Notice: Because of current public health concern, this article is being published early (on November 6, 2001). It will appear in the November 29 issue of the *Journal*.

RECOGNITION AND MANAGEMENT OF ANTHRAX — AN UPDATE

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THE events that began this September, which have been described repeatedly in the media, have heightened awareness of and concern about anthrax. The initial reports documented 12 cases of clinical anthrax. These included two cases of inhalational anthrax (one of them fatal) among employees of a tabloid publishing company in Boca Raton, Florida, and four other cases of inhalational anthrax (two of them fatal) among postal workers in Washington, D.C., and Trenton, New Jersey. The six other confirmed cases of anthrax were of the cutaneous form, including two cases of cutaneous anthrax in New York City in persons who had been in the offices of major broadcasting networks and one case in a postal worker in Trenton. Serologic testing performed by health officials in Boca Raton revealed that five other employees of the tabloid publishing company had antibodies to the anthrax bacillus, although confirmation is needed in the form of rising titers in follow-up samples. There has been widespread concern about the reports that envelopes containing anthrax spores were sent to offices in Washington, D.C., and elsewhere. Newspaper reports indicate that 28 persons in the offices of the U.S. Senate had evidence of anthrax exposure on nasal swabs. (Updated figures on confirmed and suspected cases of anthrax are available on the Centers for Disease Control and Prevention [CDC] Web site, at http://www.bt.cdc.gov.)

BACTERIOLOGY

Bacillus anthracis is a large, gram-positive, aerobic, spore-forming bacillus that measures 1.0 to 1.5 μm by 3.0 to 10.0 μm.[1] Unlike other saprobic bacillus species (*B. subtilis* and *B. cereus*), it is nonmotile, is nonhemolytic on sheep's-blood agar, grows readily at a temperature of 37°C, and forms large colonies with irregularly tapered outgrowths (a "Medusa's head"

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appearance). In vitro it grows as long chains, but in the host it appears as single organisms or chains of two or three bacilli. It forms mucoid colonies and exhibits a prominent capsule when grown on nutrient agar containing 0.7 percent sodium bicarbonate in the presence of 5 to 20 percent carbon dioxide. When nutrients are exhausted, resistant spores are formed that can survive in the soil for decades.[2] Spores do not form in host tissues unless the infected body fluids are exposed to ambient air. *B. anthracis* spores germinate when exposed to a nutrient-rich environment, such as the tissues or blood of an animal or human host.

Although *B. anthracis* is one of the most molecularly monomorphic bacteria that is known, it has been possible to separate all known strains into five categories (providing some clues to their geographic sites of origin) on the basis of variable numbers of tandem repeats in the variable region of the *vrrA* gene.[3]

PATHOGENESIS

The principal virulence factors of *B. anthracis* are encoded on two plasmids — one involved in the synthesis of a polyglutamyl capsule that inhibits phagocytosis of vegetative forms and the other bearing the genes for the synthesis of the exotoxins it secretes.[4] The exotoxins are binary, composed of a B (binding) protein that is necessary for entry into the host cell and an A (enzymatically active) protein. The B component is known as the protective antigen and is common to both toxins. The A component of the edema toxin is the edema factor, a calmodulin-dependent adenylate cyclase that is responsible for the prominent edema at sites of infection, the inhibition of neutrophil function, and the hindrance of the production by monocytes of tumor necrosis factor and interleukin-6.[1] The A component of the second toxin, lethal toxin, is a zinc metalloprotease that inactivates mitogen-activated protein kinase kinase, leading to the inhibition of intracellular signaling. Lethal toxin stimulates the release by macrophages of tumor necrosis factor α and interleukin-1β — a mechanism that appears to contribute to the sudden death from toxic effects that occurs in animals with high degrees of bacteremia (reaching 10^7 to 10^8 bacilli per milliliter of blood, visible on Gram's staining) and terminally high levels of lethal toxin.

