

Anthrax: A primary care physician's perspective

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Anthrax is a disease caused by *Bacillus anthracis*, a gram-positive, aerobic, spore-forming rod. It is also used as a biological weapon.

The primary care physician will be the public's first line of defense in the event of a widespread anthrax exposure and will play a crucial role providing postexposure prophylaxis. Understanding the disease process will allow the primary care physician to play an essential role in protecting and educating the public. Accurate diagnosis and quick treatment will save many lives and help calm the panic following a biological attack.

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A patient you previously diagnosed with a virulent strain of influenza has just returned to your family practice office. His illness has gotten worse. Other patients are returning with similar symptoms. Numerous physicians are beginning to report the same sequence of events occurring in their own offices. Then there is confirmation: terrorism, biowarfare, biological attack . . . anthrax.

Hundreds of patients begin flooding your office and nearby emergency rooms. The community is plummeted into turmoil. There is nationwide panic. Primary care physicians can no longer accommodate the steady flow of afflicted (and overanxious) patients. The office telephones ring constantly. Local medical facilities are forced to close their doors, an action that catapults your office into a catastrophic hysteria.

The scenario depicted above is fiction; however, the medical threat is real. As Americans have come to realize in the aftermath of September 11, 2001, biological terrorism is possible. In fact, most experts believe that a large-scale threat is probable.¹

Although medical experts have different opinions regarding the agent of choice that will be used to execute such a biological assault, all agree on one element: the primary care physician will be overwhelmed. To maintain a level of full national competence in dealing with something of this magnitude, the primary care physician must possess a level of education and preparedness that is equal to the threat. Physicians must arm themselves with the best defense: knowledge.

The offender

And the Lord said unto Moses and unto Aaron, Take you handfuls of ashes of the furnace, and let Moses sprinkle it toward the heaven in the sight of Pharaoh.

And it shall become small dust in all the land of Egypt, and shall be a boil breaking forth with blains upon man and upon beast, throughout the land of Egypt.

Exodus 9:8-9

This forcible passage from the King James Bible describes the fifth plague of Egypt and may be the first recorded incident of the epizootic, *Bacillus anthracis*. Anthrax is a naturally occurring disease affecting livestock and wild herbivores. It is acquired following contact with (or ingestion of) an infected animal or contaminated animal products or by-products. The soil which infected animals had contact with also spreads the pathogen, creating a natural reservoir for the disease.² *Bacillus anthracis* is a gram-positive, aerobic, spore-forming rod present in two forms, as a bacillus while in a living host or as a spore in the environment.³ The spores themselves are very hardy and resistant to extreme temperatures and most disinfectants. Further, *B anthracis* is able to survive in the environment for more than 4 decades.⁴

The organism produces a lethal exotoxin made up of 3 heat-labile, antigenically distinct components: (1) an edema factor, (2) a protective capsular antigen, and (3) a lethal factor.⁵ The lethal toxin functions as a protease, inhibiting a central signal transduction pathway of the cell that disrupts cellular function, leading to cell death and tissue necrosis.⁶

The distribution

Distribution of *B anthracis* is worldwide and there are three forms of the disease, of which cutaneous anthrax is the most common type in humans, acquired through skin abrasions or the mucous membranes. In a process that takes about 3 days, a painless pruritic papular lesion quickly enlarges, ulcerates, becomes necrotic, and eventually forms a dense black eschar. Interestingly, the word *anthrax* descends from the Greek word *anthracis* for "coal" and the Latin *anthrax* for "carbuncle."⁷

The gastrointestinal form of anthrax is rare. It comes from ingestion of *B anthracis* spores through contaminated and poorly cooked meat. The spores are then deposited throughout the submucosa of the intestinal tract where they germinate and multiply, producing toxin which results in massive edema.

The inhalational form of anthrax is also known as "wool-sorters' disease," as it occurs most frequently in the textile and tanning industries. This is a highly fatal form of anthrax

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which is often the result of inhaling dust containing *B anthracis* spores. These spores are then transported by the alveolar pneumocytes to regional lymph nodes where they germinate, multiply, and become toxic. Hemorrhagic edematous mediastinitis, pleural effusions, dyspnea, cyanosis, stridor, and shock characterize this stage of the disease. It is in the inhalational form of anthrax that *B anthracis* begins to distinguish itself as having the potential to evolve into the perfect biological weapon.

The weapon

Anthrax is precise. Although human anthrax is not considered contagious and there is no evidence of person-to-person transmission, a particular community (or race) can be targeted and eliminated.² Experts have told us over the past several years that the most probable type of biological attack will be an airborne one.⁸ For example, a suicidal bioterrorist could release a cloud of *B anthracis* spores at a specific location, such as a bus station or subway terminal. In the event of such a biological attack, the patient would become infected through inhalation of the organism. He or she would be exposed immediately but unknowingly. Symptoms would begin approximately 2 to 7 days after exposure. It is during this time that the primary care physician would receive his or her initial consult.

