The threat of bioterrorism: A reason to learn more about anthrax and smallpox

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ABSTRACT

Threats of domestic terrorism and international news about germ warfare research have forced us to recognize the potential menace of biological weapons. Both smallpox and anthrax could be used as biological weapons. It is important for physicians to reacquaint themselves with these diseases, because if a domestic attack were to occur, it might first be recognized when patients with unusual symptoms began presenting to hospitals and primary care physicians. In this article, we discuss symptoms and treatments for smallpox and anthrax, and suggest resources for physicians who wish to learn more about the subject.

Anthrax and smallpox are the most likely candidates for bioweapons

AN ADMINISTRATIVE ASSISTANT sitting alone at her desk at a Planned Parenthood clinic opens a letter. The envelope contains white powder and a threatening note saying that the powder is anthrax spores. The assistant immediately dials 911, and police arrive in minutes. The letter is sealed in a plastic bag and collected by the Federal Bureau of Investigation.

The next phone call is to you as the physician on call. While the investigation continues, you are asked for advice about preventive health measures for the administrative assistant, the police and emergency team responders, and the 31 adults and children who happened to be in the clinic when the envelope was opened.

What should you do?

Anthrax occurs so rarely under ordinary circumstances that few of us would have a clear idea of which of the people in the clinic are at risk, how to treat those exposed, or how to prevent a disease outbreak. However, international and domestic events are forcing us to realize that the possibility of bioterrorism must be taken seriously.

The most likely candidates for biological weapons are anthrax and smallpox. Both can be put into stable aerosol form in particles 5 μm or smaller (the ideal size to be inhaled), bypass the oropharynx, and reach the alveoli. Both have small infective doses: the dose for anthrax is thought to be fewer than 50,000 spores, and the dose for smallpox may be as few as 10 to 100 particles. They are inexpensive to develop, have a long shelf-life, and could cause widespread panic that could compound the terror of the disease itself.

LESSONS OF THE PLANNED PARENTHOOD CASE

The case described above actually occurred in Indiana in 1998. Hazardous materials (HAZMAT) experts responded to the scene wearing full protective gear, including self-contained respirators. All 31 people in the building were considered possibly exposed to anthrax. They were told to place all clothing and personal belongings in labeled plastic bags and take decontamination showers with soap, water, and a dilute bleach solution in a tent set up on-site. The administrative assistant underwent seven decontamination showers. All were taken to local emergency departments, where some had to undergo additional decontamination under local hospital policy, and all were started on oral ciprofloxacin. The desktop was washed with full-strength household bleach.[1]

The threat was exposed as a hoax after both the state health department and a

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Department of Defense laboratory failed to find any evidence of anthrax in the powder or the envelope.

As we will see later in this article, the response to the threat was prompt and thorough, but may actually have been more aggressive than necessary. In my opinion, even if the Planned Parenthood hoax had involved genuine anthrax, the situation would be frightening but not actually very dangerous. A review of the disease's symptoms, forms, and therapies will show why.

A BRIEF HISTORY OF BIOLOGICAL WEAPONS

Catapulted corpses

One of the earliest uses of biological weapons occurred in 1346 when besieging Tartars catapulted corpses of their own men who had died of plague, over the walls of the city of Kaffa (now Feodosia, Ukraine).

Smallpox-contaminated clothing was deliberately distributed to Native Americans by European settlers, contributing to devastating epidemics in both North and South America.

World War II and the Cold War

By World War II, biological weapons were the focus of nationally supported research in Japan, Germany, the United States, and other countries. By the end of the war, the United States had stockpiled 5,000 anthrax bombs. Research and development continued until Richard Nixon closed the program and ordered the arsenal destroyed by 1973. The international Biological Weapons Convention prohibiting bioweapons use went into effect in 1975. However, bioweapons research continued in many countries that signed the treaty as well as in others that did not.

This was dramatically confirmed in 1992 when Boris Yeltsin conceded what epidemiological evidence had already suggested, that a 1979 anthrax outbreak in Sverdlovsk (now Ekaterinburg), Russia, stemmed from an unintentional release of aerosolized anthrax from a military microbiology laboratory. Seventy-seven cases occurred downwind of the laboratory, and 66 of the victims died. Incubation periods ranged from 1 to 43 days.[2] The Soviet germ warfare program was large and well-funded, and with the fall of the Soviet Union and the collapse of the Russian economy, it is feared that Soviet scientists may be willing to sell their expertise to other nations.