Infection is initiated with the introduction of the spore through a break in the skin (cutaneous anthrax) or entry through the mucosa (gastrointestinal anthrax). After ingestion by macrophages at the site of entry, germination to the vegetative form occurs, followed by extracellular multiplication and capsule and toxin production. In rhesus monkeys, the inhalation

of spores (1 to 2 μm in diameter) results in their deposition in alveolar spaces whence surviving spores are transported by lymphatics to mediastinal lymph nodes, where germination occurs up to 60 days later. These observations were the basis for the recommendation that antibiotic prophylaxis for inhalational exposure should be given for 60 days.[5] This is consistent with the data from human exposure after the accidental discharge of anthrax spores at a military biologic-research facility in Sverdlovsk, Russia, in which all the cases occurred within six weeks of the release of spores.[4] The median lethal inhalational dose for humans, extrapolated from data on primates, has been estimated to be 2500 to 55,000 spores.[6]

EPIDEMIOLOGY

B. anthracis has a nearly worldwide distribution, existing in the soil in the form of extremely resistant spores and causing infection in humans and in farm and wild animals who have grazed on contaminated land or ingested contaminated feed. Under natural conditions, humans acquire anthrax infection (usually the cutaneous form) from contact with infected animals or contaminated animal products, such as hides, wool, hair, and ivory tusks. Rarely, gastrointestinal (or oropharyngeal) anthrax has followed the ingestion of poorly cooked infected meat. Cases of inhalational anthrax (also known as woolsorters' disease) have been linked to the large-scale processing of hides and wool in enclosed factory spaces, where aerosolized anthrax spores may be inhaled.

Between 1979 and 1985, in association with war and the interruption of veterinary public health practices, Zimbabwe was the site of the largest outbreak of anthrax, with about 10,000 cases, almost all of which were cutaneous infections. The human epidemic was directly related to a major epizootic in cattle. Several lessons were learned from this outbreak. First, it is important to vaccinate livestock in such endemic areas regularly to control and prevent outbreaks of anthrax in humans. Second, direct contact with infected livestock and meat has a major role in the acquisition of infection, and biting flies may have a minor role. Third, there seems to be little danger of cross-infection of other hospitalized patients or nursing staff. And finally, complications (such as bacteremia, sepsis syndrome, and meningitis) and death can be prevented by treatment with penicillin.

Between 20,000 and 100,000 cases of anthrax have been estimated to occur worldwide annually, but in the United States, the annual incidence was only 127 in the early part of the 20th century, and it subsequently declined to less than 1 case per year — a rate maintained for the past 20 years.[1] Until now, there had not been a case of inhalational anthrax in the United States in more than 20 years. Thus, the recent occurrence of 12 cases of anthrax, 6 involving inhalation and none with the conventional exposure to infected animals or animal products, has spotlighted the current consideration of anthrax as a weapon of bioterrorism.

We were forced to recognize the possibility that anthrax may be used as a biologic weapon in 1979, when at least 66 people in Sverdlovsk died in the largest known epidemic of inhalational anthrax. This epidemic followed the accidental release of anthrax spores into the atmosphere by a research facility involved in "weaponizing" anthrax by preparing finely milled, nonclumping (electrostatically neutral) spores that are optimal for dissemination and inhalation and that produce toxins when they germinate.[1] After the Gulf War, Iraq admitted producing and deploying such weaponized anthrax in missiles, so a clear threat remains.[7]

CLINICAL FEATURES

Inhalational Anthrax

The term inhalational anthrax is preferable to anthrax pneumonia, in view of the pathogenetic sequence involved, the prominence of hemorrhagic thoracic lymphadenitis and mediastinitis, and the absence of typical bronchopneumonia on clinical or postmortem examination. However, in about 25 percent of the fatal cases of inhalational anthrax in Sverdlovsk, there was evidence of a focal, hemorrhagic, necrotizing pulmonic lesion that was reminiscent of a focal Ghon's lesion of primary tuberculosis.

