Anthrax

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Anthrax is an often fatal bacterial infection that occurs when *Bacillus anthracis* endospores enter the body through one of three major routes: inhalational, cutaneous, or gastrointestinal [1]. Although the disease most commonly affects herbivores, which become infected after ingesting spores from the soil, humans are at risk of acquiring naturally occurring anthrax from contact with anthrax-infected animals or anthrax-contaminated animal products [2].

Before the anthrax terrorist attacks in the United States in 2001, there was very little interest in anthrax as a serious human pathogen. Anthrax was viewed mainly as a veterinarian problem of minor importance, with most cases attributed to occupational exposure. In fact, before 2001, there were only 18 cases of inhalational anthrax reported this century within the United States, the last of which was reported in 1976 [3]. However, this cavalier attitude toward anthrax changed following the 2001 terrorist attacks. From October 3, 2001 through November 16, 2001 there were 22 confirmed cases of inhalational and cutaneous anthrax in the United States, with 5 deaths [4]. Although the number of cases was relatively small, the attacks of 2001 have heightened concern about the feasibility of large-scale aerosol bioweapons attacks by terrorist groups.

**Historical perspective**

Although *B. anthracis* has caused disease and death in animals and humans for centuries, it is only over the last several decades that research on anthrax as a biologic weapon has commenced. Despite the widespread ratification of and signing of the Biologic Weapons Conference (BWC) in the early 1970s banning offensive bioweapons programs, it is believed that at least 17 nations continue to engage in such weapons programs [5].

The accidental aerosolized release of anthrax spores from a military research facility in Sverdlovsk in the former Soviet Union in 1979 gave us our first
glimpse into the lethal potential of anthrax aerosols, with 79 cases and 68 reported deaths [6]. In 1995, the United Nations Special Commission found Iraq had weaponized anthrax spores into Scud warheads [7].

Fortunately, most experts agree that the manufacture of lethal anthrax aerosol is beyond the capacity of individual groups without access to highly advanced biotechnology [8]. It is believed that for this reason, the terrorist group Aum Shinrikyo, which was responsible for the release of sarin in a Tokyo subway station in 1995, was unsuccessful when it dispersed aerosols of anthrax and botulism throughout Tokyo on at least eight separate occasions.

Nevertheless, a 1993 report by the US Congressional Office of Technology Assessment estimated that there would be more than 3 million casualties following an aerosolized release of 100 kg of properly weaponized anthrax spores upwind of the Washington, DC area [9].

Many, if not most patients, would require some degree of critical care in the form of ventilator or hemodynamic support. It is for this reason that anesthesiologists and other critical care physicians have specific knowledge of the diagnosis, treatment, and prevention of anthrax.

Microbiology

*B. anthracis* is derived from the Greek word for coal, *anthrakis*, because in its cutaneous form it causes black, coal-like lesions. *B. anthracis* is an aerobic, gram-positive, endospore-forming Bacillus species that is encapsulated, nonmotile, and nonhemolytic.

Anthrax endospores do not divide, are metabolically inert, and are resistant to drying, heat, ultraviolet light, gamma radiation, and many disinfectants [10].

Anthrax spores germinate in the blood or tissues of animal or human hosts rich in amino acids, nucleosides, and glucose. The vegetative bacilli, however, have poor survival outside of an animal or human host, and will form spores when local nutrients are exhausted. In some types of soil, anthrax spores can remain dormant for decades [11].

Pathogenesis

*B. anthracis* endospores introduced into the body by abrasion, inhalation, or ingestion are phagocytosed by macrophages and carried to regional lymph nodes. Within hours, most spores germinate into vegetative bacteria that produce various virulence factors. The vegetative bacteria are then released from the macrophages and enter the bloodstream.