Inspections in Iraq have documented research into biological and chemical weapons.

The Aum Shinrikyo cult in Japan, which killed 12 and injured 5,000 with a release of sarin nerve gas into a Tokyo subway in 1995, had a bioterrorism research program and had stockpiled anthrax and botulinum toxins.

Recent US incidents

In 1998, there were 38 anthrax hoaxes affecting 5,000 people in the United States. But bioterrorism in this country should not be considered only a hoax. A 1984 salmonella outbreak in Oregon was traced to the Rajneeshee cult, whose members had contaminated salad bars in at least 10 restaurants in a training exercise for a larger attack designed to influence a local election.[1]

ANTHRAX

In 1998, there were 38 anthrax hoaxes in the U.S.

Anthrax is caused by spore-forming gram-positive bacilli, and is primarily a disease of sheep and cattle which under natural circumstances infects humans very rarely. Outbreaks in US cattle have declined steadily since 1945. The last fatal human case in this country was contracted in 1976 from wool imported from Pakistan. Since 1988, there has been no more than one human case per year. Thus, a single case of human anthrax is a sentinel event, and the possibility of bioterrorism should be considered.

Forms of anthrax

Cutaneous anthrax, which accounts for 95% of naturally occurring human anthrax infections, develops when spores encounter traumatized skin, often on the face or hands. A painless black eschar develops and is generally accompanied by marked edema. This form of anthrax, which can occasionally be transmitted by contact, can usually be cured with antibiotics. However, untreated cases may become systemic and fatal. The incubation period can be from 1 to 7 days.

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TABLE 1

Diagnosis and treatment of anthrax and smallpox

AGENT	DIAGNOSTIC SAMPLES	DIAGNOSTIC ASSAY	PATIENT ISOLATION PRECAUTIONS	THERAPY	POSTEXPOSURE PROPHYLAXIS	VACCINE
Anthrax	Blood (handled at biosafety level 2)	Gram stain Antigen ELISA Serology	Standard precautions	Ciprofloxacin 400 mg IV every 8–12 hr Doxycycline 200 mg IV, then 100 mg IV every 8–12 h*	Ciprofloxacin 500 mg PO twice a day for 4 weeks; if unvaccinated begin initial doses of vaccine	Licensed vaccine 0.5 mL SC at 0, 2, 4 weeks and 6, 12, 18 mo; annual booster
Smallpox	Pharyngeal swab Scab material (handled at biosafety level 2–3)	ELISA PCR Virus isolation	Precautions for airborne pathogens	Cidofovir is effective in vitro	Vaccinia immune globulin 0.6 mL/kg IM within 3 days of exposure (best within 24 h) Vaccination if > 3 years since last vaccination	Licensed vaccine is Wyeth calf lymph vaccinia Investigational cell-culture vaccinia has been developed by Department of Defense

*Other alternatives include penicillin, gentamicin, erythromycin, and chloramphenicol
ELISA=enzyme-linked immunosorbent assay; PCR = polymerase chain reaction; PO=by mouth, IV=intravenously; SC=subcutaneously

SOURCE: ADAPTED FROM FRANZ DR, JAHRLING PB, FRIEDLAND AM, ET AL. CLINICAL RECOGNITION AND MANAGEMENT OF PATIENTS EXPOSED TO BIOLOGICAL WARFARE AGENTS. JAMA 1997; 278:399–411.

Inhalational anthrax, a rapidly fatal illness commonly known as woolsorters' disease, accounts for most of the remaining natural cases. Inhaled spores are ingested by pulmonary macrophages and carried to hilar and mediastinal lymph nodes, where they germinate and multiply. The incubation period may range from 2 to 60 days. Nonspecific flulike symptoms develop first, followed after 2 to 4 days by abrupt respiratory failure, hemodynamic collapse, pronounced pulmonary edema, and death. Meningitis occurs in half of cases. Chest radiographs may show a widened mediastinum and pleural effusions. Gram-positive bacilli may be noted in blood cultures. Transmission from person to person has never been documented.

