Anthrax

Woolsorters' Disease, Cumberland Disease, Maladi Charbon, Malignant Pustule, Malignant Carbuncle, Milzbrand, Splenic Fever, Siberian Fever

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Importance

Anthrax is a serious zoonotic disease that affects mammals and, rarely, birds. It is caused by a spore-forming bacterium, *Bacillus anthracis*, which animals usually acquire from contaminated vegetation, soil or feed products such as bone meal. Anthrax spores are extremely resistant to inactivation, and they can potentially survive in the environment for decades. Species of animals differ in their susceptibility to anthrax: domesticated and wild herbivores tend to be very susceptible and often die rapidly, while omnivores and carnivores are more resistant to developing clinical signs, and may recover without treatment if they become ill. In endemic regions, anthrax can be a serious problem in unvaccinated ruminants. Epizootics in wildlife are also a concern, and can kill large numbers of susceptible ungulates.

People usually develop anthrax after exposure to infected animals and animal products. Outbreaks are possible, although clinical cases often occur infrequently and sporadically as an occupational hazard among veterinarians, agricultural workers and people who process hides, hair, wool and bone products. Cutaneous anthrax accounts for more than 95% of natural infections, and it is rarely fatal if treated with appropriate antibiotics. The gastrointestinal form is less common but more serious, and typically occurs after eating contaminated undercooked or raw animal tissues. Inhalational anthrax is the most serious form of anthrax, and the case fatality rate is high unless it is treated early. Natural cases of inhalational anthrax are rare; however, anthrax has been used as a weapon by bioterrorists, and weaponized anthrax can form aerosols readily. An uncommon form of anthrax, caused by injecting *B. anthracis* spores, has been reported recently in Europe, where it has been associated with contaminated heroin.

Etiology

Anthrax results from infection by *Bacillus anthracis*, a spore forming, Gram positive aerobic rod in the family Bacillaceae. Fully virulent *B. anthracis* isolates have two plasmids: pX01, which codes for a tripartite protein exotoxin complex, and pX02, which encodes the capsule genes.

B. anthracis is a member of the *Bacillus cereus* sensu lato group, which also contains the closely related organisms *B. cereus* and *Bacillus thuringiensis*, as well as a few other species. A few *B. cereus* isolates that contain plasmids closely related to pX01 have caused anthrax-like diseases. Isolates that carry both pX01 and pX02-like plasmids have been termed *Bacillus cereus* biovar *anthracis.* Studies suggest that this organism may be as virulent as *B. anthracis*. *B. cereus* that have only a pX01-like plasmid, but can produce a capsule with other genes, can also cause similar illnesses.

Species Affected

Virtually all mammals can contract anthrax, but susceptibility varies widely. Most clinical cases occur in domesticated and wild herbivores. Cases of anthrax are common in cattle and small ruminants, and they have also been reported in water buffalo, horses, camels and South American camelids. Pigs, other omnivores and carnivores are more resistant to disease, but they can become ill if the dose is high. Outbreaks have been reported in mink and wild species in zoos, as well as in free-living wildlife. Birds appear to be highly resistant, although a few clinical cases have been seen. Species that were affected included ostriches, poultry, eagles and pigeons.

B. cereus biovar *anthracis* is also likely to have a broad host range. As of 2017, this organism has been documented in several species of nonhuman primates (including chimpanzees, *Pan troglodytes*), duikers (*Cephalophus* spp.), mongooses (family Herpestidae) and porcupines (family Hystricidae). Other *B. cereus* that carry anthrax-like plasmids have not yet been reported in naturally infected animals.

Zoonotic potential

Clinical cases in humans are mainly caused by *B. anthracis*, but a few illnesses resulted from infection by *B. cereus* isolates containing pX01-like plasmids. *B. cereus* biovar *anthracis* has not yet been reported in people, although there is no reason to think that humans are not susceptible to this organism.

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Geographic Distribution

Although *B. anthracis* has been found on most continents and some islands, anthrax is only endemic in limited areas. In general, outbreaks are more common in areas characterized by alkaline soils rich in calcium and other minerals. In domesticated animals and people, anthrax is particularly common in parts of Africa, Asia and the Middle East where control measures in animals are inadequate. It also occurs in South and Central America. This disease is infrequently reported in North America and Europe. In Europe, it is mostly seen in the south, while cases in North America currently occur in limited foci in western and midwestern U.S. states and in parts of Canada. Wildlife cycles have been documented in some regions, such as Africa and North America.