Full virulence requires the presence of an antiphagocytic capsule and three toxin components: protective antigen, lethal factor, and edema factor. The three exotoxin components combine to form two binary toxins, edema toxin and lethal toxin, which are responsible for overt symptoms and death.
Edema toxin is a calmodulin-dependent adenylate cyclase that alters water homeostasis causing edema and impairs neutrophil function, rendering the host further susceptible to infection. Lethal toxin leads to the release of reactive oxygen intermediates as well as the production of proinflammatory cytokines tumor necrosis factor and interleukin-1β responsible for rapid circulatory collapse. The release of these toxins results in a histopathologic picture characterized by profuse hemorrhage, tissue edema, and a paucity of acute inflammatory reaction [1].

Clinical manifestations

Inhalational anthrax

Inhalational anthrax follows the deposition of spore-bearing particles into alveolar spaces. For a particle to reach the alveolus, its size cannot be too large or too small. Spores larger than 5 μm in size are deposited in the upper airway (pharynx, larynx, and trachea) and are effectively trapped and cleared by the mucociliary system, whereas small particles (<1 μm) adhere to the mucus of the bronchial wall and never reach the alveolus. Spore-bearing particles of 1 to 5 μm, however, are of optimal size to reach the alveolar spaces [12].

Although the lung is the initial site of contact, inhalational anthrax is not considered a true pneumonia because there is no infection in the lung. Rather, the spores are engulfed by alveolar macrophages and carried to mediastinal and hilar lymph nodes.

Once germination occurs, replicating bacteria produce large amounts of toxin. The regional nodes are overwhelmed, a hemorrhagic mediastinitis ensues, and large amounts of toxin are released into the blood leading to edema, hemorrhage, necrosis, and septic shock [13].

Clinically, inhalational anthrax typically presents as a biphasic illness. The onset of symptoms in the United States attacks occurred between 4 to 6 days post-exposure; by contrast, in Sverlosk, the onset of symptoms was 2 to 43 days, suggesting that the use of antibiotics among high-risk persons exposed may be effective in preventing later infections due to delayed germination [6,14].

Early diagnosis of inhalation anthrax is difficult and requires a high index of suspicion.

The initial symptoms, lasting from hours to days, begin with the insidious onset of flu-like symptoms with fever, chills, sweats, malaise, fatigue, myalgias, headache, and nonproductive cough. Pulmonary complaints are often minimal or absent; however, many patients do have significant gastrointestinal complaints such as nausea and vomiting. Sore throat and rhinorrhea are typically absent. Signs of illness and laboratory findings are often nonspecific, and a chest radiograph may appear only mildly abnormal during the early stages of infection.

The second stage of this illness has been reported to begin abruptly as a fulminating illness characterized by chest discomfort, dyspnea, and stridor resulting from a hemorrhagic, necrotizing mediastinitis. There may be meningial
involvement with subarachnoid hemorrhage in up to 50% of patients. Shock and multiorgan failure ensues with rapid progression to death [15]. Physical findings are nonspecific, and a chest radiograph often reveals mediastinal widening consistent with lymphadenopathy in association with bilateral pleural effusions. These effusions are often massive and hemorrhagic in nature. Although mediastinal widening in and of itself is nonspecific, a chest CT scan may be diagnostically important, because it will often reveal characteristic abnormalities such as pleural effusions, perihilar infiltrates, and mediastinal edema [16]. Although not well documented in humans, physiologic sequelae of severe anthrax infection in animal models reveal hypocalcemia, hypoglycemia, hyperkalemia, depression of the respiratory center, and terminal acidosis and suggest that in addition to antibiotics, correction of electrolyte disturbances and acid-base imbalance, glucose infusion, and early mechanical ventilation may improve survival [17].

Cutaneous anthrax

Cutaneous anthrax accounts for more than 90% of all anthrax infections reported and often occurs following deposition of spores into skin with previous cuts or abrasions. Patients often have a history of occupational contact with animals or animal products. Areas of exposed skin, such the head, neck, and extremities, are most frequently affected [18].