Gastrointestinal anthrax is a rare consequence of eating contaminated meat. Symptoms are pain, nausea, vomiting, and fever, with bloody diarrhea and hematemesis, with progression to toxemia and sepsis. This form is difficult to diagnose and almost universally fatal. Incubation is 1 to 7 days.[3]

Anthrax as a weapon

Aerosolized anthrax could be a potent weapon that could be released from aircraft or into a building, with a mortality rate of up to 80%. Fortunately, there are limitations to the danger posed by anthrax. The spores are not volatile, so they will not aerosolize spontaneously. Spores can infect cutaneously only through breaks in the skin, posing little risk to intact skin. In addition, person-to-person spread has never been documented, meaning that an infected person would not trigger an epidemic.[4]

Anthrax vaccine

An anthrax vaccine was developed in the 1950s using an avirulent strain that elaborates only protective antigen and produces a protective antibody response in 7 days. The current vaccine requires an onerous schedule, with doses at 0, 2, and 4 weeks, and 6, 12, and 18 months, followed by annual boosters (TABLE 1).[5] This vaccine has not been the subject of any controlled studies; the only study has shown a

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protective effect against cutaneous anthrax, but numbers were too small to determine whether the vaccine also protects against the inhalational form. The US military first vaccinated troops during the Gulf War and now routinely vaccinates all personnel, a practice that has sparked a political controversy about the vaccine's safety.

Therapies for anthrax

Antibiotic prophylaxis for inhalational anthrax appears to be most effective before respiratory symptoms develop, but it is difficult in naturally occurring cases to begin therapy early because the nonspecific prodrome is virtually impossible to distinguish from flu or other less serious diseases.

The Centers for Disease Control and Prevention (CDC) recommends postexposure prophylaxis with ciprofloxacin or another fluoroquinolone twice daily, with doxycycline the second agent of choice. Although natural anthrax is very susceptible to penicillin, military experts decided in 1991 that Iraq and Russia both had the technology to develop penicillin-resistant strains. The quinolones would also be effective against plague and tularemia, which may be difficult to distinguish from anthrax in the field. Antibiotics would have to be taken for at least 8 weeks after exposure, because the spores can lie dormant in the hilar lymph nodes for up to 6 weeks before germinating. Alternately, antibiotics could be given for 4 weeks while the first 3 doses of vaccine are administered.[1,3] In either case, these procedures would clearly strain local supplies of antibiotics as well as vaccine in the event of a large-scale exposure.

CDC recommendations for anthrax threats

Standards published by the CDC[1] after several recent anthrax hoaxes recommend decontamination showers with soap and water only, with no bleach. They also state that exposed surfaces should be decontaminated with dilute bleach solution, not full-strength bleach. Chemoprophylaxis is recommended for 8 weeks in the absence of a vaccine, for 4 weeks in combination with the first 3 doses of the vaccine, or until the threat of anthrax has been excluded.

The Planned Parenthood case described earlier in this article would have posed little serious threat of disease, even if the powder in the envelope had been anthrax. As anthrax spores are not volatile, it was unlikely that the administrative assistant inhaled the spores and very unlikely that anybody else did. The self-contained respirators used by emergency personnel responding to the scene were probably not necessary. The spores would be likely to cause cutaneous infection only if the assistant had preexisting breaks in her skin. Decontamination showers and prophylaxis were probably indicated for the assistant, but not for the others in the building.

SMALLPOX

It is important to reeducate physicians about smallpox because it has not been seen in the United States since the 1940s. The last naturally occurring case in the world occurred in 1977 in Somalia, and in 1980, the World Health Organization declared smallpox eradicated. Routine childhood vaccination was discontinued in the United States in 1972. The strength of any remaining immunity among those who were vaccinated as children is not known, but only about 15% of the population is thought to have any immunity.

Smallpox rash often develops on the soles and palms

Smallpox, caused by the variola virus, used to be a universal disease of childhood, killing many victims but leaving the survivors with prolonged immunity. The disease begins with high fever and myalgia, with the characteristic rash forming on about the fourth day, starting as macules and progressing to papules and vesicles, scabbing over at 1 to 2 weeks. It typically begins on the face, oropharynx, and arms, spreading later to the trunk and legs, and the vesicles often develop on the palms and soles. Smallpox is contagious from the formation of the rash until scabs separate at about 3 weeks. The lesions have a synchronous onset. Death, which generally occurs in the second week of illness, apparently results from toxemia. Smallpox is transmitted most often through airborne droplets but can also be passed by contact. Its incubation period ranges from 7 to 17 days, averaging 12 days.[6]

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Forms of smallpox

Variola major, the most severe form of smallpox, has a case-fatality rate of about 30% in unvaccinated populations. When the rash and mucous membranes become **hemorrhagic,** a phenomenon occurring mostly in pregnant women, the course of the disease is more severe and mortality even higher. A **confluent** rash indicates a severe form of smallpox, and a **discrete** rash a less serious one. **Variola minor** or **alastrim** is a much less virulent form of smallpox with a case-fatality rate of about 1%.

