Anthrax as a Biological Weapon
Medical and Public Health Management

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Objective To develop consensus-based recommendations for measures to be taken by medical and public health professionals following the use of anthrax as a biological weapon against a civilian population.

Participants The working group included 21 representatives from staff of major academic medical centers and research, government, military, public health, and emergency management institutions and agencies.

Evidence MEDLINE databases were searched from January 1966 to April 1998, using the Medical Subject Headings *anthrax*, *Bacillus anthracis*, *biological weapon*, *biological terrorism*, *biological warfare*, and *biowarfare*. Review of references identified by this search led to identification of relevant references published prior to 1966. In addition, participants identified other unpublished references and sources.

Consensus Process The first draft of the consensus statement was a synthesis of information obtained in the formal evidence-gathering process. Members of the working group provided formal written comments which were incorporated into the second draft of the statement. The working group reviewed the second draft on June 12, 1998. No significant disagreements existed and comments were incorporated into a third draft. The fourth and final statement incorporates all relevant evidence obtained by the literature search in conjunction with final consensus recommendations supported by all working group members.

Conclusions Specific consensus recommendations are made regarding the diagnosis of anthrax, indications for vaccination, therapy for those exposed, postexposure prophylaxis, decontamination of the environment, and additional research needs.

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OF THE NUMEROUS BIOLOGICAL agents that may be used as weapons, the Working Group on Civilian Biodefense has identified a limited number of organisms that could cause disease and deaths in sufficient numbers to cripple a city or region. Anthrax is one of the most serious of these diseases.

High hopes were once vested in the Biological Weapons and Toxins Convention, which prohibited offensive biological weapons research or production and was signed by most countries. However, Iraq and the former Soviet Union, both signatories of the convention, have subsequently acknowledged having offensive biowarfare programs; a number of other countries are believed to have such programs, as have some autonomous terrorist groups. The possibility of a terrorist attack using bioweapons would be especially difficult to predict, detect, or prevent, and thus, it is among the most feared terrorist scenarios.[1]

Biological agents have seldom been dispersed in aerosol form, the exposure mode most likely to inflict widespread disease. Therefore, historical experience provides little information about the potential impact of a biological attack or the possible efficacy of postattack measures such as vaccination, antibiotic therapy, or quarantine. Policies and strategies must therefore rely on interpretation and extrapolation from an incomplete knowledge base. The Working Group on Civilian Biodefense reviewed the available literature and expertise and developed consensus recommendations for medical and public health measures to be taken following such an attack.

CONSENSUS METHODS

The working group comprised 21 representatives from academic medical cen-

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The first draft of the working group's consensus statement was the result of synthesis of information obtained in the formal evidence-gathering process. Members of the working group were asked to make formal written comments on this first draft of the document in May 1998. Suggested revisions were incorporated into the second draft of the statement. The working group was convened to review the second draft of the statement on June 12, 1998, at the Johns Hopkins Center for Civilian Biodefense Studies, Baltimore, Md. Consensus recommendations were made; no significant disagreements existed at the conclusion of this meeting. The third draft incorporated changes suggested at the conference and working group members had an additional opportunity to review the draft and suggest final revisions. The final statement incorporates all relevant evidence obtained by the literature search in conjunction with final consensus recommendations supported by all working group members. Funding for the development of the working group consensus statement was primarily provided by each representative's institution or agency. The Office of Emergency Preparedness, Department of Health and Human Services (DHHS), provided travel funds for 4 members of the group.

The assessment and recommendations provided herein represent the best professional judgment of the working group based on data and expertise currently available. The conclusions and recommendations need to be regularly reassessed as new information becomes available.

HISTORY OF CURRENT THREAT

For centuries, anthrax has caused disease in animals and, uncommonly, serious illness in humans throughout the world.[2] Research on anthrax as a biological weapon began more than 80 years ago.[3] Today, at least 17 nations are believed to have offensive biological weapons programs[4]; it is uncertain how many are working with anthrax. Iraq has acknowledged producing and weaponizing anthrax.[5]

Most experts concur that the manufacture of a lethal anthrax aerosol is beyond the capacity of individuals or groups without access to advanced biotechnology. However, autonomous groups with substantial funding and contacts may be able to acquire the required materials for a successful attack. One terrorist group, Aum Shinrikyo, responsible for the release of sarin in a Tokyo, Japan, subway station in 1995,[6] dispersed aerosols of anthrax and botulism throughout Tokyo on at least 8 occasions. For unclear reasons, the attacks failed to produce illness.[7]

The accidental aerosolized release of anthrax spores from a military microbiology facility in Sverdlovsk in the former Soviet Union in 1979 resulted in at least 79 cases of anthrax infection and 68 deaths and demonstrated the lethal potential of anthrax aerosols.[8] An anthrax aerosol would be odorless and invisible following release and would have the potential to travel many kilometers before disseminating.[9,10] Evidence suggests that following an outdoor aerosol release, persons indoors could be exposed to a similar threat as those outdoors.[11]

In 1970, a World Health Organization (WHO) expert committee estimated that casualties following the theoretical aircraft release of 50 kg of anthrax over a developed urban population of 5 million would be 250 000, 100 000 of whom would be expected to die without treatment.[9] A 1993 report by the US Congressional Office of Technology Assessment estimated that between 130 000 and 3 million deaths could follow the aerosolized release of 100 kg of anthrax spores upwind of the Washington, DC, area—lethality matching or exceeding that of a hydrogen bomb.[12] An economic model developed by the Centers for Disease Control and Prevention (CDC) suggested a cost of $26.2 billion per 100 000 persons exposed.[13]

EPIDEMIOLOGY

Naturally occurring anthrax is a disease acquired following contact with anthrax-infected animals or anthrax-contaminated animal products. The disease most commonly occurs in herbivores, which are infected by ingesting spores from the soil. Large anthrax epizootics in herbivores have been reported; during a 1945 outbreak in Iran, 1 million sheep died.[14] Animal vaccination programs have reduced drastically the animal mortality from the disease.[15] However, anthrax spores continue to be documented in soil samples from throughout the world.[16-18]

