Zoonosis Update

Anthrax

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Anthrax is an ancient zoonotic disease that continues to threaten human and animal health. It remains enzootic in many regions of the world, and cases of anthrax among humans are frequently reported. Outbreaks occur annually among wild and domestic herbivores in North America, although this infection is no longer a substantial cause of human disease in the United States. As a result of the occurrence of anthrax worldwide, and because of its bioterrorist potential, veterinarians should understand the epidemiology, clinical signs, treatment, and control of anthrax.

Background

Anthrax is the infection caused by the spore-forming bacterium *Bacillus anthracis*. In Europe in the 19th century, anthrax outbreaks caused substantial loss of livestock and human life, stimulating early study of the disease. In 1877, Robert Koch isolated a bacillus from animals that had died from anthrax and grew the organism in a sterile medium; the spores produced were used to infect mice.[1] On the basis of the results of that experiment, anthrax was the first disease for which a single microorganism was proven to be the etiologic agent and what are now known as Koch's postulates were demonstrated for the first time. The development of the highly effective Sterne vaccine in 1937[2,3] and the introduction of penicillin for treatment of infected animals provided the means to control anthrax among livestock and to reduce spread of the disease to humans. Nevertheless, anthrax epizootics still occur every year, resulting in the deaths of hundreds of animals and development of disease among humans.

Microbiologic Characteristics

Bacillus anthracis is a sporulating, nonmotile, gram-positive rod bacterium. It grows well on various bacterial culture media, with optimal growth occurring at 37°C (98.6°F). In blood or tissues of infected hosts, the large bacilli grow in chains and produce a characteristic capsule that is visible when stained with polychrome methylene blue (M'Fadyean reaction).[4] *Bacillus anthracis* can be differentiated from other bacilli on the basis of the presence of a capsule, susceptibility to penicillin, lack of motility, absence or delayed hemolysis when cultured on blood agar, and susceptibility to γ phage.[4–6] The bacillus sporulates during nutrient deprivation and exposure to air, as occurs during in vitro cultivation or when an infected carcass is disrupted by scavengers or during necropsy. The spores have no measurable metabolic activity and can remain dormant in the environment for decades; they are resistant to aridity, heat, UV light, and many chemical disinfectants.[7,8] In contrast, the vegetative bacilli are susceptible to desiccation, high temperatures, and chemical disinfectants.

Germination of *B anthracis* spores is influenced by temperature, pH, moisture, oxygen, carbon dioxide, and the presence of nutrients such as L-alanine.[9] Germination is triggered following entry into a host through ingestion or inhalation or via introduction through the skin.

Abbreviations

ET	Edema toxin
LT	Lethal toxin
MIC	Minimum inhibitory concentration
PA	Protective antigen
PEP	Postexposure prophylaxis

Pathogenesis

Bacillus anthracis has 3 main virulence factors: the poly-D-glutamic acid capsule and 2 protein exotoxins, ET and LT.[10] These 3 virulence factors are encoded on 2 plasmids, pXO1 and pXO2. Attenuated vaccine strains carry only 1 of the 2 plasmids, such as the Sterne strain that contains only pXO1 and the Pasteur strain that contains only pXO2.[11]

The pXO1 plasmid encodes for 3 components that comprise the 2 exotoxins: edema factor, lethal factor, and PA. Protective antigen, named for the protective immunity it induces against *B anthracis* infection, combines with either edema factor or lethal factor to form ET or LT, respectively.[12,13] After a certain critical stage in infection, animals may still die as a result of the effects of the toxins despite antimicrobial-assisted clearance of bacteremia.[14]

In animals, injection of ET causes development of tissue edema[15,16] and impairs host defenses, including inhibition of neutrophil function and phagocytosis, which may play a factor in host susceptibility to *B anthracis* infection.[17–19] Lethal toxin causes hypoxic tissue injury, liver failure, and shock[20]; injection of LT results in death in various susceptible animals.[20–23] Further-

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more, LT inhibits the expression of proinflammatory cytokines and chemokines,[24,25] induces macrophage apoptosis and lysis,[26–28] and decreases macrophage clearance of phagocytosed spores.[29] In combination, ET and LT inhibit the clearance of bacteria by phagocytes and facilitate the escape of bacilli from macrophages, thus allowing overwhelming bacteremia and toxemia to develop.[30] Together, they also allow *B anthracis* to evade killing by polymorphonuclear leukocytes.[19] Lethal toxin additionally blocks B-cell proliferation and immunoglobulin production,[31] and ET and LT suppress T-cell activation and proliferation, even at low concentrations.[32,33]