The classic clinical description of inhalational anthrax is that of a biphasic illness.[8] In the initial phase that follows an incubation period of one to six days, it appears as a nonspecific illness characterized by mild fever, malaise, myalgia, nonproductive cough, and some chest or abdominal pain. There are generally no objective findings. The illness progresses to the second phase within two or three days. This phase begins abruptly and involves further fever, acute dyspnea, diaphoresis, and cyanosis. Stridor is present in some patients because of extrinsic obstruction of the trachea by enlarged lymph nodes, mediastinal widening, and subcutaneous edema of the chest and neck. In up to half of patients, obtundation and nuchal rigidity have developed as a result of complicating anthrax meningitis. The second stage of illness is rapidly progressive, with shock, associated hypothermia, and death occurring within 24 to 36 hours; 16 of the 18 cases reported in the United States between 1900 and 1978 were fatal.[8]

Very rarely, the primary lesion of inhalational anthrax has occurred in the nasal mucosa or a nasal accessory sinus. Marked facial edema and a thick, gelatinous nasal discharge have been prominent findings.

Cutaneous Anthrax

More than 95 percent of naturally occurring anthrax is the cutaneous form. The spore is introduced at the site of a cut or abrasion, usually on the arms, face, or

neck. The primary lesion — a painless, pruritic papule — appears one to seven days after the introduction of the endospore. Within one to two days, small vesicles surround the papule, or a vesicle develops that is 1 to 2 cm in diameter and is filled with clear or serosanguineous fluid containing very rare leukocytes and numerous large, gram-positive bacilli. The vesicle enlarges, and satellite vesicles may develop. A striking, nonpitting, gelatinous edema surrounds the lesion. Low-grade fever and malaise are frequent. The vesicle ruptures, undergoes necrosis, and enlarges, forming an ulcer covered by a characteristic black eschar. The edema may become massive, particularly when the lesions are on the face or neck, and occasionally, multiple bullae develop along with marked toxic effects. Incision or débridement of such early lesions should be avoided, since this may increase the possibility of bacteremia. The eschar dries and falls off in one to two weeks with little ultimate scarring. Regional lymphadenopathy is present initially. Secondary infection with streptococci or *Staphylococcus aureus* is uncommon but would be suggested by the recurrence of fever with lymphangitis, local pain, and purulent drainage.

Bacteremia is a rare complication. Without antibiotic treatment, mortality can be as high as 20 percent.

Gastrointestinal Anthrax

The symptoms of gastrointestinal anthrax appear two to five days after the ingestion of undercooked meat containing spores and consist of nausea, vomiting, fever, and abdominal pain. The manifestations progress rapidly to severe, bloody diarrhea and signs suggestive of an acute abdomen. The primary intestinal lesions are ulcerative and occur mainly in the terminal ileum or caecum. Gastric ulcers may be associated with hematemesis. Hemorrhagic mesenteric lymphadenitis is also a feature of gastrointestinal anthrax, and marked ascites may occur. Mortality is greater than 50 percent.

The deposition and germination of spores in the oropharynx can produce oropharyngeal anthrax. The symptoms include a severe sore throat, fever, dysphagia, and sometimes respiratory distress, which is caused by associated marked lymphadenitis and massive edema.[1] Oral or pharyngeal ulcers covered with a pseudomembrane may be seen.

Anthrax Meningitis

Anthrax meningitis may occur as a result of bacteremia after inhalational anthrax and is less common after other forms of anthrax. The cerebrospinal fluid is hemorrhagic in most instances, and there is a polymorphonuclear pleocytosis. Numerous large, encapsulated, gram-positive bacilli are present. Mortality approaches 100 percent, but occasionally, patients treated with antibiotics have survived.[1]

DIAGNOSIS

Differential Diagnosis

In the past, the diagnosis of anthrax was made on the basis of the clinical findings and the history of exposure to animal products from abroad, either in a processing plant or at home. The history of exposure has changed with the recent delivery of anthrax spores through the mail and the concern about biologic warfare involving the airborne delivery of weaponized anthrax spores capable of widespread dissemination.

