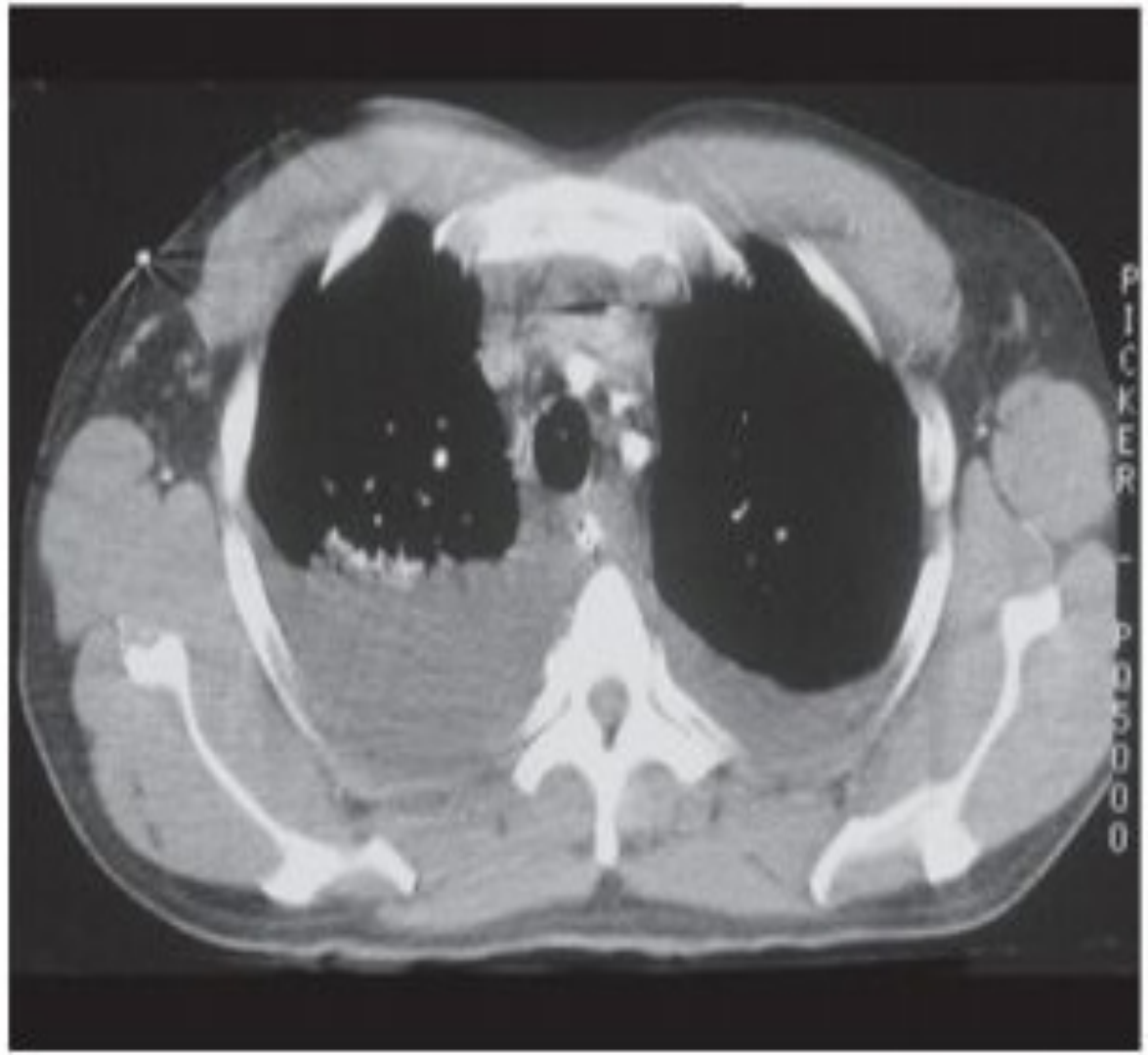


FIG. 207.7 Chest radiographs and computed tomography (CT) scan from a 47-year-old postal worker who had been ill for 5 days when he presented to the hospital with inhalational anthrax. Note progressive bilateral perihilar and infrahilar infiltrates, widened mediastinum, and rapid evolution. CT scan demonstrates mediastinitis and large right and smaller left pleural effusions. *ER,* Emergency room (department). *(Modified from Borio L, Frank D, Mani V, et al. Death due to bioterrorism-related inhalational anthrax. JAMA. 2001;286:2554–2559.)*