The pXO2 plasmid contains the genes for the capsule.[5] The capsule is weakly antigenic and protects vegetative bacilli from phagocytosis by host macrophages; unencapsulated strains that do not carry the pXO2 plasmid are effectively phagocytosed and killed by macrophages.[34]

Ecologic and Epidemiologic Features

The natural reservoir of *B anthracis* is soil. Outbreaks in animals are often associated with low-lying areas with soil that has high moisture and organic contents and alkaline pH.[35,36] Grazing animals are thought to become infected when they ingest *B anthracis* spores on vegetation in an area where the soil or water sources are contaminated by the spores. Vegetative bacilli are shed in blood and other discharges from infected animals that are dying or dead. Those bacilli then sporulate and contaminate the underlying and immediately surrounding soil and water sources. Sporulation also occurs when infected carcasses are disrupted by scavenger activity. The spores are concentrated by water runoff into low-lying areas[8,37,38] and can remain viable and infective in soil for decades.[7] In the intact carcass of an animal that has died as a result of anthrax, the vegetative bacilli are unable to compete with anaerobic bacteria, and at temperatures greater than 25°C, the vegetative bacilli will die within 2 to 3 days because of the putrefactive processes in the decomposing carcass.[39,40] Only if the carcass is disrupted or discharges are released will the vegetative bacilli be able to reach an aerobic environment and sporulate. In a nonintact carcass, drying of tissues and aerosolization of body fluids occur; by these processes, the vegetative bacilli are exposed to nutrient-depleted microenvironments in which sporulation is stimulated.[36]

Anthrax most commonly develops in domestic and wild herbivores, such as cattle, sheep, goats, bison, antelope, and deer. In North America, outbreaks of the disease typically occur in the summer during prolonged periods of hot, dry weather that follow heavy rain and flooding. Additionally, outbreaks may be triggered by disruption of the soil in areas where anthrax-affected carcasses have been buried or may develop as a result of animal consumption of contaminated foodstuffs, such as animal-origin feed, or water contaminated by wastewaters from industries, such as tanneries, that process anthrax-contaminated animal materials.[41–43] The activity of scavenging animals and birds may help disseminate the spores in the environment as well as disrupt infected carcasses.[39,44] Blowflies may contaminate vegetation after feeding on infected carcasses, and biting flies may act as mechanical vectors,[8,39,45] thereby contributing to disease transmission.

The incidence of anthrax in animal populations varies geographically, but the disease is detected globally. It is most common in agricultural regions in South and Central America, sub-Saharan Africa, central and southwestern Asia, and southern and eastern Europe.[46,47] Outbreaks may be devastating and frequently involve both wildlife and livestock.[39,47,48] In North America, there has been a notable decrease in the incidence of anthrax in animals over the past half century as a result of disease control programs (**Figure 1**). Individual cases or outbreaks are still reported annually in the United States; an outbreak in cattle and bison that occurred in North Dakota in 2005 was more extensive than any anthrax epizootic previously recorded in the history of that state.[49,50]

In humans, anthrax primarily develops following exposure to infected animals, tissues, or products from infected animals or to spores of *B anthracis*.[51,52] Anthrax in humans has historically been grouped into either agricultural (nonindustrial) or industrial exposures.[4,52] Both of these occupational exposures are considered naturally occurring, as opposed to resulting from biological warfare or terrorist activity. Agricultural exposures occur among persons with direct contact with sick or dying *B anthracis*–infected animals or through handling of the carcasses or tissues of such animals.[53–56] At-risk

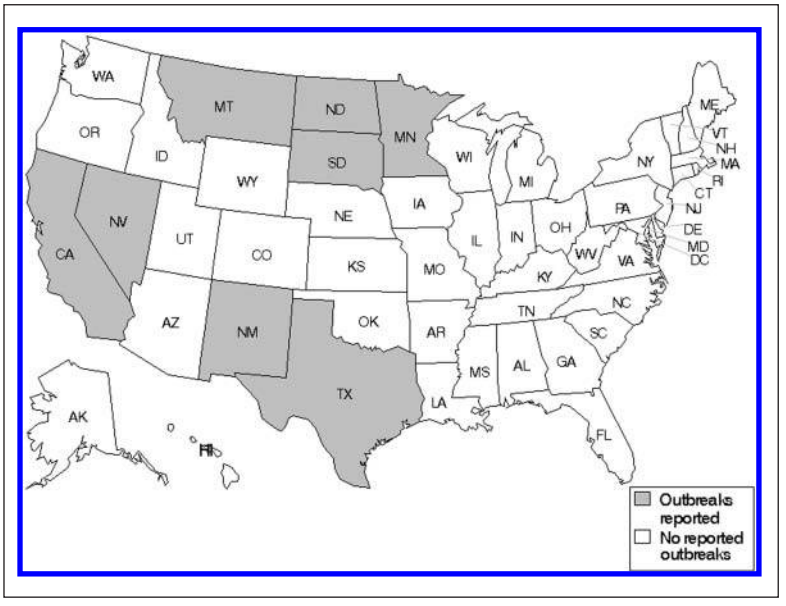

Figure 1—Geographic distribution (by state) of epizootic anthrax cases or outbreaks in the United States reported in livestock and wildlife populations during the 10-year period from 1997 through 2006.[49,50] By comparison, in 1952, there were 1,644 anthrax outbreaks reported in 32 states.[43]