Other skin lesions that should be considered in the differential diagnosis of cutaneous anthrax include a staphylococcal furuncle or skin infection (usually painful), ecthyma (usually without edema or systemic manifestations), ecthyma gangrenosum (usually in patients with neutropenia and *Pseudomonas aeruginosa* bacteremia), orf (in which gelatinous edema is absent and a scab forms but there is no distinctive large eschar), and the bite of a brown recluse spider (causing pain with incipient necrosis).

Prominent influenza-like symptoms of recent origin in a patient with a widened mediastinum would suggest a diagnosis of anthrax nowadays, particularly if there were more than one such case. However, tularemia may produce similar acute mediastinal lymphadenopathy.

Local or state health departments, hospital epidemiologists, and the local or state health laboratory should be notified promptly when anthrax is suspected. Guidelines are available from the CDC for clinical and laboratory diagnosis, specimen handling, decontamination of equipment, and postexposure prophylaxis.[9]

Laboratory Diagnosis

Presumptive identification in a hospital laboratory is based on the direct Gram's-stained smear of a skin lesion (vesicular fluid or eschar), cerebrospinal fluid, or blood showing encapsulated, broad, gram-positive bacilli. It is also made on the basis of indicators of growth apparent on sheep's-blood–agar cultures — nonhemolytic colonies and large, nonmotile, nonencapsulated, gram-positive, spore-forming rods. Growth does not occur on MacConkey agar.

Confirmatory diagnostic tests are performed at a level B laboratory of the Laboratory Response Network for Bioterrorism (LRN), where the growth of virulent strains on nutrient agar in the presence of 5 percent carbon dioxide (or other basal mediums supplemented with 0.8 percent sodium bicarbonate) produces heavily encapsulated bacilli that may be visualized with India-ink staining. Additional criteria for the confirmation of the presence of *B. anthracis* include susceptibility to lysis by gamma phage or direct fluorescent-antibody staining of cell-wall polysaccharide antigen. Rapid screening assays for use directly on clinical specimens (including nasal swabs) and envi-

ronmental samples are investigative tools for use by LRN-associated state and CDC laboratories; they include nucleic acid signatures and antigen detection (enzyme-linked immunosorbent assay [ELISA] for protective antigen and capsule).

Nasal-swab culture to determine whether there may have been inhalational exposure to *B. anthracis* is an investigative tool and is not known to accurately predict the risk of subsequent clinical illness. Its use should be limited to public health teams at present.

Serologic testing is useful only retrospectively and requires specimens from the acute and convalescent phases of illness for comparison. In cases of cutaneous and oropharyngeal anthrax, antibodies to protective antigen or to capsule develop (in 68 to 92 percent of cases and 67 to 94 percent of cases, respectively).[1] In one study, in which serum samples from 12 patients with cutaneous anthrax were analyzed six weeks after an outbreak, 11 of the 12 patients had a positive titer of antibodies to protective antigen ($\geq$1:128) on electrophoretic immunotransblotting, and 11 of the 12 were positive (at a cutoff of 1:32) for anticapsule antibodies on ELISA.[10] Performing such assays on serum samples obtained from patients with known and suspected cases of anthrax during the acute and convalescent phases would be of value in validating these serologic tests and possibly in confirming the diagnosis in cases in which direct culture has not yielded the organism. Serologic tests of contacts would probably not be of help in making decisions about someone with recent exposure, in view of the fact that a serum sample obtained during the convalescent phase some weeks later would be necessary for serologic diagnosis. However, such tests might be of epidemiologic value for the later diagnosis of possible subclinical cases by public health authorities.

POSTEXPOSURE PROPHYLAXIS

Treatment with antimicrobial drugs is not warranted for asymptomatic persons unless public health or law-enforcement authorities have ascertained that there is an evident risk of exposure to a substance documented to be anthrax. Indeed, the prolonged unnecessary use of antibiotics may be deleterious since it may encourage the selection of resistant strains of commensals.