Diagnostics

- It is important to notify the laboratory that anthrax is in the differential diagnosis because the typical clinical laboratory may discard gram positive rods as probable contaminants.
- Recently developed, more specific PCR assays have become available that should aid in rapid diagnosis and minimize the number of false-positive samples

- The role of nasal swabs in the “diagnosis” of anthrax must also be clarified. In the 2001 outbreak, patients considered nasal swabs as a determination of whether they had been exposed or not. The reality is that although a positive nasal culture for anthrax clearly indicates an exposure, a negative culture does not rule out an exposure.

- Nasal swabs essentially use the nose to sample whether the individual has filtered anthrax spores in the recently (nasally) inhaled air. They are therefore helpful as a public health tool in determining the zone of exposure.
- Demonstrating that one individual in a space has a positive nasal swab requires that everyone in that space receive PEP regardless of negative nasal swabs for the others.

- The optimal timing of obtaining nasal swabs after exposure has not been determined, but clearly the sooner the better, and it is likely that the yield 24 hours later is much lower. Thus obtaining nasal swabs more than 24 hours after exposure should be discouraged.

- In evaluation of future exposures, efforts to determine if an individual was exposed might also include culturing pharyngeal washings because a study of wool mill workers revealed that addition of such cultures doubled the number of individuals with positive cultures compared with culturing only nasal swabs.

- Gram stain of cutaneous or oral lesions, pleural fluid, CSF, or even buffy coats of blood may be positive for gram-positive rods indicative of anthrax, and culture will confirm the diagnosis. Nasal swab, pharyngeal washes, and stool samples should be cultured for anthrax, but Gram staining of these samples is not helpful.