persons include ranchers, veterinarians, slaughterhouse workers, and butchers. Among 24 anthrax outbreaks in agricultural settings that were investigated by the CDC between 1952 and 2001, cutaneous anthrax developed in 6 veterinarians who performed necropsies on infected animals. In 1 of those 6 cases, the individual did not wear gloves during the procedure, and in another, the lesion developed on potentially uncovered skin on the wrist.[54] Industrial exposures result from cutaneous inoculation or inhalation of particles containing anthrax spores that are generated during the cleaning and industrial processing of contaminated hides, hair, or wool from infected animals. Workers in wool- and mohair-processing facilities were particularly at risk for disease.[51,54]

The incidence of naturally occurring anthrax in humans decreased during the past century, and it is now relatively infrequent in developed countries as a result of animal disease control; improvements in industrial hygiene; and a decrease in the use of imported, contaminated raw materials. In the United States, the incidence in humans declined from an estimated 130 cases annually in the early 1900s to no more than 2 cases/y by the end of the century.[57] However, a more recent manifestation of industrial exposure has emerged with the occurrence of anthrax in workers who use contaminated animal hides for drum making,[58] and cutaneous or inhalation anthrax among persons who have played contaminated goatskin drums has been reported.[59,60] The disease in humans also develops following domestic uses of products derived from animals with anthrax,[43,61] such as persons working with anthrax-contaminated wool yarn[62] or bone-meal fertilizer.[63] An additional occupational risk exists for laboratory workers, who are at risk for infection when working with cultures of *B anthracis*, especially cultures that contain spores.[64,65]

Anthrax has a history of use as a biological agent against both human and animal populations and is regarded as a serious antilivestock agent.[66,67] It is considered to be an important biowarfare or bioterrorism threat because of the persistence of the *B anthracis* spores, the ability of aerosolized spores to readily cause infection after inhalation, and the high mortality rate among resultant anthrax cases.[52,68] In 2001, the threat that anthrax poses as a bioterrorism agent for groups of workers or entire populations not previously at risk was revealed. In October and November of 2001, 22 confirmed or suspected cases of anthrax (including 5 associated deaths) were identified in the eastern United States after *B anthracis* spores were sent through the mail in powder-containing envelopes to news media companies and US congressional leaders. Twenty of the cases were either mail handlers or persons exposed to buildings in which contaminated mail was processed or received.[69]

Anthrax in Nonhuman Animals

Nonhuman animals most often develop anthrax following ingestion of spore-contaminated foodstuffs. Among domestic species, herbivores (eg, cattle, sheep, and goats) are considered to be most susceptible; carnivorous and omnivorous species (eg, felids, pigs, and canids) are generally more resistant to anthrax than herbivores.[39,70] In some outbreaks, the attack rate has been reported to be higher in horses than in cattle.[71,72]

In livestock, the incubation period after exposure to *B anthracis* spores is typically 3 to 7 days, but may range from < 1 day to 14 days or more. Once clinical signs appear, animals usually die within 2 days. In susceptible species, the disease may rapidly progress (within hours) from mild nonspecific illness to death.[71] Often, the first indication of an outbreak of anthrax is finding dead animals. The principle lesions in animals that are dying from anthrax are those of fulminant systemic disease with widespread edema, hemorrhage and hemorrhagic discharges from the orifices, and necrosis. Rapid postmortem decomposition follows with bloating and incomplete development of rigor mortis, often with petechiae and ecchymoses.[44,73] If anthrax is suspected as the cause of death in any animal, the carcass should not be incised to prevent sporulation and dissemination of spores. Such animals should not be butchered nor their meat handled to prevent potential human cutaneous or gastrointestinal exposure.

Anthrax in Humans

Anthrax in humans may develop in 3 forms depending on the route of exposure. Introduction of the spores through the skin via direct contact can result in cutaneous anthrax. Ingestion of infected and undercooked or raw meat can result in gastrointestinal anthrax. Inhalation of aerosolized spores can result in inhalation anthrax. Anthrax in humans is not generally considered to be contagious. Susceptibility among humans most likely varies with the route of inoculation; relatively few spores are required to cause cutaneous anthrax, whereas exposures to larger amounts of spores are necessary to cause gastrointestinal or inhalation anthrax.