Cutaneous cases generally appear within 5 days of exposure; however, in Sverdlovsk, cases occurred as late as 12 days postexposure [6]. The primary skin lesion usually begins as a small, painless, pruritic papule. Within 24 to 36 hours the lesion forms a vesicle that undergoes central necrosis and drying, leaving a painless, depressed, characteristic black eschar surrounded by gross edema and a number of purplish vesicles. The eschar dries, loosens, and sloughs off within 1 to 3 weeks. Lymphangitis and a painful lymphadenopathy often accompany the lesions. Untreated cutaneous anthrax may cause systemic disease with complications of hyponatremia, thrombocytopenia, disseminated intravascular coagulation, renal failure, microangiopathic hemolytic anemia, and septic shock. Without antibiotic therapy, the mortality rate is 20% or more, whereas treated cutaneous anthrax has a mortality rate of less than 1% [17].

Gastrointestinal anthrax

Gastrointestinal anthrax has not been reported in the United States, but outbreaks are continually reported in Africa and Asia following ingestion of insufficiently cooked, contaminated meat. Symptoms generally appear 2 to 5 days after the ingestion of endospore-contaminated meat from diseased animals [19]. The two distinct recognized syndromes are oropharyngeal and abdominal, both presumably secondary to bacterial inoculation by way of mucosal breaches.

Abdominal anthrax occurs following deposition and subsequent germination of spores in the lower gastrointestinal tract. The primary intestinal lesions are in the terminal ileum and cecum, where there is gross evidence of mesenteric
lymphadenitis and ulcerations [15]. The bacteria then spread systemically. Initially, patients may present with fever, diffuse abdominal pain, nausea, vomiting, and malaise progressing rapidly to bloody diarrhea, coffee ground emesis, an acute abdomen, and sepsis [20]. Ascites develops, with a concomitant reduction in abdominal pain, 2 to 4 days after the onset of symptoms; this fluid, ranging from clear to purulent, often yields colonies of *B. anthracis* when cultured [1]. Major morbidity and mortality results from massive blood loss, fluid and electrolyte imbalance, intestinal perforation, and subsequent shock. Advanced infection may mirror the sepsis syndrome seen in inhalational or cutaneous anthrax.

Oropharyngeal anthrax is less common than the intestinal form, is milder, and has a more favorable prognosis. Lesions in the form of pseudomembranous ulcerations can be seen in the oropharynx. Symptoms vary but patients typically present with fever, cervical edema, painful lymphadenopathy, dysphagia, and respiratory difficulties [10]. Even with proper treatment, fatalities do occur.

**Diagnosis**

As the initial symptoms of inhalational anthrax are very nondescript and similar to other flu-like illnesses, a high level of clinical suspicion is needed. Diagnosis of acute anthrax should be considered in any previously healthy patient presenting with evidence of an overwhelming flu-like illness and a widened mediastinum on chest radiograph as this is virtually pathognomonic of advanced anthrax and warrants prompt treatment and notification of authorities [21]. While initiation of treatment at advanced stages may do little to alter the outcome of the illness, it may aide in the early recognition of, diagnosis, and prompt treatment of others.

At the present time, *rapid* diagnostic tests for anthrax such as ELISA for circulating toxin and capsular antigen and PCR are only available at national research laboratories. Given the limited availability and time required to dispatch specimens, rapid diagnostic testing is primarily used for confirmation of diagnosis and determining in vitro susceptibility to antibiotics [8]. Fortunately, preliminary diagnostic tests can be performed in hospital laboratories. The most useful microbiologic test is the standard blood culture, which should show evidence of growth within 6 to 24 hours. Sputum culture and Gram stain are unlikely to be diagnostic given the lack of a pneumonic process. However, if cutaneous anthrax is suspected, a Gram stain and culture of the vesicular fluid will confirm the diagnosis.

**Treatment**

Given the rapid course of inhalational anthrax, treatment must not be delayed. A delay of early antibiotic administration may substantially decrease chances for
survival. Therefore, all patients with suspected anthrax must be treated until the disease can be excluded.