In humans, 3 types of anthrax infection occur: inhalational, cutaneous, and gastrointestinal. Naturally occurring inhalational anthrax is now a rare cause of human disease. Historically, wool sorters at industrial mills were at highest risk. Only 18 cases were reported in the United States from 1900 to 1978, with the majority occurring in special-risk groups, including goat hair mill or goatskin workers and wool or tannery workers. Two of the 18 cases were laboratory associated.[19]

Cutaneous anthrax is the most common naturally occurring form, with an estimated 2000 cases reported annually.[18] Disease typically follows exposure to anthrax-infected animals. In the United States, 224 cases of cutaneous anthrax were reported between 1944 and 1994.[20] The largest reported epidemic occurred in Zimbabwe between 1979 and 1985, when more than 10 000 human cases of anthrax were reported, nearly all of them cutaneous.[21]

Gastrointestinal anthrax is uncommonly reported.[18,22,23] However, gastrointestinal outbreaks have been reported

in Africa and Asia.[24] Gastrointestinal anthrax follows ingestion of insufficiently cooked contaminated meat and includes 2 distinct syndromes, oral-pharyngeal and abdominal.[22,24-27] In 1982, there were 24 cases of oral-pharyngeal anthrax in a rural northern Thailand outbreak following the consumption of contaminated buffalo meat.[24] In 1987, there were 14 cases of gastrointestinal anthrax reported in northern Thailand with both oral-pharyngeal and abdominal disease occurring.[25]

No case of inhalational anthrax has been reported in the United States since 1978,[19,20] making even a single case a cause for alarm today. As was demonstrated at Sverdlovsk in 1979, inhalational anthrax is expected to account for most morbidity and essentially all mortality following the use of anthrax as an aerosolized biological weapon.[8,28] In the setting of an anthrax outbreak resulting from an aerosolized release, cutaneous anthrax would be less common than inhalational anthrax, easier to recognize, simpler to treat, and associated with a much lower mortality. In the Sverdlovsk experience, there were no deaths in patients developing cutaneous anthrax.[8] There is little information available about the risks of direct contamination of food or water with anthrax spores. Although human infections have been reported, experimental efforts to infect primates by direct gastrointestinal instillation of anthrax spores have not been successful.[29]

MICROBIOLOGY

Bacillus anthracis derives from the Greek word for coal, *anthrakis*, because the disease causes black, coal-like skin lesions. *Bacillus anthracis* is an aerobic, gram-positive, spore-forming, nonmotile *Bacillus* species. The nonflagellated vegetative cell is large (1-8 µm in length, 1-1.5 µm in breadth). Spore size is approximately 1 µm. Spores grow readily on all ordinary laboratory media at 37°C, with a "jointed bamboo-rod" cellular appearance and a unique "curled-hair" colonial appearance, and display no hemolysis on sheep agar (FIGURE 1). This cellular and colonial morphology theoretically should make its identification by an experienced microbiologist straightforward, although few practicing microbiologists outside the veterinary community have seen anthrax colonies other than in textbooks.[30]

Anthrax spores germinate when they enter an environment rich in amino acids, nucleosides, and glucose, such as that found in the blood or tissues of an animal or human host. The rapidly multiplying vegetative anthrax bacilli, on the contrary, will only form spores after local nutrients are exhausted, such as when anthrax-infected body fluids are exposed to ambient air.[16,17] Full virulence requires the presence of both an antiphagocytic capsule and 3 toxin components (ie, protective antigen, lethal factor, and edema factor).[30] Vegetative bacteria have poor survival outside of an animal or human host; colony counts decline to undetectable within 24 hours following inoculation into water.[17] This contrasts with the environmentally hardy properties of the *B anthracis* spore, which can survive for decades.[30]

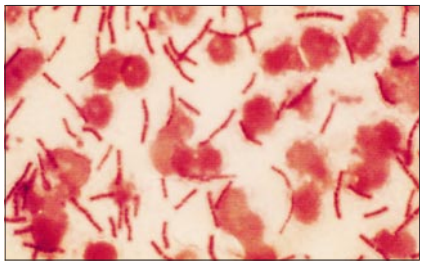
PATHOGENESIS AND CLINICAL MANIFESTATIONS

Inhalational Anthrax

Inhalational anthrax follows deposition of spore-bearing particles of 1 to 5 µm into alveolar spaces.[31,32] Macrophages ingest the spores, some of which undergo lysis and destruction. Surviving spores are transported via lymphatics to mediastinal lymph nodes, where germination may occur up to 60 days later.[28,29,33] The process responsible for the delayed transformation of spores to vegetative cells is poorly understood but well documented. In Sverdlovsk, cases occurred from 2 to 43 days after exposure.[8] In experimental monkeys, fatal disease occurred up to 58 days[28] and 98 days[34] after exposure. Viable spores have been demonstrated in the mediastinal lymph nodes of monkeys 100 days after exposure.[35]

Once germination occurs, disease follows rapidly. Replicating bacteria release toxins leading to hemorrhage, edema, and necrosis.[23,36] In experimental animals, once toxin production has reached critical threshold, death occurs even if sterility of the bloodstream is achieved with antibiotics.[19] Based on primate data, it has been estimated that for humans the LD 50 (lethal dose sufficient to kill 50% of persons exposed to it) is 2500 to 55 000 inhaled anthrax spores.[37]

Figure 1. Gram Stain of *Bacillus anthracis*



Gram-positive anthrax bacilli in a peripheral blood smear from a rhesus monkey that died of inhalational anthrax. Reprinted with permission from Zajtchuk and Bellamy.[23]