A long period of prophylaxis is recommended because of the prolonged latency period that may elapse before the germination of spores acquired through inhalational exposure to *B. anthracis*.[5] Because of the threat of a bioterrorist attack and because a strain of *B. anthracis* has been produced overseas that is resistant to multiple antibiotics (penicillin, doxycycline, chloramphenicol, macrolides, and rifampin), ciprofloxacin is the drug of choice for initial therapy (Table 1).[1]

An anthrax vaccine, consisting of a noninfectious, sterile culture filtrate of an attenuated strain of *B. anthracis* adsorbed to an aluminum hydroxide adjuvant, has been given to members of the armed forces of the United States since 1998. The protective component is protective antigen. The vaccine is administered at 0, 2, and 4 weeks and again at 6, 12, and 18 months. Its efficacy has been demonstrated in studies in which it provided complete protection against aerosol challenge in monkeys at 8 weeks and 88 percent protection against similar challenge at 100 weeks.[6] Annual boosters are necessary to maintain immunity. No serious

TABLE 1. RECOMMENDATIONS FOR POSTEXPOSURE PROPHYLAXIS.*

TYPE OF THERAPY	ADULTS (INCLUDING PREGNANT WOMEN AND THE IMMUNOCOMPROMISED)	CHILDREN
Initial therapy	Ciprofloxacin, 500 mg orally every 12 hr or Doxycycline, 100 mg orally twice a day	Ciprofloxacin, 10–15 mg/kg of body weight orally every 12 hr or Doxycycline, 100 mg orally twice a day in children >8 yr old and >45 kg
Optimal therapy if strain has proved susceptible	Amoxicillin, 500 mg orally every 8 hr or Doxycycline, 100 mg orally every 12 hr	Amoxicillin, 500 mg orally every 8 hr in children ≥20 kg; 40 mg/kg orally, divided into 3 doses (every 8 hr), in children <20 kg

*Adapted from Inglesby et al.[6] and the CDC guidelines.[9] Although fluoroquinolones (including ciprofloxacin) are not recommended for use during pregnancy, because of an association with arthropathy in young animals and children, the possible risk of engineered antibiotic-resistant strains warrants the initial use of ciprofloxacin in exposed pregnant women. Although tetracyclines (including doxycycline) have been associated with hepatotoxicity in pregnant women and adverse effects on the developing teeth and bones of fetuses, the initial use of doxycycline is recommended in view of the potential for life-threatening illness when the use of penicillin and ciprofloxacin is precluded by the results of antimicrobial-susceptibility testing, drug allergy, or the exhaustion of drug supplies. The use of tetracyclines and fluoroquinolones in children has adverse effects, and these must be weighed carefully against the risk of life-threatening anthrax infection. The total duration of treatment (initial therapy plus subsequent optimal therapy) should be 60 days.

adverse events related to its use have been reported.[6] Vaccine supplies are extremely limited, however, and at present the vaccine is not recommended for use by health care workers or the public. In primates, optimal postexposure prophylaxis has been provided by the combination of antibiotic therapy and immunization.[5] Should the vaccine become widely available, it has been proposed that its use at 0, 2, and 4 weeks might shorten the period of postexposure antimicrobial therapy to 30 to 45 days.[1]

ANTIMICROBIAL THERAPY

Penicillin has been the drug of choice for anthrax for many decades, and only very rarely has penicillin resistance been found in naturally occurring isolates. In vitro, *B. anthracis* is also susceptible to most other commonly used antimicrobial drugs, such as ciprofloxacin, ofloxacin, levofloxacin, tetracyclines, chloramphenicol, macrolides, aminoglycosides, clindamycin, imipenem, rifampin, vancomycin, cefazolin, and other first-generation cephalosporins. It is resistant to cefuroxime, extended-spectrum cephalosporins such as cefotaxime and ceftazidime, aztreonam, trimethoprim, and sulfamethoxazole.