The patient will present with a fever, fatigue, and other generic influenza-like symptoms. Two to 3 days after symptoms appear, the patient will have a false sense of wellness. Suddenly, the patient will become cyanotic and develop shock, ultimately dying in the next 24 to 36 hours. By the time the physician can make a diagnosis of anthrax, hundreds upon thousands might already be infected.

The history

Until the terrorist attacks in New York City, Washington, DC, and Pennsylvania on September 11, 2001, most Americans were unaware of the general level of terrorist activities around the world. One reason for this lack of knowledge is that, until that point, statistically few violent (ie, high casualty) attacks of this nature actually took place on American soil^{9,10}—with the one great exception of the 1995 bombing of the Alfred P Murrah Federal Building in Oklahoma City, Okla (see <http://www.oklahomacitynationalmemorial.org/>).

However, many terrorist plots and acts of terrorism did get national coverage in the United States and overseas in the pre-September 2001 era. At the Alaska-Yukon border in April 1993, for example, Canadian customs agents stopped an Arkansas man who was in possession of neo-Nazi literature, 20,000 rounds of ammunition, 6 kilograms of gunpowder, about \$89,000 in cash—and an extremely toxic nerve agent, ricin, in a Ziploc bag.¹⁰⁻¹² Ricin is a phototoxin readily produced from the castor bean plant, *Ricinus communis*. The 130 grams of ricin he attempted to transport into Canada is thought to have been capable of killing more than 30,000 people.¹¹

In March 1995, the Japanese apocalyptic cult *Aum Shinrikyo*

released an organophosphate nerve gas known as sarin gas in the Tokyo subway system. Sarin gas is a colorless and odorless gas that is 26 times more deadly than cyanide gas.¹³ The attack killed 11 people and injured more than 5500 others.^{10,14}

In 1998, an Ohio man was arrested in Henderson, Nev, with enough *B anthracis* spores to “wipe out Las Vegas”—this was 3 years after his 1995 arrest and conviction in Ohio for misrepresenting himself so that he could order three vials of the bubonic plague bacteria, *Yersinia pestis*, from a supplier in Maryland.¹⁵ At that time, the man intended to plant a “globe” of *Yersinia pestis* in the New York City subway system where it would be broken by a passing train, thus dispersing the pathogen to infect “hundreds of thousands of people.”¹⁵

The terrorist

Japan originally weaponized anthrax in the 1930s and the United States followed in the 1950s.⁷ Although *B anthracis* has never been used in a traditional combat setting, it has many characteristics of a perfect biological weapon—not the least of which is the fact that anthrax is highly lethal with a mortality rate estimated at 90%.¹⁶ *Bacillus anthracis* occurs naturally in many parts of the world. Further, *B anthracis* is cheap and easy to produce. *Bacillus anthracis* spores are also easy to deliver. In its aerosolized form, *B anthracis* is odorless and invisible with legendary portability.² Finally, anthrax has the key attribute of being virtually undetectable until 2 to 7 days after exposure, when a large number of seriously ill people can be expected to present simultaneously with the signs and symptoms of infection.

The World Health Organization estimates that 110 pounds of *B anthracis* spores released upwind of a population center of 5 million people would result in the deaths of 100,000 people and the incapacitation of an additional 150,000 people.² “In 1993, a report from the United States Congressional Office of Technology Assessment estimated that 130,000 to 3 million deaths could follow the aerosolized release of 100 kilograms of anthrax spores upwind of the Washington, DC, area—a lethality matching or exceeding that of a hydrogen bomb.”²

The disease

The scientific, medical, and military communities have learned much about the inhalational form of anthrax following the unintentional release of *B anthracis* in 1979 at a military microbiology facility in Sverdlovsk, north central Russia. This incident resulted in 66 local deaths.¹⁷

Inhaled *B anthracis* spores penetrate the terminal bronchi and lodge in the alveoli of the lungs where they germinate. The spores are then phagocytized by macrophages and transported to the mediastinal and hilar lymph nodes.¹⁸ *Bacillus anthracis* spores do not manufacture toxins before germination and cause no inflammatory reaction in the body; therefore, a person remains asymptomatic during this time.