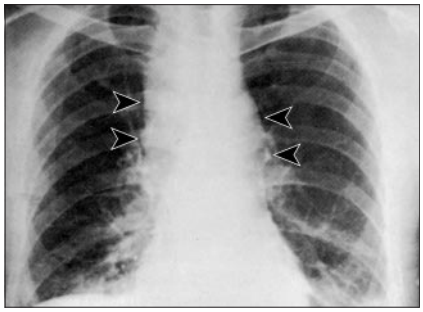
The term *inhalational anthrax* reflects the nature of acquisition of the disease. The term *anthrax pneumonia* is misleading. Typical bronchopneumonia does not occur. Postmortem pathological study of patients who died because of inhalational anthrax in Sverdlovsk showed hemorrhagic thoracic lymphadenitis and hemorrhagic mediastinitis in all patients. In up to half of the patients, hemorrhagic meningitis also was seen. No patients who underwent autopsy had evidence of a bronchoalveolar pneumonic process, although 11 of 42 patients undergoing autopsy had evidence of a focal, hemorrhagic, necrotizing pneumonic lesion analogous to the Ghon complex associated with tuberculosis.[38] These findings are consistent with other human case series and experimentally induced inhalational anthrax in animals.[33,39,40]

Early diagnosis of inhalational anthrax would be difficult and would require a high index of suspicion. Clinical information is available from only some of the 18 cases reported in the United States in this century and from the limited available information from Sverdlovsk. The clinical presentation has been described as a 2-stage illness. Pa-

tients first developed a spectrum of nonspecific symptoms, including fever, dyspnea, cough, headache, vomiting, chills, weakness, abdominal pain, and chest pain.[8,19] Signs of illness and laboratory studies were nonspecific. This stage of illness lasted from hours to a few days. In some patients, a brief period of apparent recovery followed. Other patients progressed directly to the second, fulminant stage of illness.[2,19,41]

This second stage developed abruptly, with sudden fever, dyspnea, diaphoresis, and shock. Massive lymphadenopathy and expansion of the mediastinum led to stridor in some cases.[42,43] A chest radiograph most often showed a widened mediastinum consistent with lymphadenopathy (FIGURE 2).[42] Up to half of patients developed hemorrhagic meningitis with concomitant meningismus, delirium, and obtundation. In this second stage of illness, cyanosis and hypotension progress rapidly; death sometimes occurs within hours.[2,19,41]

Figure 2. Chest Radiograph of a Patient With Inhalational Anthrax



Chest radiograph of a 51-year-old laborer with occupational exposure to airborne anthrax spores taken on day 2 of illness. Lobulated mediastinal widening (arrowheads) is present, consistent with lymphadenopathy, with a small parenchymal infiltrate at the left lung base. Reprinted with permission from Zajtchuk and Bellamy.[23]

The mortality rate of occupationally acquired cases in the United States is 89%, but the majority of cases occurred before the development of critical care units and, in some cases, before the advent of antibiotics.[19] At Sverdlovsk, it is reported that 68 of the 79 patients with inhalational anthrax died, although the reliability of the diagnosis in the survivors is questionable.[8] Patients who had onset of disease 30 or more days after release of organisms had a higher reported survival rate compared with those with earlier disease onset. Antibiotics, antianthrax globulin, and vaccine were used to treat some residents in the affected area some time after exposure, but which patients received these interventions and when is not known. In fatal cases, the interval between onset of symptoms and death averaged 3 days. This is similar to the disease course and case fatality rate in untreated experimental monkeys, which have developed rapidly fatal disease even after a latency as long as 58 days.[28]

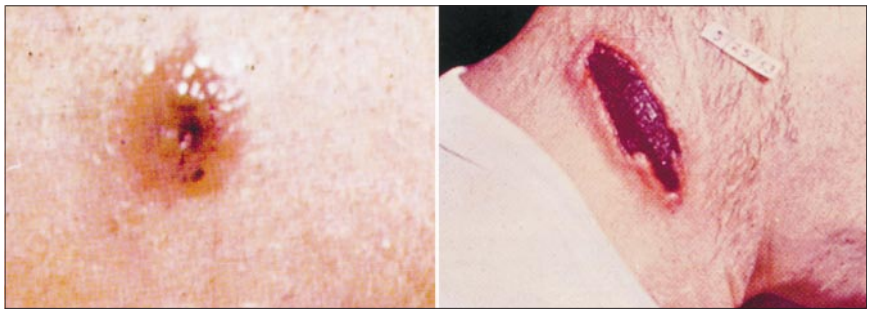
Modern mortality rates in the setting of contemporary medical and supportive therapy might be lower than those reported historically. However, the 1979 Sverdlovsk experience is not instructive. Although antibiotics, antianthrax globulin, corticosteroids, and mechanical ventilation were used, individual clinical records have not been made public.[8] It is also uncertain if the *B anthracis* strain to which patients were exposed was susceptible to the predominant antibiotics that were used during the outbreak.

Physiological sequelae of severe anthrax infection in animal models have been described as hypocalcemia, profound hypoglycemia, hyperkalemia, depression and paralysis of respiratory center, hypotension, anoxia, respiratory alkalosis, and terminal acidosis.[44,45] Those animal studies suggest that in addition to the rapid administration of antibiotics, survival might improve with vigilant correction of electrolyte disturbances and acid-base imbalance, glucose infusion, and early mechanical ventilation and vasopressor administration.