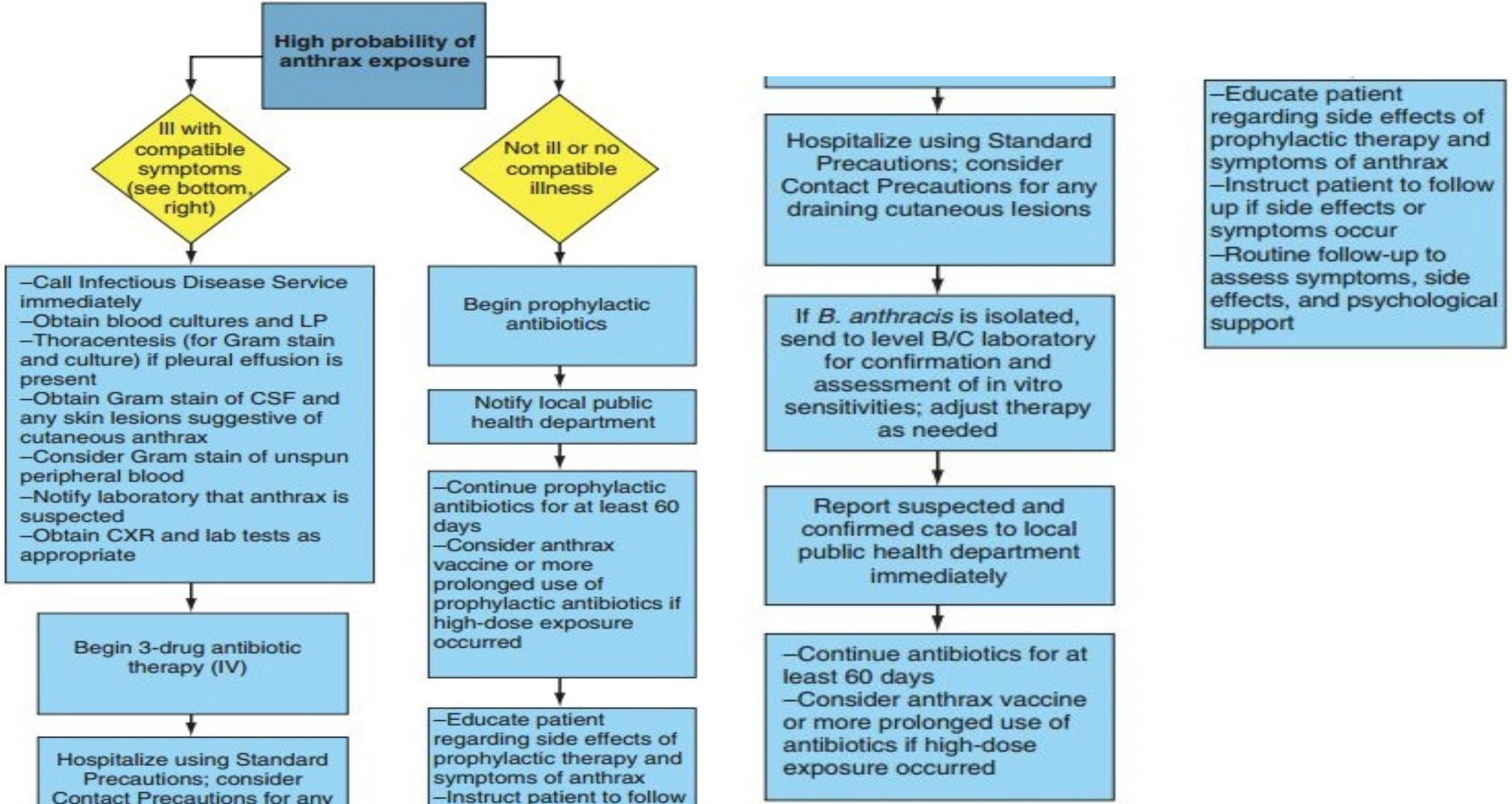
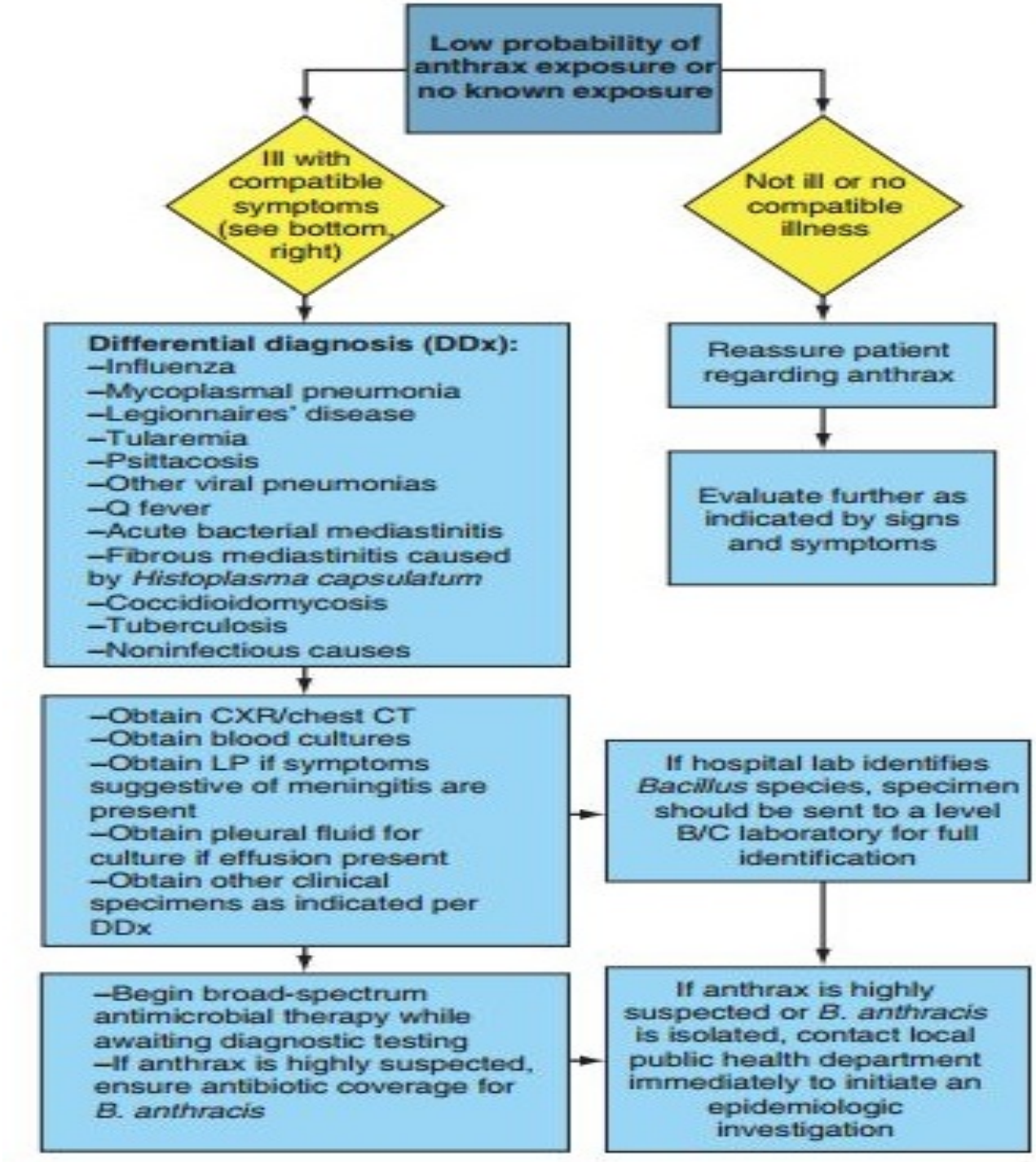