Penicillin had been the treatment of choice for anthrax for decades; however, penicillin-resistant strains have been identified recently. Therefore, the Centers for Disease Control and Prevention (CDC) recommends ciprofloxacin 400 mg intravenously every 12 hours or doxycycline 100 mg intravenously every 12 hours for empiric treatment of inhalational anthrax in adults. In addition, these medications should be given with another one or two antibiotics predicted to be effective. Other agents with in vitro activity suggested for use in conjunction with ciprofloxacin or doxycycline include rifampin, vancomycin, imipenem, chloramphenicol, penicillin and ampicillin, clindamycin, and clarithromycin. Cephalosorins and trimethoprim-sulfamethoxazole should not be used for therapy. If the strain of the organism is susceptible, 4 million units of penicillin G can be given every 4 hours and may provide better central nervous system penetration in cases associated with meningitis. Corticosteroids have been suggested as adjunct therapy for anthrax associated with extensive edema, respiratory compromise, and meningitis [22].

Although the duration of treatment is not definitively known, the CDC recommends a 60-day course. Patients who have inhalational, intestinal, or oropharyngeal anthrax should initially be treated intravenously; patients may be switched to an oral equivalent when clinically appropriate. For cutaneous anthrax, oral ciprofloxacin or doxycycline is first-line therapy. As for inhalational disease, intravenous therapy with a multidrug regimen is recommended for cutaneous anthrax with signs of systemic involvement, for extensive edema, or for lesions on the head and neck [22].

Prophylaxis is indicated for persons who have been exposed to an airspace contaminated with aerosolized B anthracis. Because person-to-person transmission does not occur, prophylaxis is not indicated for health care workers who care for patients using standard precautions. Prophylaxis for inhalational anthrax exposure indicates the use of either ciprofloxacin or doxycycline as first-line agents. High-dose penicillin may be an option when ciprofloxacin or doxycycline is contraindicated [22].

The duration of postexposure prophylaxis is somewhat controversial. Inhaled spores do not germinate at the same time. Consequently, a certain percentage of inhaled spores may remain dormant for extended periods. In fact, viable spores have been demonstrated to be present in the lungs of monkeys 100 days after inhalation [4]. The original CDC recommendations called for a 60-day course of antimicrobials for postexposure prophylaxis. These recommendations were subsequently modified to permit one of three options: (1) a 60-day course of antibiotics followed by careful clinical observation, (2) extension of the course of antibiotics to 100 days, or (3) extension of antibiotic therapy to 100 days combined with administration of anthrax vaccine in three doses at 2-week intervals [23].

The anthrax vaccine currently available in the United States is a cell-free filtrate of an attenuated, nonencapsulated strain of B anthracis. The vaccine is given at a dose of 0.5 mL subcutaneously at 0, 2, and 4 weeks, and again at 6, 12,
and 18 months. Annual boosters are given to maintain immunity. The vaccine has been in use since 1959 and appears to be safe and to afford efficacy in the prevention of both cutaneous and inhalational anthrax. Following the terrorist attacks of 2001, the Advisory Committee on Immunization Practices (ACIP) reaffirmed its position that pre-exposure use of the anthrax vaccine should be reserved for individuals who have a quantifiable risk of exposure. The ACIP recommends that groups at risk for repeated exposure to B anthracis spores should be given priority for pre-exposure vaccination. Pre-exposure vaccination is not recommended for persons who are not at risk for repeated exposures to aerosolized B anthracis spores through their occupation. Although not licensed for post-exposure prophylaxis, because of a potential preventative benefit of combined antimicrobial postexposure prophylaxis and vaccine, the ACIP endorses making the vaccine available in a three-dose regimen (0, 2, 4 weeks) in combination with antimicrobial prophylaxis [24].

Summary

In this new era of bioterrorism, inhalational anthrax must be considered in the differential diagnosis of many common as well as enigmatic conditions. Prompt recognition and early initiation of treatment are mandated before widespread hematogenous dissemination of bacteria and toxin lead to rapid circulatory collapse. Because of the nonspecific nature of its presentation, it is extremely difficult to establish an early diagnosis of inhalational anthrax; therefore, heightened awareness of an anthrax threat on the part of an astute clinician remains the cornerstone in the fight against bioterrorism.

References