Cutaneous Anthrax

Cutaneous anthrax occurs following the deposition of the organism into skin with previous cuts or abrasions especially susceptible to infection.[21,46] Areas of exposed skin, such as arms, hands, face, and neck, are the most frequently affected. There are no data to suggest the possibility of a prolonged latency period in cutaneous anthrax. In Sverdlovsk, cutaneous cases occurred only as late as 12 days after the original aerosol release.[8] After the spore germinates in skin tissues, toxin production results in local edema (FIGURE 3). An initially pruritic macule or papule enlarges into a round ulcer by the second day. Subsequently, 1- to 3-mm vesicles may appear, which discharge clear or serosanguinous fluid containing numerous organisms on Gram stain. As shown in Figure 3, development of a painless, depressed, black eschar follows, often associated with extensive local edema. The eschar dries, loosens, and falls off in the next 1 to 2 weeks, most often leaving no permanent scar. Lymphangitis and painful lymphadenopathy can occur with associated systemic symptoms. Although antibiotic therapy does not appear to change the course of eschar formation and heal-

Figure 3. Cutaneous Anthrax



Left, Forearm lesion on day 7 of illness shows vesiculation and ulceration of the initial macular or papular anthrax skin lesion. Right, Eschar of the neck on day 15 of illness is typical of the last stage of the lesion before it resolves over 1 to 2 weeks. Reprinted with permission from Binford CH, Connor DH, eds. *Pathology of Tropical and Extraordinary Diseases.* Vol 1. Washington, DC: Armed Forces Institute of Pathology; 1976:119. AFIP negative 71-1290-2.

ing, it does decrease the likelihood of systemic disease. Without antibiotic therapy, the mortality rate has been reported to be as high as 20%; with antibiotics, death due to cutaneous anthrax is rare.[2]

Gastrointestinal Anthrax

Gastrointestinal anthrax occurs following deposition and subsequent germination of spores in the upper or lower gastrointestinal tract. The former results in the oral-pharyngeal form of disease.[24-26] An oral or esophageal ulcer leads to development of regional lymphadenopathy, edema, and sepsis.[24-26] The latter results in primary intestinal lesions occurring predominantly in the terminal ileum or cecum,[38] presenting initially with nausea, vomiting, and malaise and progressing rapidly to bloody diarrhea, acute abdomen, or sepsis.[22] Massive ascites has occurred in some cases of gastrointestinal anthrax.[27] Advanced infection may appear similar to the sepsis syndrome occurring in either inhalational or cutaneous anthrax.[2] Some authors suggest that aggressive medical intervention such as would be recommended for inhalational anthrax may reduce mortality, although, given the difficulty of early diagnosis, mortality almost inevitably would be high.[2,22]

DIAGNOSIS

Given the rarity of anthrax infection and the possibility that early cases are a harbinger of a larger epidemic, the first suspicion of an anthrax illness must lead to immediate notification of the local or state health department, local hospital epidemiologist, and local or state health laboratory. By this mechanism, definitive tests can be arranged rapidly through a reference laboratory and, as necessary, the US Army Medical Research Institute of Infectious Diseases (USAMRIID), Fort Detrick, Md.

The first evidence of a clandestine release of anthrax as a biological weapon most likely will be patients seeking medical treatment for symptoms of inhalational anthrax. The sudden appearance of a large number of patients in a city or region with an acute-onset flulike illness and case fatality rates of 80% or more, with nearly half of all deaths occurring within 24 to 48 hours, is highly likely to be anthrax or pneumonic plague (TABLE 1). Currently, there are no effective atmospheric warning systems to detect an aerosol cloud of anthrax spores.[47]

Table 1. Diagnosis of Inhalational Anthrax Infection

Epidemiology	Sudden appearance of multiple cases of severe flulike illness with fulminant course and high mortality
Diagnostic studies	Chest radiograph: widened mediastinum
	Peripheral blood smear: gram-positive bacilli on unspun smear
Microbiology	Blood culture growth of large gram-positive bacilli with preliminary identification of *Bacillus* species
Pathology	Hemorrhagic mediastinitis, hemorrhagic thoracic lymphadenitis, hemorrhagic meningitis

Rapid diagnostic tests for diagnosing anthrax, such as enzyme-linked immunosorbent assay for protective antigen and polymerase chain reaction, are available only at national reference laboratories. Given the limited availability of these tests and the time required to dispatch specimens and perform assays, rapid diagnostic testing would be primarily for confirmation of diagnosis and determining in vitro susceptibility to antibiotics. In addition, these tests will be used in the investigation and management of anthrax hoaxes, such as the series occurring in late 1998.[48] They would also be of value should suspicious materials in the possession of a terrorist be identified as possibly containing anthrax.

If only small numbers of cases present contemporaneously, the clinical similarity of early inhalational anthrax to other acute respiratory tract infections may delay initial diagnosis for some days. However, diagnosis of anthrax could soon become apparent through the astute recognition of an unusual radiological finding, identification in the microbiology laboratory, or recognition of specific pathologic findings. A widened mediastinum on chest radiograph (Figure 2) in a previously healthy patient with evidence of overwhelming flulike illness is essentially pathognomonic of advanced inhalational anthrax and should prompt immediate action.[23,42] Although treatment at this stage would be unlikely to alter the outcome of illness in the patient concerned, it might lead to earlier diagnosis in others.

Microbiologic studies can also demonstrate *B anthracis* and may be the means for initial detection of an outbreak. The bacterial burden may be so great in advanced infection that bacilli are visible on Gram stain of unspun peripheral blood, as has been demonstrated in primate studies (Figure 1). While this is a remarkable finding that would permit an astute clinician or microbiologist to make the diagnosis, the widespread use of automated cell-counter technology in diagnostic laboratories makes this unlikely.[41]

The most useful microbiologic test is the standard blood culture, which should show growth in 6 to 24 hours. If the laboratory has been alerted to the possibility of anthrax, biochemical testing and review of colonial morphology should provide a preliminary diagnosis 12 to 24 hours later. Definitive diagnosis would require an additional 1 to 2 days of testing in all but a few national reference laboratories. It should be noted, however, that if the laboratory has not been alerted to the possibility of anthrax, *B anthracis* may not be correctly identified. Routine laboratory procedures customarily identify a *Bacillus* species from a blood culture approximately 24 hours after growth, but most laboratories do not further identify *Bacillus* species unless specifically requested to do so. In the United States, the isolation of *Bacillus* species most often represents growth of *Bacillus cereus*. The laboratory and clinician must determine whether its isolation represents specimen contamination.[49] There have been no *B anthracis* bloodstream infections reported for more than 20

years. However, given the possibility of anthrax being used as a weapon and the importance of early diagnosis, it would be prudent for laboratory procedures to be modified so that *B anthracis* is excluded after identification of a *Bacillus* species bacteremia.

