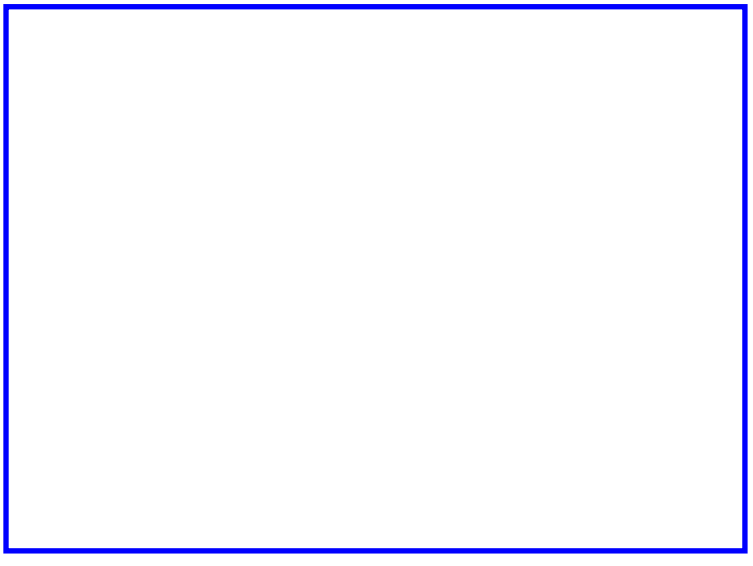
Anthrax is an ancient zoonotic disease that continues to threaten human and animal health. It remains enzootic in many regions of the world, and cases of anthrax among humans are frequently reported. Outbreaks occur annually among wild and domestic herbivores in North America, although this infection 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.

Anthrax is the infection caused by the spore-forming bacterium *Bacillus anthracis*. In Europe in the 19th

toxin
LT Lethal toxin
MIC Minimum inhibitory concentration
PA Protective antigen



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]

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 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 ulvs with and devd de.4les. In humans, the of e

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 epitheliumrepih

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.

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.

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 elimi-

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

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