Cutaneous anthrax—Cutaneous anthrax comprises 95% to 99% of cases among humans worldwide.[4,74] Cutaneous anthrax develops following inoculation of spores into subcutaneous tissues, usually through contact with infected animal products. Cuts or abrasions increase susceptibility to infection[75]; however, cutaneous anthrax in humans with no history or evidence of preexisting skin lesions has been reported.[76,77] In a laboratory study,[78] cutaneous anthrax was induced in mice via epicutaneous inoculation of spores onto unshaved, intact skin; infective foci were subsequently detected in hair follicles. In humans, the incubation period for cutaneous anthrax is approximately 5 to 7 days (range, 1 to 12 days).[79] Most cutaneous lesions develop in exposed areas such as the face, neck, arms, and hands. Typically, a lesion begins as a small, painless, often pruritic papule that enlarges and develops a central vesicle or bulla; the bulla becomes hemorrhagic and ruptures, leaving an underlying necrotic ulcer. A characteristic black eschar develops over the surface of the ulcer. Satellite vesicles and ulcers may also form.[80] Edematous swelling of the surrounding tissues is present, often with regional lymphadenopathy and lymphangitis. The painless ulcer with blackened eschar and surrounding area of edema is considered the hallmark appearance of cutaneous anthrax. Fever, malaise, and headache can also develop.[56] The case fatality rate among hu-

mans with cutaneous anthrax can be as high as 20% without appropriate treatment but is typically < 1% if antimicrobials are administered.[4,52] Complications may include edema-associated tracheal compression and asphyxiation.[81] Malignant edema involving severe edema, induration, and shock may develop.

Inhalation anthrax—Inhalation anthrax in humans results from the inhalation of aerosolized *B anthracis* spore–containing particles (≤ 5 µm in size) that are deposited on alveolar ducts or alveoli.[82] The spores are phagocytosed by alveolar macrophages.[83] Some spores are lysed,[34,84] whereas others are transported to pulmonary-associated lymph nodes where they germinate, multiply, and release toxins. Hemorrhagic necrosis of the thoracic lymph nodes and hemorrhagic mediastinitis develop. As bacilli are released into the bloodstream, bacteremia and toxemia result. Necrotizing pneumonitis may also develop at the portal of entry in the lungs.[85,86]

The incubation period reported for inhalation anthrax in humans ranges from 1 to 43 days.[61,87] In animal studies,[88–90] the incubation period is inversely related to the size of the inhaled inoculum. In 1 nonhuman primate study,[88] viable spores were detected for as long as 100 days following experimental aerosol exposure in the lungs of monkeys receiving antimicrobial and vaccine prophylaxis. In another nonhuman primate study,[91] inhalation anthrax developed as long as 58 days following experimental aerosolized spore exposure in monkeys that received 30 days of postexposure antimicrobial treatment.

Early clinical signs of inhalation anthrax in humans are nonspecific, making diagnosis difficult. The disease course may be biphasic, and initial symptoms of myalgia, fever, and malaise may mimic those of influenza. Two to 3 days later, the condition of infected patients dramatically worsens with development of stridor, severe dyspnea, hypoxemia, diaphoresis, shock, and cyanosis. Case-fatality rate estimates are > 85%.[61,87] Among inhalation anthrax patients in 2001, the mortality rate was 45% despite the provision of aggressive supportive care.[69]

Gastrointestinal anthrax—The gastrointestinal form of anthrax develops following consumption of contaminated meat from anthrax-infected animals and is often identified in point-source outbreaks following the slaughter or salvage butchering of infected animals.[92–94] The incubation period ranges from 1 to 6 days. In humans, gastrointestinal anthrax has 2 clinical forms: oropharyngeal and intestinal disease. The oropharyngeal form is associated with infection of the oropharyngeal epithelium. Edematous lesions develop and progress to necrotic ulcers that are covered with pseudomembranes. Edema and swelling develop in the oropharynx and neck, accompanied by cervical lymphadenopathy, pharyngitis, and fever.[94,95] The intestinal form develops following infection of the gastrointestinal tract epithelium with *B anthracis* spores. Symptoms range from inapparent to severe and include diarrhea, nausea, vomiting, fever, anorexia, and abdominal pain. Hematemesis, bloody diarrhea, and abdominal distension with hemorrhagic ascites may also be present.[95–97] The disease may progress to septicemia and toxemia, cyanosis, and shock, and deaths with both the oropharyngeal and intestinal forms have been reported. A more severe course of disease with a higher proportion of deaths has been reported in children.[92–94,97] The case fatality rate for gastrointestinal anthrax in humans is estimated to be ≥ 50%, but is < 40% with treatment.[95,97]