Sputum culture and Gram stain are unlikely to be diagnostic, given the lack of a pneumonic process.[30] If cutaneous anthrax is suspected, a Gram stain and culture of vesicular fluid will confirm the diagnosis.

A diagnosis of inhalational anthrax also might occur at postmortem examination following a rapid, unexplained terminal illness. Thoracic hemorrhagic necrotizing lymphadenitis and hemorrhagic necrotizing mediastinitis in a previously healthy adult are essentially pathognomonic of inhalational anthrax.[38,43] Hemorrhagic meningitis should also raise strong suspicion of anthrax infection.[23,38,43,50] Despite pathognomonic features of anthrax on gross postmortem examination, the rarity of anthrax makes it unlikely that a pathologist would immediately recognize these findings. If the case were not diagnosed at gross examination, additional days would likely pass before microscopic slides would be available to suggest the disease etiology.

VACCINATION

The US anthrax vaccine, an inactivated cell-free product, was licensed in 1970 and is produced by Bioport Corp, Lansing, Mich (formerly called the Michigan Biologic Products Institute). The vaccine is licensed to be given in a 6-dose series and has recently been mandated for all US military active- and reserve-duty personnel.[51] The vaccine is made from the cell-free filtrate of a nonencapsulated attenuated strain of *B anthracis*.[52] The principal antigen responsible for inducing immunity is the protective antigen.[18,23] A similar vaccine has been shown in 1 small placebo-controlled human trial to be efficacious against cutaneous anthrax.[53] As of March 1, 1999, approximately 590 000 doses of anthrax vaccine have been administered to US Armed Forces (Gary Strawder, Department of Defense, Falls Church, Va, oral communication, April 1999); no serious adverse events have been causally related (Miles Braun, Food and Drug Administration, Rockville, Md, written communication, April 1999). In a study of experimental monkeys, inoculation with this vaccine at 0 and 2 weeks was completely protective against an aerosol challenge at 8 and 38 weeks and 88% effective at 100 weeks.[54]

A human live attenuated vaccine is produced and used in countries of the former Soviet Union.[55] In the Western world, live attenuated vaccines have been considered unsuitable for use in humans.[55]

Current vaccine supplies are limited and the US production capacity is modest. It will be years before increased production efforts can make available sufficient quantities of vaccine for civilian use. However, even if vaccine were available, populationwide vaccination would not be recommended at this time, given the costs and logistics of a large-scale vaccination program and the unlikely occurrence of a bioterrorist attack in any given community. Vaccination of some essential service personnel should be considered if vaccine becomes available. Postexposure vaccination following a biological attack with anthrax would be recommended with antibiotic administration to protect against residual retained spores, if vaccine were available.

THERAPY

Recommendations regarding antibiotic and vaccine use in the setting of a biological anthrax attack are conditioned by a limited number of studies in experimental animals, current understanding of antibiotic resistance patterns, and the possible requirement to treat large numbers of casualties. A number of possible therapeutic strategies have yet to be fully explored experimentally or submitted for approval to the FDA. For these reasons, the working group offers consensus recommendations based on the best available evidence. The recommendations do not represent uses currently approved by the FDA or an official position on the part of any of the federal agencies whose scientists participated in these discussions and will need to be revised as further relevant information becomes available.

Given the rapid course of symptomatic inhalational anthrax, early antibiotic administration is essential. A delay of antibiotic treatment for patients with anthrax infection even by hours may substantially lessen chances for survival.[56,57] Given the difficulty in achieving rapid microbiologic diagnosis of anthrax, all persons with fever or evidence of systemic disease in an area where anthrax cases are occurring should be treated for anthrax until the disease is excluded.

There are no clinical studies of the treatment of inhalational anthrax in humans. Thus, antibiotic regimens commonly recommended for empirical treatment of sepsis have not been studied in this setting. In fact, natural strains of *B anthracis* are resistant to many of the antibiotics used in these empirical regimens, such as those of the extended-spectrum cephalosporins.[58,59] Most naturally occurring anthrax strains are sensitive to penicillin, and penicillin historically has been the preferred therapy for the treatment of anthrax. Penicillin is approved by the FDA for this indication,[41,56,57] as is doxycycline.[60] In studies of small numbers of monkeys infected with susceptible strains of *B anthracis*, oral doxycycline has proved efficacious.[41]

Doxycycline is the preferred option from the tetracycline class of antibiotics because of its proven efficacy in monkey studies and its ease of administration. Other members of this class of antibiotics are suitable alternatives. Although treatment of anthrax infection with ciprofloxacin has not been studied in humans, animal models suggest excellent efficacy.[28,41,61] In vitro data suggest that other fluoroquinolone antibiotics would have equivalent efficacy in treating anthrax infection, although no animal data exist for fluoroquinolones other than ciprofloxacin.[59]

Reports have been published of a *B anthracis* vaccine strain that has been engineered by Russian scientists to resist the tetracycline and penicillin classes of antibiotics.[62] Although the engineering of quinolone-resistant *B anthracis* may also be possible, to date there have been no published accounts of this.

Balancing considerations of efficacy with concerns regarding resistance, the working group recommends that ciprofloxacin or other fluoroquinolone therapy be initiated in adults with presumed inhalational anthrax infection. Antibiotic resistance to penicillin- and tetracycline-class antibiotics should be assumed following a terrorist attack until laboratory testing demonstrates otherwise. Once the antibiotic susceptibility of the *B anthracis* strain of the index case has been determined, the most widely available, efficacious, and least toxic antibiotic should be administered to patients and persons requiring postexposure prophylaxis.

In a contained casualty setting (a situation in which a modest number of patients require therapy), the working group recommends intravenous antibiotic therapy, as shown in TABLE 2. If the number of persons requiring therapy is sufficiently high (ie, a mass casualty setting), the working group recognizes that intravenous therapy will no longer be possible for reasons of logistics and/or exhaustion of equipment and antibiotic supplies, and oral therapy will need to be used (TABLE 3). The threshold number of cases at which parenteral therapy becomes impossible depends on a variety of factors, including local and regional health care resources.