FIG. 207.10 **Clinical pathway: anthrax inhalational exposure.** ©


Low probability of anthrax exposure or no known exposure
Ill with compatible symptoms (see bottom, right)
Not ill or no compatible illness
Differential diagnosis (DDx):
–Influenza
–Mycoplasmal pneumonia
–Legionnaires' disease
–Tularemia
–Psittacosis
–Other viral pneumonias
–Q fever
–Acute bacterial mediastinitis
–Fibrous mediastinitis caused by Histoplasma capsulatum
–Coccidioidomycosis
–Tuberculosis
–Noninfectious causes
Reassure patient regarding anthrax
Evaluate further as indicated by signs and symptoms
–Obtain CXR/chest CT
–Obtain blood cultures
–Obtain LP if symptoms suggestive of meningitis are present
–Obtain pleural fluid for culture if effusion present
–Obtain other clinical specimens as indicated per DDx
If hospital lab identifies Bacillus species, specimen should be sent to a level B/C laboratory for full identification
–Begin broad-spectrum antimicrobial therapy while awaiting diagnostic testing
–If anthrax is highly suspected, ensure antibiotic coverage for B. anthracis
If anthrax is highly suspected or B. anthracis is isolated, contact local public health department immediately to initiate an epidemiologic investigation

Inhalational Anthrax

Early-phase symptoms:
Fever or chills
Fatigue
Malaise
Minimal or nonproductive cough
Dyspnea
Profound sweating
Nausea, vomiting
Rhinorrhea usually not present
Pleuritic pain

Late-phase symptoms:
Fever
Severe respiratory distress
Symptoms of meningitis
Shock

Laboratory findings:
CXR shows widened mediastinum, pleural effusion, or infiltrates (effusions are hemorrhagic)
WBC high or normal with left shift
SGOT or SGPT may be elevated
Hypoxemia (alveolar-arterial O_2 gradient >30 mm Hg on room air, O_2 sat <94%)

CT findings:
Hilar and mediastinal lymph node enlargement and pleural effusions
Paucity of parenchymal infiltrates

- In the 2001 outbreak, there were no serologic tests readily available for anthrax. In the aftermath, numerous serologic assays have been in development and a number of rapid ELISAs that measure total antibody have been approved by the FDA. These assays can be used on serum to diagnose all types of anthrax or demonstrate seroconversion after immunization.