Bacteremic dissemination and meningitis—Following primary infection via any route, hematogenous and lymphatic dissemination can result in spread of *B anthracis* to other organ systems. Systemic effects including high fever and shock may rapidly develop, and death usually follows in a short time. In patients with systemic anthrax, there is a high likelihood of meningitis, likely resulting from hematogenous spread. Anthrax meningitis is characterized by fulminant disease and a rapidly deteriorating clinical condition despite aggressive treatment.[98] Among 82 individuals with inhalation anthrax that were reported from 1900 to 2005, meningoencephalitis developed in 31 (38%) and was fatal in all cases.[99]

Diagnosis of Anthrax in Nonhuman Animals

In livestock, anthrax should be suspected in instances of sudden death with exudative hemorrhage. This applies even to geographic areas that have a remote history of the disease because outbreaks have occurred in regions in which the most recent cases were reported > 20 to 30 years previously.[41,72] Differential diagnoses may include lightning strike, dehydration, acute plant or chemical poisoning, salmonellosis, leptospirosis, babesiosis, or clostridial infections.[39,100] Necropsy of suspected cases of anthrax should not be performed to prevent contamination of the environment with spores and minimize the risk of human infection. Specimens recommended for diagnostic testing include aseptically collected and prepared blood samples or dried blood swabs from a peripheral vessel such as the jugular vein and edematous tissue samples or fluids such as mesenteric fluid; in swine, samples of localized lesions in the throat or neck can be used.[39,100] For older or decomposed carcasses, blood-contaminated soil samples obtained from underneath the carcass and swabs of vascularized regions may be useful for isolation of the organism. Specimens from suspected *B anthracis*–infected animals should be submitted to a state veterinary diagnostic laboratory for bacterial culture and identification because of specialized requirements for handling and containment and the technical capabilities of the laboratories and because of public health and regulatory concerns.

Because of the overwhelming bacteremia associated with fulminant anthrax, *B anthracis* is usually identifiable from results of capsule staining (M'Fadyean reaction) or Giemsa staining of smears of blood obtained from dying or dead animals (within a few hours of death).[39,101] The organism is readily isolated in culture if antimicrobial treatment has not been initiated. Bacterial culture and isolation is considered the gold standard and most important diagnostic tool for identification of *B anthracis*. For specific and rapid identification of *B anthracis* from cultures, reference laboratories

such as state veterinary diagnostic laboratories or the CDC Laboratory Response Network may apply phenotypic and molecular tests, including susceptibility to γ phage lysis[102] or PCR assay.[103] Although PCR assays can identify *B anthracis* directly in samples of tissues and soil as well as in culture specimens[104,105] and have superior performance over culture methods for detection of *B anthracis* in blood smears and samples,[101] these assays are not yet widely used and standardized in all reference laboratories.

An immunochromatographic field assay[a] has been developed by the United States Naval Medical Research Center, Silver Spring, Md, to detect PA in samples of blood or tissue exudates. The assay has been used to detect *B anthracis* in animals, even several days after death. The assay has high sensitivity for the detection of *B anthracis* in an infected animal and has high specificity (regarded as 100%; 95% confidence interval, 98.5% to 100%) for detection of the organism in cattle.[106] Among 10 recently vaccinated bovids in 1 study,[106] the assay yielded no false-positive reactions.

Diagnosis of Anthrax in Humans

Diagnostic procedures for anthrax in humans depend on the clinical syndrome. Clinical diagnostic procedures for suspected inhalation anthrax should include thoracic imaging (eg, thoracic radiography and computed tomography) for detection of an abnormally wide mediastinum or pleural effusions. Laboratory diagnosis of anthrax currently depends on positive results of bacterial culture and isolation of *B anthracis*, detection of the bacterial DNA or antigens, or evidence of specific host antibody responses. In systemic infections, organisms can easily be cultured from blood samples collected prior to administration of antimicrobial agents. Before commencement of treatment, the organism can be recovered from rectal swabs and samples of exudates from skin or oropharyngeal lesions, CSF, pleural fluid, sputum, or ascitic fluid. For suspected cutaneous anthrax, full-thickness biopsy specimens collected from lesion sites can be evaluated via histologic examination and immunohistochemistry. The nonculture diagnostic methods are important because bacterial culture of samples collected after initiation of antimicrobial treatments seldom yields positive results.