In experimental animals, antibiotic therapy during anthrax infection has prevented development of an immune response.[28,62] This suggests that even if the antibiotic-treated patient survives anthrax infection, risk for recurrence remains for at least 60 days because of the possibility of delayed germination of spores. Therefore, the working group recommends that antibiotic therapy be continued for 60 days, with oral therapy replacing intravenous therapy as soon as a patient's clinical condition improves. If vaccine were to become widely available, postexposure vaccination in patients being treated for anthrax infection might permit the duration of antibiotic administration to be shortened to 30 to 45 days, with concomitant administration of 3 doses of anthrax vaccine at 0, 2, and 4 weeks.

The treatment of cutaneous anthrax historically has been with oral penicillin. The working group recommends that oral fluoroquinolone or tetracycline antibiotics as well as amoxicillin in the adult dosage schedules described in Tables 2 and 3 would be suitable alternatives if antibiotic susceptibility is proved. Although previous guidelines have suggested treating cutaneous anthrax for 7 to 10 days,[23,49] the working group recommends treatment for 60 days in the setting of bioterrorism, given the presumed exposure to the primary aerosol. Treatment of cutaneous anthrax generally prevents progression to systemic disease, although it does not prevent the formation and evolution of the eschar. Topical therapy is not useful.[2]

Other antibiotics effective against *B anthracis* in vitro include chloramphenicol, erythromycin, clindamycin, extended-spectrum penicillins, macrolides, aminoglycosides, vancomycin hydrochloride, cefazolin, and other first-generation cephalosporins.[58,59,64] The efficacy of these antibiotics has not been tested in humans or animal studies. The working group recommends the use of these antibiotics only if the previously cited antibiotics are unavailable or if the strain is otherwise antibiotic resistant. Natural resistance of *B anthracis* strains exists against sulfamethoxazole, trimethoprim, cefuroxime, cefotaxime sodium, aztreonam, and ceftazidime.[58,59,64] Therefore, these antibiotics should not be used in the treatment or prophylaxis of anthrax infection.

Postexposure Prophylaxis

Guidelines regarding which populations would require postexposure prophylaxis following the release of anthrax as a biological weapon would need to be developed quickly by state and local health departments in consultation with national experts. These decisions require estimates of the timing and location of the exposure and the relevant weather conditions in an outdoor release.[65] Ongoing monitoring of cases would be needed to define the

Table 2. Working Group Recommendations for Medical Therapy for Patients With Clinically Evident Inhalational Anthrax Infection in the Contained Casualty Setting[28,41,60,62,63]*

	Initial Therapy†	Optimal Therapy if Strain Is Proven Susceptible	Duration, d‡
Adults	Ciprofloxacin, 400 mg intravenously every 12 h	Penicillin G, 4 million U intravenously every 4 h Doxycycline, 100 mg intravenously every 12 h§	60
Children‖	Ciprofloxacin, 20-30 mg/kg per day intravenously divided into 2 daily doses, not to exceed 1 g/d	Age <12 y: penicillin G, 50 000 U/kg intravenously every 6 h Age ≥12 y: penicillin G, 4 million U intravenously every 4 h	60
Pregnant women¶	Same as for nonpregnant adults		
Immunosuppressed persons	Same as for nonimmunosuppressed adults and children		

*Most recommendations are based on animal studies or in vitro studies and are not approved by the US Food and Drug Administration (FDA). These recommendations are not FDA approved but were reached by consensus of the working group. See text for explanations and alternatives.
†In vitro studies suggest ofloxacin, 400 mg intravenously every 12 hours, or levofloxacin, 500 mg intravenously every 24 hours, could be substituted for ciprofloxacin.
‡Oral antibiotics should be substituted for intravenous antibiotics as soon as clinical condition improves.
§In vitro studies suggest tetracycline could be substituted for doxycycline.
‖Doxycycline could also be used. For children heavier than 45 kg, use adult dosage. For children 45 kg or lighter, use 2.5 mg/kg doxycycline intravenously every 12 hours. Refer to management of pediatric population in text for details.
¶Refer to section on management of pregnant women in text for details.

high-risk areas, direct follow-up, and guide the addition or deletion of groups to receive postexposure prophylaxis.

There are no FDA-approved postexposure antibiotic regimens following exposure to an anthrax aerosol. For postexposure prophylaxis, the working group recommends the same antibiotic regimen as that recommended for treatment of mass casualties; prophylaxis should be continued for 60 days (Table 3).

Management of Special Groups

Consensus recommendations for special groups as set forth herein reflect the clinical and evidence-based judgments of the working group and at this time do not necessarily correspond with FDA-approved use, indications, or labeling.

Children. It has been recommended that ciprofloxacin and other fluoroquinolones should not be used in children younger than 16 to 18 years because of a link to permanent arthropathy in adolescent animals and transient arthropathy in a small number of children.[60] However, balancing these risks against the risks of anthrax caused by an engineered antibiotic-resistant strain, the working group recommends that ciprofloxacin be used in the pediatric population for initial therapy or postexposure prophylaxis following an anthrax attack (Table 2). If antibiotic susceptibility testing allows, penicillin should be substituted for the fluoroquinolone.

As a third alternative, doxycycline could be used. The American Academy of Pediatrics has recommended that doxycycline not be used in children younger than 9 years because the drug has resulted in retarded skeletal growth in infants and discolored teeth in infants and children.[60] However, the serious risk of infection following an anthrax attack supports the consensus recommendation that doxycycline be used in children if antibiotic susceptibility testing, exhaustion of drug supplies, or allergic reaction preclude use of penicillin and ciprofloxacin.

In a contained casualty setting, the working group recommends that children receive intravenous antibiotics (Table 2). In a mass casualty setting and as postexposure prophylaxis, the working group recommends that children receive oral antibiotics (Table 3).