Differential diagnoses

During the onset of smallpox, nonspecific fever and myalgia may simulate **flu**. **Measles** may be ruled out if the mouth and throat have no Koplik's spots. **Chickenpox** rash is centripetal, denser on the trunk than on the extremities, and virtually never develops on the palms and soles. Also, in chickenpox, eruptions of different stages of maturation are found next to each other, whereas smallpox is generally at the same stage of development everywhere on the body. **Monkeypox** is a rare disease very similar to smallpox that may be ruled out by the absence of history of travel to western Africa. **Generalized vaccinia infection**, an occasional consequence of the vaccinia vaccine still given to a few high-risk workers, may also resemble smallpox.[3]

Diagnosis can be confirmed by electron microscopy of vesicular scrapings or gel diffusion testing of vesicular fluid antigen against vaccinia antiserum. Light microscopy can reveal intracytoplasmic variola particles, the Guarnieri bodies.

Smallpox as a weapon

Smallpox weapons could be developed in small laboratories with only a few thousand dollars' worth of equipment. Like anthrax, smallpox can be aerosolized for maximum effect. Although surviving smallpox cultures are kept in only two labs, a CDC lab in Atlanta, and a Russian one, the security of the Russian lab has been in question ever since the fall of the Soviet Union.

Smallpox could be an even more devastating weapon than anthrax because it is easily spread from person to person. The extreme contagiousness of smallpox was demonstrated by one of the last European outbreaks. A German returning from a trip to Pakistan in 1970 developed a fever and was quarantined with suspected typhoid. He developed the characteristic smallpox rash 4 or 5 days later and was immediately taken to a special smallpox isolation hospital that had been maintained for just such emergencies. Mass vaccinations were conducted in the region, and a number of sick patients were also given vaccinia immune globulin (VIG). Even though the index patient had been quarantined at the first hospital and the German population was already well vaccinated, 19 additional cases developed among the patients and staff at the first hospital. It is thought that the patient's cough, unusual in smallpox, helped disperse more virus than usual in aerosolized form. Most alarming, one of the cases developed in a visitor who opened a hallway door about 30 feet from the patient's room to ask directions, spending no more than about 15 minutes in the hospital.[7]

Vaccines and therapies

There are no known treatments for smallpox. Cidofovir is effective in vitro (TABLE 1).

The vaccine may prevent or ameliorate illness if given within 3 or 4 days of exposure. Passive immunization in the form of vaccinia immune globulin is most effective when administered in the first 24 hours after exposure.[1,3]

Smallpox vaccine is effective but has serious risks, including death

Although the vaccinia vaccine is very effective, it would be difficult to reinstitute a universal vaccine program. First, we have only a small stockpile of vaccine (5 to 10 million doses in the United States and perhaps 70 million worldwide) and no technology for rapidly manufacturing more.

The vaccine is not benign. At least one death per 1 million can be expected, as well as serious complications including secondary autoinoculations, generalized vaccinia infection, eczema vaccinatum, and post-vaccine encephalitis.

TO LEARN MORE

Physicians who wish to learn more about biological weapons should begin with the CDC Web site (**www.cdc.gov**), which contains a wealth of resources accessible with the search-term "bioterrorism."

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MEDICAL GRAND ROUNDS

One important document available on the site is the "Bioterrorism Readiness Plan: A Template for Healthcare Facilities," a set of guidelines for managing patients with diseases that may be related to bioweapons.[8]

Guidelines for responding to both genuine anthrax attacks and anthrax hoaxes have been published by the CDC in *Morbidity and Mortality Weekly Report*.[1]

The August 6, 1997 issue of JAMA was dedicated to bioterrorism and contains a valuable review by Franz et al[3] of the signs and symptoms of diseases with possible bioweapons significance. The July-August 1999 issue of *Emerging Infectious Diseases* was also dedicated to coverage of bioterrorism, focusing on the National Symposium on Bioterrorism held at Johns Hopkins University in February 1999.[9] A recent review article in the *New England Journal of Medicine* contains additional in-depth information about anthrax.[10]

In an emergency, physicians are urged to contact their local health departments. Further information on diagnostics, medical management, and vaccines can be obtained from the **Commander, US Army Military Research Institute for Infectious Diseases, at (phone) 301-619-2833 or (fax) 301-619-4625.**

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