An incubation period of 1 to 6 days is followed by an influenza-like prodrome that lasts 24 to 72 hours. The pro-

drome is characterized by fever, malaise, nonproductive cough, chills, vomiting, headache, abdominal pain, and mild chest discomfort or pressure.¹⁷

A temporary improvement in these symptoms can occur over the next 48 to 72 hours. Soon afterward, sudden hypoxia, respiratory distress, high fevers, stridor, diaphoresis, and cyanosis develop.¹⁸

Death occurs rapidly, anywhere from 3 to 11 days after the initial exposure, but is secondary to septic shock, meningitis, or necrotizing hemorrhagic mediastinitis.⁷

Inhalational anthrax is hard to diagnose, especially in the early stages when treatment would yield the most beneficial results (see Cymet et al, pages 41-43, this issue). Further, physical findings are nonspecific, making the diagnosis difficult—and patient death likely without recognition, and swift and appropriate treatment. Occasionally, a chest radiograph will reveal a widened mediastinum or pleural effusion.⁷

There are no standard laboratory tests that are specific for an anthrax diagnosis. If anthrax is suspected, however, an enzyme-linked immunoadsorbent assay test can measure antibodies to the edema and lethal factors, helping to support the diagnosis. Also available is the polymerase chain reaction test that amplifies small amounts of DNA to document that the bacteria is present. In the later stages of the illness, blood cultures may become positive; but, at this point, death is usually imminent.¹⁹

The treatment

Although there are limited human studies in treating inhalational anthrax, the evidence suggests penicillin G is effective.¹⁸ However, the treatment must begin before the onset of symptoms and as early as possible in the course of the disease because the second phase of the illness is catastrophic.³

Unfortunately, penicillin resistance is easily induced in the laboratory so it must be assumed that a determined terrorist organization would be able to render penicillin ineffective against this organism. The Working Group on Civilian Biodefense, a group of top physicians and scientists from all sectors, met in May 1998 to discuss anthrax and its use as a biological weapon. At that time, the group recommended the following 60-day intravenous antibiotic therapy for patients with “clinically evident inhalational anthrax infection”: ciprofloxacin (Cipro) 400 mg every 12 hours until the sensitivity of the organism is known—and then a change to 4 million units of penicillin G every 4 hours, or doxycycline 100 mg every 12 hours.² Treatment must continue for 60 days due to the risk of delayed germination of spores, after which time the therapy should be withdrawn under medical surveillance.

The physician

The office-based primary care physician will have a dual purpose following a biological attack on our nation. In addition to the paramount responsibility of postexposure prophylaxis, the primary care physician will have to educate the general

public, helping calm the hysteria following a widespread exposure to *B anthracis*.

The Working Group on Civilian Biodefense developed a final consensus recommendation on postexposure prophylaxis (see <http://jama.ama-assn.org/issues/v281n18/full/jst80027.html>). Based on the best available evidence, the same antibiotics used for treatment should be used for postexposure prophylaxis—the crucial difference being that medication prescribed for prophylaxis can be administered orally.

For postexposure prophylaxis, adults (including pregnant women) should be given the following antibiotic therapy by mouth for 60 days: ciprofloxacin 500 mg every 12 hours with a switch to amoxicillin 500 mg every 8 hours or doxycycline 100 mg every 12 hours following sensitivity to the organism.² Children can be given a 60-day course of ciprofloxacin 20 mg to 30 mg per day by mouth, divided into 2 daily doses (not to exceed 1 g/d).² Once resistance of the organism is ruled out, a child can be changed to amoxicillin taken by mouth with the dosage determined by the child's weight (< 20 kg: 40 mg/kg—divided into 3 daily doses; ≥ 20 kg: 500 mg) and taken every 8 hours.² Children are generally not given fluoroquinolones because of the risk of permanent arthropathy found in some animal studies; however, the high mortality rate of anthrax¹⁶ outweighs the risk of this side effect.

A vaccination series of 6 injections could also be initiated immediately postexposure, continuing at 2 and 4 weeks, and then at 6, 12, and 18 months, followed by annual boosters.¹⁸ While current supplies of the anthrax vaccine could, unfortunately, be very limited after such a large-scale attack, there is little scientific evidence to suggest that this vaccine would protect patients from aerosolized *B anthracis*.¹⁸ Further, suspicion about the vaccine and its possible long-term side effects arose after it was routinely given to military personnel during the Persian Gulf War, 1990-1991.²⁰

Summary

Anthrax is a potential threat to the world's population and may play a murderous role in future acts of terrorism. While the threat itself is gruesome, the effect of such an attack on already-burdened primary care facilities is no less terrifying. Understanding the disease process will allow the primary care physician to play an essential role in protecting the public from biological terrorism.

Accurate diagnosis, quick treatment, and education may save many lives and help calm the panic following an assault. The primary care physician will be one of the public's first lines of defense in the event of large-scale anthrax exposure and could play a crucial role providing postexposure prophylaxis.

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Coverage of September 11, 2001 events, including information on bioterrorism, appeared in the November 2001 issue of *The DO*. Coverage of lectures on bioterrorism that were delivered at the 106th Annual AOA Convention and Scientific Seminar, held in San Diego, California, during October 2001, appeared in the December 2001 issue of *The DO*.

The full text of most of those articles are available at www.aoa-net.org/Publications/DO/domagazine.htm.