Treatment and Prevention in Nonhuman Animals

The control of anthrax outbreaks among domestic animals is primarily dependent on rapid identification and treatment of affected animals; enhanced surveillance for additional cases; implementation of control measures including quarantine, prophylaxis, and vaccination; prevention of animal access to suspected sources such as potentially contaminated feed or pastures; and appropriate disposal of infected carcasses and disinfection of affected premises.

Prompt treatment of infected animals with antimicrobial agents is necessary because of the rapidly progressive and often fatal nature of the disease. Although affected animals appear to respond well to treatment even after clinical signs appear, treatment may not always prevent death. Practitioners should refer to manufacturer label directions and current references for species-specific antimicrobial dosages and regimens, particularly with consideration of species-specific treatment concerns such as withdrawal times and potential drug hypersensitivity reactions. *Bacillus anthracis* is susceptible in vitro to several broad-spectrum antimicrobial agents.[107–113] For years, penicillin has been considered the treatment of choice in many parts of the world and has been used extensively to treat anthrax in animals. Variable penicillin resistance and inducible β-lactamase production in *B anthracis* isolates have been reported,[109,111,112] and β-lactamase genes have been identified in the *B anthracis* chromosome.[114] Failure of penicillin treatment in animals has been reported[115]; however, naturally occurring penicillin resistance in *B anthracis* isolated from clinical cases is considered rare.[109] For effective treatment with penicillin, adequate dosages should be administered, thereby preventing β-lactamase induction such as that observed in vitro following use of subinhibitory concentrations of flucloxacillin.[112] If penicillin treatment is considered, initial treatment should include high doses of penicillin administered IV, followed by daily IM administrations of the antimicrobial.[46] In recent studies,[109–111,113,116] 88% to 100% of *B anthracis* detected in clinical and environmental samples and other laboratory isolates were susceptible to penicillin in vitro at an MIC of 0.12 μg/mL, which is the penicillin susceptibility breakpoint for *B anthracis*.[117] In cattle, IM injection of a single dose of either a 1:1 combination of penicillin G procaine and penicillin benzathine (24,000 U/kg [10,909 U/lb]) or penicillin G benzathine alone (12,000 U/kg [5,455 U/lb]) resulted in plasma penicillin concentrations greater than that MIC through a 24-hour period following administration. However, following SC administration at the US-approved labeled dosage of 8,800 U/kg (4,000 U/lb), plasma penicillin concentrations were < 0.1 μg/mL after 12 hours.[118] In horses, repeated IM injection of 22,000 U/kg (10,000 U/lb) of penicillin G procaine once or twice daily sustained serum penicillin concentrations > 0.12 μg/mL for more than 24 hours.[119] Administration of streptomycin in combination with penicillin has been recommended because of the synergistic action.[46,120,121] Parenteral administration of oxytetracycline is also highly effective for treatment of anthrax and has been reported to be superior to administration of penicillin alone[46,122]; moreover, naturally occurring resistance of *B anthracis* to tetracyclines or streptomycin in vitro has not been reported.[100,115] Antimicrobial treatment of affected animals should be continued for a minimum of 5 days to prevent relapse. For dogs, recommendations for antimicrobial prophylaxis or treatment (eg, in relation to potential bioterrorism-related exposures) include administration of oxytetracycline, penicillin G potassium, or enrofloxacin.[123]

In North America, animal cases and outbreaks are reportable to agriculture and public health officials; regulations vary by state or province, but both clinically suspect cases and confirmed cases may be reportable. Suspect cases and animals exposed to suspected sources should be separated from apparently unaffected animals and monitored. In the face of an outbreak, vaccination of affected herds has reduced mortality rates

beginning 8 days after vaccine administration.[72] Prophylaxis of potentially exposed animals with an effective antimicrobial agent such as a tetracycline or penicillin, followed by vaccination 7 to 10 days later, may treat incubating infections and reduce the number of deaths. However, antimicrobial agents should not be administered to animals within 7 days of vaccination with live-spore veterinary vaccines. Affected premises should be quarantined, and any marketing and slaughtering of infected animals must be prevented to eliminate introduction of infected meat or other products into the food chain. Additionally, surrounding premises should be quarantined and susceptible resident animals should be vaccinated; active case surveillance at those sites should be conducted. Release from quarantine of affected and surrounding premises should be determined by the appropriate animal health authorities.

Investigation of anthrax outbreaks in animals must identify the source of *B anthracis* to prevent additional exposures. Potential sources of the organism may include contaminated pastures, especially in low-lying areas and around bodies of water; the access of livestock to such areas should be restricted. Investigation may identify other sources, such as contaminated bone meal or feed, which should be eliminated to prevent additional cases.