- Retrospectively, it was positive in 100% of both cutaneous and inhalation cases from 2001. However, it becomes positive only after approximately 1 week of symptoms.

Antibiotics

- Current recommendations for PEP have been repeatedly updated and are for initiation of 60 days of antibiotic prophylaxis with appropriate drugs and use of anthrax vaccine.
- Initiation of antibiotics as soon as possible after (or before) exposure. Ungerminated spores, sequestered in the lung or macrophages, do not appear to be affected by antibiotics, which are active only on germinated spores or vegetative bacilli.

- The question of how long antibiotics should be maintained remains unanswered. A competing-risks model to determine the optimal duration of PEP suggests that this is dependent on the size of the inhaled inoculum, with small exposures requiring shorter courses and large exposures requiring courses of 4 months or more.

TABLE 207.7 Centers for Disease Control and Prevention Recommendations for Postexposure Prophylaxis After Exposure to *Bacillus Anthracis* Spores

Recommended Initial Antibiotic

Ciprofloxacin 500 mg orally bid[b]
or
Doxycycline 100 mg orally bid[b]
or
Levofloxacin 750 mg orally once daily
or
Moxifloxacin 400 mg orally once daily
or
Clindamycin 600 mg orally q8h

Alternatives: Penicillin-Sensitive Strains

Amoxicillin 1 g orally q8h
or
Penicillin VK 500 mg orally q6h

[a]Duration 60 days (or with anthrax vaccine administered continue for 14 days after third dose of vaccine).
[b]Ciprofloxacin and doxycycline are considered equal preferred initial agents.[42]

Vaccines

- Current CDC guidelines are for 60 days of PEP with either doxycycline or ciprofloxacin and initiation of postexposure anthrax immunization
- The recommendation to add postexposure anthrax immunization to antibiotic PEP is due to the concern that retained spores may still be present at the end of 60 days and could germinate and lead to inhalational anthrax after discontinuance of antibiotics

- By initiating anthrax immunization, antibodies develop while the individual is protected by antibiotics. After the 60-day course of antibiotics is completed, there should be an adequate immune response to immunization to prevent any remaining spores that might germinate from causing anthrax.
- For PEP, AVA given as three doses subcutaneously at 0, 2, and 4 weeks results in excellent antibody responses in nearly 100% of recipients

TABLE 207.8 Comparison of Anthrax Vaccine Adsorbed for Preexposure and Postexposure Use

CLINICAL SETTING	NO. AND ROUTE OF DOSES	SCHEDULE
Preexposure	5, intramuscular	Weeks 0, 4 Months 6, 12, 18
Postexposure	3, subcutaneous	Weeks 0, 2, 4

Infection Control

- Inhalational anthrax is an airspace disease and is usually not associated with sputum production. Furthermore, vegetative anthrax bacteria, in contrast to the spores, are not hardy in the environment.
- Anthrax-infected patients may be managed in a standard hospital room with standard universal precautions.

- Cutaneous lesions should be covered and dressings from lesions, chest tube drainage, blood, should be considered potentially infectious and incinerated or autoclaved. Hand washing with soap and water, 2% chlorhexidine, or chlorine-containing towels decreased spores of other *Bacillus* spp.

- Patients’ clothes should be removed and bagged, they should shower, and skin and hair should be washed thoroughly with soap and water. Surfaces they contact (e.g., ambulances, benches) should be wiped down with a solution of 1 : 10 household bleach. PEP antibiotic prophylaxis should be considered for people who have cared for patients before their decontamination.

- One of the least expensive and most commonly available compounds used to destroy anthrax spores is household bleach. Bleach, chlorine dioxide, ethylene oxide, hydrogen peroxide, peroxy acetic acid, methyl bromide, paraformaldehyde, and vaporized hydrogen peroxide all were used to some degree decontamination process.

- Contaminated individuals should be advised to remove clothing and place it in a bag either before entering their home or immediately after entering (to minimize spores coming off clothes into the home). They should shower using soap and water and shampoo their hair. Clothes can be decontaminated by washing in hot water with bleach and machine drying. Dry cleaning will also destroy spores.

Thanks for your attention