The US vaccine is licensed for use only in persons aged 18 to 65 years because studies to date have been conducted exclusively in this group.[52] No data exist for children, but based on experience with other inactivated vaccines, it is likely that the vaccine would be safe and effective.

Pregnant Women. Fluoroquinolones are not generally recommended during pregnancy because of their known association with arthropathy in adolescent animals and small numbers of children. Animal studies have discovered no evidence of teratogenicity related to ciprofloxacin, but no controlled studies of ciprofloxacin in pregnant women have been conducted. Balancing these possible risks against the concerns of anthrax due to engineered antibiotic-resistant strains, the working group recommends that ciprofloxacin be used in pregnant women for therapy and postexposure prophylaxis following an anthrax attack (Tables 2 and 3). No adequate controlled trials of penicillin or amoxicillin administration during pregnancy exist. However, the CDC recommends penicillin for the treatment of syphilis during pregnancy and amoxicillin as a treatment alternative for chlamydial infections during pregnancy.[60]

The working group recommends that pregnant women receive fluoroquinolones in the usual adult dosages. If susceptibility testing allows, intravenous penicillin in the usual adult dosages should be substituted for fluoroquinolones. As a third alternative, intravenous doxycycline could be used. The tetracycline class of antibiotics has been associated with both toxic effects in the liver in pregnant women and fetal toxic effects, including retarded skeletal growth.[60] Balancing the risks of anthrax infection with those associated with doxycycline use in pregnancy, the working group recommends that doxycycline be used in pregnant women for therapy and postexposure prophylaxis if antibiotic susceptibility testing, exhaustion of drug supplies, or allergic sensitivity preclude the use of penicillin and ciprofloxacin. If doxycycline is used in pregnant women, periodic liver function testing should be performed if possible.

Table 3. Working Group Recommendations for Medical Therapy for Patients With Clinically Evident Anthrax Infection in the Mass Casualty Setting or for Postexposure Prophylaxis[41]*

	Initial Therapy†	Optimal Therapy if Strain Is Proven Susceptible	Duration, d
Adults	Ciprofloxacin, 500 mg by mouth every 12 h	Amoxicillin, 500 mg every 8 h Doxycycline, 100 mg by mouth every 12 h‡	60
Children§	Ciprofloxacin, 20-30 mg/kg per day by mouth divided into 2 daily doses, not to exceed 1 g/d	Weight ≥20 kg: amoxicillin, 500 mg by mouth every 8 h Weight <20 kg: amoxicillin, 40 mg/kg divided into 3 doses to be taken every 8 h	60
Pregnant women‖	Ciprofloxacin, 500 mg by mouth every 12 h	Amoxicillin, 500 mg by mouth every 8 h	60
Immunosuppressed persons	Same as for nonimmunosuppressed adults and children		

*Most recommendations are based on animal studies or in vitro studies and are not approved by the US Food and Drug Administration (FDA). These recommendations are not FDA approved but were reached by consensus of the working group. See text for explanations and alternatives.
†In vitro studies suggest ofloxacin, 400 mg by mouth every 12 hours, or levofloxacin, 500 mg by mouth every 24 hours, could be substituted for ciprofloxacin.
‡In vitro studies suggest tetracycline, 500 mg by mouth every 6 hours, could be substituted for doxycycline.
§Doxycycline could also be used. For children heavier than 45 kg, use adult dosage. For children 45 kg or lighter, use 2.5 mg/kg doxycycline by mouth every 12 hours. Refer to management of pediatric population in text for details.
‖Refer to management of pregnant population in text for details.

Ciprofloxacin (and other fluoroquinolones), penicillin, and doxycycline (and other tetracyclines) are each excreted in breast milk. Therefore, a breast-feeding woman should be treated or given prophylaxis with the same antibiotic as her infant based on what is most safe and effective for the infant (see pediatric guidelines herein) to minimize risk to the infant.

Immunosuppressed Persons. The antibiotic treatment or postexposure prophylaxis for anthrax among those who are immunosuppressed has not been studied in human or animal models of anthrax infection. Therefore, the working group consensus recommendation is to administer antibiotics as for immunocompetent adults and children (Tables 2 and 3).

INFECTION CONTROL

There are no data to suggest patient-to-patient transmission of anthrax occurs.[8,46] Thus, standard barrier isolation precautions are recommended for hospitalized patients with all forms of anthrax infection, but the use of high-efficiency particulate air filter masks or other measures for airborne protection are not indicated.[66] There is no need to immunize or provide prophylaxis to patient contacts (eg, household contacts, friends, coworkers) unless a determination is made that they, like the patient, were exposed to the aerosol at the time of the attack.

In addition to immediate notification of the hospital epidemiologist and state health department, the local hospital microbiology laboratories should be notified at the first indication of anthrax so that safe specimen processing under biosafety level 2 conditions can be undertaken.[41,67] A number of disinfectants used for standard hospital infection control, such as hypochlorite, are effective in cleaning environmental surfaces contaminated with infected bodily fluids.[17,66]

Proper burial or cremation of humans and animals who have died because of anthrax infection is important in preventing further transmission of the disease. Serious consideration should be given to cremation. Embalming of bodies could be associated with special risks.[66] If autopsies are performed, all related instruments and materials should be autoclaved or incinerated.[66] Animal transmission might occur if infected animal remains are not cremated or buried.[16,21]

Figure 4. Day of Onset of Inhalational Anthrax Following Sverdlovsk Accident

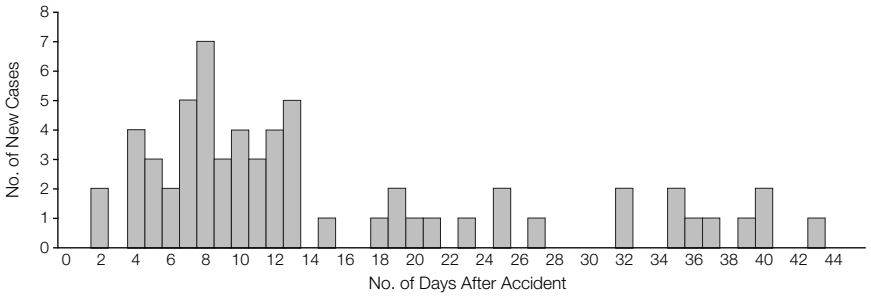


Figure is based on data from Guillermin.[68]