Incineration is the most effective method for disposal of carcasses of animals that die as a result of *B anthracis* infection and contaminated material, such as bedding or soil. If that is not feasible, an infected carcass should be buried at a depth of at least 2 m (3.28 feet) with a covering of chloride of lime (calcium hydroxide, calcium chloride, and calcium hypochlorite, with 25% active chlorine) and soil (1:3 ratio).[39,100] However, anthrax outbreaks can occur where carcasses have previously been buried because *B anthracis* spores may be brought to the surface by soil disruption or erosion.[39,41] The use of 5% formaldehyde is effective in decontamination of soil that contains *B anthracis*.[124] Treatment of carcasses with 5% formaldehyde can prevent disruption of the carcass by scavengers and will provide superficial decontamination at the carcass site and immediate surrounding environs.[125] This allows the putrefactive process to reduce the anthrax bacillus population in the carcass.

All items or materials that become contaminated with *B anthracis* should undergo decontamination. Spores can be eliminated via steam sterilization under pressure (autoclaving) at 121°C (249.8°F) for 30 minutes or via ethylene oxide gas sterilization with a contact time of at least 18 hours. Soaking articles in 10% formaldehyde or 4% glutaraldehyde for at least 2 hours is also effective. A 10% hypochlorite bleach solution may also be used for decontaminating items and surfaces; however, chlorine is unstable and susceptible to inactivation by organic material, and free chlorine concentrations should be verified. Fumigation with chlorine dioxide or vaporized hydrogen peroxide and exposure to γ radiation are also effective means of decontamination. Items that cannot be decontaminated by the aforementioned means could be boiled; although boiling for at least 10 minutes should effectively kill spores, it has been recommended that the duration of boiling is as long as 30 minutes.[46,126,127]

Annual vaccination of livestock is the principal tool for the prevention of anthrax. This is particularly true in regions where outbreaks occur in wildlife populations (eg, deer) in which the disease cannot be controlled. Outbreaks of anthrax among livestock may be attributable in part to a lapse in vaccination practices. Since its introduction, the avirulent Sterne strain vaccine has been proven effective and is the most commonly used animal vaccine.[46] Livestock should be vaccinated 2 to 4 weeks before the start of the expected outbreak season.

Treatment and Prevention in Humans

Treatment of cutaneous anthrax—To determine appropriate treatment, it is essential to differentiate cases of naturally occurring cutaneous anthrax from cases that result from exposure to aerosolized *B anthracis* spores (eg, intentional or bioterrorism-related exposure). Early treatment of cutaneous anthrax will limit the size of the lesion; however, treatment with antimicrobial agents will not alter the pathologic changes associated with the cutaneous lesion because edema and eschar development are likely toxin mediated.

In humans with localized or uncomplicated naturally occurring cutaneous anthrax, oral administration of ciprofloxacin or doxycycline for 7 to 10 days is recommended. If results of antimicrobial susceptibility testing are supportive, oral administration of penicillin or amoxicillin may be used to complete the course of treatment. For severe naturally occurring cutaneous anthrax with systemic involvement, extensive edema, or lesions of the head and neck or for cutaneous anthrax in children < 2 years of age, IV administration of ciprofloxacin or doxycycline for 7 to 10 days is recommended. For severely affected individuals, administration of 1 or 2 additional antimicrobial agents with known efficacy against *B anthracis* is recommended.[68,128]

For bioterrorism-related cutaneous anthrax, it must be assumed that any patient with cutaneous infection could have simultaneous aerosol exposure and be at risk for inhalation anthrax. Following treatment of the cutaneous infection, treatment with antimicrobial agents should be continued according to the recommendations for PEP. For persons with localized or uncomplicated cutaneous infections, oral administration of ciprofloxacin or doxycycline is recommended. For persons with signs of systemic involvement, extensive edema, or lesions of the head or neck, treatment should follow the multidrug approach and regimen implemented for inhalation anthrax and severe disease.[68,128]

Treatment of inhalation or gastrointestinal anthrax and severe disease including meningitis—For treatment of individuals with serious systemic anthrax, such as inhalation anthrax, gastrointestinal anthrax, anthrax meningitis, or cutaneous anthrax with systemic involvement, multiple-drug antimicrobial treatment is recommended. Rapid and effective treatment with antimicrobial agents is essential to treat inhalation anthrax because the disease may progress extensively between the time of exposure and clinical intervention and the condition of patients may rapidly decline following initial signs.[99,128] Intravenous administration of ciprofloxacin is recommended as the primary antimi-

crobial treatment, with the inclusion of 2 or more additional antimicrobial agents that have in vitro activity against the *B anthracis* strain isolated. The antimicrobial regimen for treatment of anthrax may be switched to oral administration when clinically appropriate to complete the 60-day regimen. For affected individuals for whom there may be safety concerns regarding the first-line antimicrobial agents, such as pediatric patients and nursing or pregnant women, amoxicillin may be administered orally (if use of this drug is supported by results of antimicrobial susceptibility testing and clinical response).[128] Adjunctive treatment for inhalation anthrax should include aggressive use of chest tubes or serial thoracocentesis for drainage of pleural effusions. Protection from the effects of ET and LT is antibody mediated, and anthrax immune globulin has been successfully used as part of inhalation anthrax treatment.[129]