Clinically Evident Inhalational Anthrax

The recommended initial therapy for adults with clinically evident inhalational anthrax is 400 mg of ciprofloxacin given intravenously every 12 hours (Table 2). The use of dual initial therapy (ciprofloxacin plus penicillin) may be considered, in view of the frequent and rapid development of complicating meningitis and the clinical experience of cerebrospinal-fluid penetration with high-dose intravenous penicillin. More complete recommendations for special groups, such as pregnant women, immunosuppressed patients, and children, are available elsewhere.[6]

Cutaneous Anthrax

For mild cases of cutaneous anthrax in adults, oral treatment with ciprofloxacin (500 mg every 12 hours) is recommended. If the strain is susceptible, oral doxycycline (100 mg every 12 hours) or amoxicillin (500 mg every 8 hours) is a suitable alternative.[6] Treatment should continue for 60 days in the context of bioterrorism, as opposed to 7 to 10 days for naturally acquired disease. Severe cutaneous anthrax is treated with the same drugs and dosages as inhalational anthrax.

HOSPITAL INFECTION CONTROL AND DECONTAMINATION

Since there are no data indicating the occurrence of person-to-person transmission even in the case of patients with inhalational anthrax, patients with anthrax may be hospitalized in a standard hospital room with standard precautions. Contact precautions should be used with patients who have draining cutaneous lesions. Dressings containing drainage should be considered to be hazardous waste and should be incinerated or autoclaved.

The state public health laboratory should be notified immediately of any suspected isolate of *B. anthracis*. Consultation with the state public health laboratory is necessary regarding any suspected *B. anthracis* isolate, and the communicable-disease epidemiology service of the state department of health may have to establish communication with the local field office of the Federal Bureau of Investigation, which may need to become involved.

For the decontamination of contaminated areas,

TABLE 2. RECOMMENDATIONS FOR ANTIMICROBIAL THERAPY OF CLINICAL INHALATIONAL ANTHRAX.*

TYPE OF THERAPY	ADULTS (INCLUDING PREGNANT WOMEN AND THE IMMUNOCOMPROMISED)	CHILDREN
Initial therapy	Ciprofloxacin, 400 mg IV every 12 hr†	Ciprofloxacin, 20–30 mg/kg of body weight per day IV, divided into 2 daily doses
Optimal therapy if strain has proved susceptible	Penicillin G, 4 million U IV every 4 hr or Doxycycline, 100 mg IV every 12 hr	Ciprofloxacin, 20–30 mg/kg per day IV, divided into 2 daily doses or Penicillin G, 50,000 U/kg IV every 6 hr in children <12 yr old; 4 million U IV every 4 hr in children ≥12 yr old

*Adapted from Inglesby et al.[6] Oral antimicrobial therapy may be substituted for intravenous (IV) therapy when clinical status has improved. Doxycycline can also be used in children when the use of ciprofloxacin and penicillin is precluded by the results of susceptibility testing, drug hypersensitivity, or the exhaustion of drug supplies. The adult dosage may be used for those weighing more than 45 kg; for those weighing 45 kg or less, the dose should be 2.2 mg per kilogram of body weight given intravenously every 12 hours. The total duration of treatment (initial therapy plus subsequent optimal therapy) should be 60 days.

†As an alternative, ofloxacin, 400 mg given intravenously every 12 hours, or levofloxacin, 500 mg given intravenously every 24 hours, can be used.

sporicidal solutions approved for hospital use should be employed. Commercially available bleach or 0.5 percent hypochlorite solution (a 1:10 dilution of household bleach) may be used, but it may be corrosive to some surfaces. CDC guidelines for state health departments provide further information.[9]

Note added in proof: The most recent (October 26, 2001) CDC recommendations for treatment of inhalational anthrax involve the initial use of either ciprofloxacin or doxycycline plus one or two additional antimicrobial agents with in vitro activity against *B. anthracis*.[11] Because preliminary data have shown the presence of constitutive and inducible beta-lactamases in recent *B. anthracis* isolates from Florida, New York, and Washington D.C., treatment of systemic anthrax with penicillin G, ampicillin, or amoxicillin alone is not recommended.[11]

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