DECONTAMINATION

Recommendations regarding decontamination in the event of an intentional aerosolization of anthrax spores are based on evidence concerning aerosolization, anthrax spore survival, and environmental exposures at Sverdlovsk and among goat hair mill workers. The greatest risk to human health following an intentional aerosolization of anthrax spores occurs during the period in which anthrax spores remain airborne, called *primary aerosolization*. The duration for which spores remain airborne and the distance spores travel before they become noninfectious or fall to the ground is dependent on meteorological conditions and aerobiological properties of the dispersed aerosol.[8,65] Under circumstances of maximum survival and persistence, the aerosol would be fully dispersed within hours to 1 day at most, well before the first symptomatic cases would be seen. Following the discovery that a bioweapon has been used, anthrax spores may be detected on environmental surfaces using rapid assay kits or culture, but they provide no indication as to the risk of reaerosolization.

The risk that anthrax spores might pose to public health after the period of primary aerosolization can be inferred from the Sverdlovsk experience, investigations in animal hair processing plants, and modeling analyses by the US Army. At Sverdlovsk, new cases of inhalational anthrax developed as late as 43 days after the presumed date of release, but none occurred during the months and years afterward.[68] Some have questioned whether any of those cases with onset of disease beyond 7 days might have represented illness following resuspension of spores from the ground or other surfaces, a process that has been called *secondary aerosolization*. While it is impossible to state with certainty that secondary aerosolizations did not occur, it appears unlikely. It should be noted that few efforts were made to decontaminate the environment after the accident and only 47 000 of the city's 1 million inhabitants were vaccinated.[8] The epidemic curve (FIGURE 4) is typical for a common-source epidemic, and it is possible to account for virtually all patients having been within the area of the plume on the day of the accident. Moreover, if secondary aerosolization had been important, new cases almost certainly would have continued for a period well beyond the observed 43 days.

Although persons working with animal hair or hides are known to be at increased risk of developing inhalational or cutaneous anthrax, surprisingly few of those exposed in the United States have developed disease. During the first half of this century, a significant number of goat hair mill workers were likely exposed to aerosolized spores. Mandatory vaccination became a requirement

for working in goat hair mills only in the 1960s. Meanwhile, many unvaccinated person-years of high-risk exposure had occurred, but only 13 cases of inhalational anthrax were reported.[19,44] One study of environmental exposure was conducted at a Pennsylvania goat hair mill at which workers were shown to inhale up to 510 *B anthracis* particles of at least 5 µm in diameter per person per 8-hour shift. These concentrations of spores were constantly present in the environment during the time of this study,[44] but no cases of inhalational anthrax occurred.

Modeling analyses have been carried out by US Army scientists seeking to determine the risk of secondary aerosolization. One study concluded that there was no significant threat to personnel in areas contaminated by 1 million spores per square meter either from traffic on asphalt-paved roads or from a runway used by helicopters or jet aircraft.[69] A separate study showed that in areas of ground contaminated with 20 million *Bacillus subtilis* spores per square meter, a soldier exercising actively for a 3-hour period would inhale between 1000 and 15 000 spores.[70]

Much has been written about the technical difficulty of decontaminating an environment contaminated with anthrax spores. A classic case is the experience at Gruinard Island in the United Kingdom. During World War II, British military undertook explosives testing with anthrax spores on this island off the Scottish coast. Spores persisted and remained viable for 36 years following the conclusion of testing. Decontamination of the island occurred in stages, beginning in 1979 and ending in 1987, when the island was finally declared fully decontaminated. The total cost is unpublished, but materials required included 280 tons of formaldehyde and 2000 tons of seawater.[17,71]

If an environmental surface is proved to be heavily contaminated with anthrax spores in the immediate area of a spill or close proximity to the point of release of an anthrax aerosol, decontamination of that area may decrease the slight risk of acquiring anthrax by secondary aerosolization. However, decontamination of large urban areas or even a building following an exposure to an anthrax aerosol would be extremely difficult and is not indicated. Although the risk of disease caused by secondary aerosolization would be extremely low, it would be difficult to offer absolute assurance that there was not risk whatsoever. Postexposure vaccination, if vaccine were available, might be a possible intervention that could further lower the risk of anthrax infection in this setting.

In the setting of an announced alleged anthrax release, such as the series of anthrax hoaxes occurring in many areas of the United States in 1998,[48] any person coming in direct physical contact with a substance alleged to be anthrax should perform thorough washing of the exposed skin and articles of clothing with soap and water.[72] Further decontamination of directly exposed individuals or of others is not indicated. In addition, any person in direct physical contact with the alleged substance should receive postexposure antibiotic prophylaxis until the substance is proved not to be anthrax. If the alleged substance is proved to be anthrax, immediate consultation with experts at the CDC and USAMRIID should be obtained.

ADDITIONAL RESEARCH

To develop a maximally effective response to a bioterrorist incident involving anthrax, the medical community will require new knowledge of the organism, its genetics and pathogenesis, improved rapid diagnostic techniques, improved prophylactic and therapeutic regimens, and an improved second-generation vaccine.[47] A recently published Russian study indicates that genes transferred from the related *B cereus* can act to enable *B anthracis* to evade the protective effect of the live attenuated Russian vaccine in a rodent model.[73] Research is needed to determine the role of these genes with respect to virulence and ability to evade vaccine-induced immunity. Furthermore, the relevance of this finding for the US vaccine needs to be established. An accelerated vaccine development effort is needed to allow the manufacture of an improved second-generation product that requires fewer doses. Finally, an expanded knowledge base is needed regarding possible maximum incubation times after inhalation of spore-containing aerosols and optimal postexposure antibiotic regimens.

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