The use of immune globulins may limit or prevent the toxin-mediated morbidity and death associated with anthrax, and hyperimmune serum of animal origin has been used for years in the treatment of anthrax in humans.[130] Results of laboratory studies[131,132] suggest that optimal treatment for *B anthracis* infection may include early administration of antiserum in combination with antimicrobial agents, and high-affinity antibodies obtained from persons vaccinated against anthrax protect rats from injections of anthrax toxin. Over the past decade, a substantial amount of research has been conducted in the development of therapeutic agents for the treatment of anthrax, such as monoclonal antibodies directed against *B anthracis* targets including the toxins, PA, or capsule.[133–137] However, the only immune globulin product to be introduced into the US Strategic National Stockpile is a polyclonal anthrax immune globulin that is derived from human donor serum.[136] The lack of product availability and costs make immune therapy in veterinary patients unlikely at this time, and data regarding the optimal timing for efficacious administration of immune globulin are lacking.

Prevention of anthrax in humans—Prevention of anthrax in humans is primarily dependent on the control of the disease in other animals, especially livestock, and minimization of exposure to potentially infected animals, their carcasses, or the products of such animals. The use of appropriate personal protective methods (protective work clothing such as impermeable gowns, gloves, and boots) is recommended, and direct skin contact with potential sources of *B anthracis* should be prevented to minimize cutaneous exposure.

Vaccination against anthrax is recommended for persons in high-risk categories, such as laboratory personnel working with *B anthracis* cultures, persons engaged in activities with a high potential for production of or exposure to *B anthracis* spore-containing aerosols, military personnel, and workers in settings where repeated exposure to aerosolized *B anthracis* spores might occur. Routine vaccination of veterinarians in the United States is not recommended because of the generally low incidence of animal cases. However, vaccination might be indicated for veterinarians and other persons handling potentially infected animals in areas with a high incidence of anthrax.[57,138] The only licensed product[b] for vaccination of humans against anthrax immunization in the United States requires 6 SC injections over a period of 18 months, with annual boosters thereafter.

In the event of a naturally occurring cutaneous exposure, PEP is generally not recommended unless the exposure is substantial or there is concomitant gastrointestinal or inhalational exposure; however, should substantial cutaneous exposure or gastrointestinal exposure occur, antimicrobial PEP for 7 to 14 days may be considered.[57] Appropriate medical and public health personnel should be notified, and exposed persons should be evaluated and treated if a suspect lesion develops. The meat of animals suspected of being infected with *B anthracis* should not be consumed.

Postexposure prophylaxis involving oral administration of an antimicrobial agent for 60 days combined with a 3-dose vaccination series provides optimal protection against inhalation anthrax. In the event of inhalation exposure to *B anthracis* spore–containing aerosols, antimicrobial prophylaxis should be initiated as soon as possible. Ciprofloxacin and doxycycline are recommended as equivalent first-line antimicrobial agents of choice. The vaccine, available under an investigational new drug protocol, is given in 3 doses at 2-week intervals. Specific recommendations for PEP, including regimens for special populations such as pediatric patients, nursing mothers, and pregnant women, are available.[139]

Overview

Anthrax has been an important cause of disease in humans and other animals throughout history and remains a major zoonotic concern. Annual epizootics occur in North America with occasional human exposure associated with those outbreaks. Anthrax additionally poses a threat to persons not previously at risk for infection as a result of bioterrorism. Timely recognition of *B anthracis* infection is necessary for appropriate treatment, identification of outbreaks, and veterinary and public health responses. Suspected cases should be immediately reported to appropriate animal and public health officials for investigation, and control measures should be taken to minimize morbidity and death in populations of humans and other animals.

a. *Bacillus anthracis* immunochromatographic field assay, US Naval Medical Research Center (NMRC), Silver Spring, Md. Enquiries from veterinary and public health authorities should be directed to the NMRC by calling 301-319-7409 or in writing to Naval Medical Research Center, 503 Robert Grant Ave, Silver Spring, MD 20910. (Czarnecki J, NMRC, Silver Spring, Md: Personal communication, 2007)

b. Anthrax Vaccine Adsorbed (AVA), BioThrax, BioPort, Lansing, Mich.

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