Bacillus cereus biovar *anthracis* has been found in tropical forests of sub-Saharan Africa, where surveys suggest it may be widespread. Similar organisms that have only pX01-like (toxin) plasmids have been reported from human cases in several southern U.S. states (Florida, Texas, Louisiana). A similar *B. cereus* causing anthrax-like cutaneous lesions was found in India.

Transmission

Anthrax is usually transmitted by bacterial endospores, although vegetative cells might establish infections in some forms of anthrax (e.g., the oropharyngeal form acquired by eating contaminated meat). Animals are mainly thought to become infected when they ingest spores; however, inhalation could also play a role, and entry through skin lesions may be possible. While the vegetative cells of *B. anthracis* are destroyed in the acid environment of the stomach, spores are resistant to digestion and can germinate when they reach the intestines. Animals, including herbivores, must eat fairly large doses of *B. anthracis* to become infected by the oral route. Herbivores usually acquire spores from soil or plants in pastures; however, contaminated feed (e.g., forage, bone meal) has been responsible for some outbreaks outside endemic areas. Other routes of transmission may also be possible. At least one case of anthrax mastitis was reported in a cow, with the organisms likely to have gained entry through the teats. In most cases, animals that recover from anthrax are thought to completely eliminate the bacteria. Limited evidence suggests that prolonged localized infections might be possible in some species. In particular, *B. anthracis* has been reported to persist for months in the lymph nodes and tonsils of some healthy pigs.

Direct transmission between living animals is not thought to be significant in anthrax, but carcasses are important in contaminating the environment. Large numbers of bacteria are present in body fluids and hemorrhages that may exude from orifices after death. When they are exposed to air, these bacteria form spores and contaminate soil, plant roots and nearby vegetation. Bacteria in the tissues also sporulate if a carcass is opened. The optimum temperature for sporulation is between 21°C and 37°C. It does not occur at or below 9°C. Sporulation does not seem to occur inside a closed carcass, where the organisms are thought to be destroyed within a few days by putrefaction. Biting and non-biting flies can disseminate *B. anthracis* mechanically when they feed on carcasses. In many cases, these flies may only spread organisms to nearby vegetation; however, biting flies have been suggested to transmit *B. anthracis* to animals during some widespread outbreaks.

Carnivores usually become infected when they eat contaminated animal tissues. Scavengers, including vultures, may disseminate anthrax mechanically after feeding on carcasses. While the number of spores that pass through the digestive tract of these animals may be small, water might become contaminated when large numbers of vultures feed on a carcass, then fly to bathing sites nearby. Spores from carcasses are also thought to be concentrated in certain locations, such as ponds or low-lying depressions, by rain and flooding. Some sites were reported to be contaminated by effluents from tanneries or processing facilities for wool/ hair. *B. anthracis* is traditionally not thought to replicate outside the body. However, some studies suggest that spores may germinate under certain conditions, and limited replication might occur in some environments. Replication has been demonstrated inside soil-dwelling amoebae in the laboratory, in a simulated environment of stagnant water and moist soil. However, it has not been shown to occur, to date, under natural conditions outside the laboratory.

Anthrax spores can remain viable for long periods in the soil or animal products such as hides (including processed hides) and wool. In some cases, they have been reported to survive for decades. Laboratory experiments detected viable spores after 2 years in water and 10 years in milk, and for up to 71 years on silk threads. How long spores are of practical concern at contaminated sites is less clear. While large numbers of spores have been found in the soil and on vegetation during the first 1-2 years, several studies suggest that the risk of infection may decrease significantly after a few years if the soil is not disturbed. At some carcass sites in African savannahs, spores were rare or undetectable on vegetation after 3 years, though they persisted in soil and grass roots (which may be eaten by herbivores when they graze). In Israel, unvaccinated animals have not become infected at outbreak sites after 10 years. The type and moisture content of soil may also influence spore persistence. Permanently contaminated sites have been documented, but they seem to be rare.

Humans usually develop the cutaneous form of anthrax after skin contact with infected animal tissues or animal products. A few cases were suspected to have been acquired from biting flies. People can develop inhalational anthrax when spores from animal products, laboratory cultures or other sources are aerosolized. Gastrointestinal anthrax typically results from the ingestion of raw or undercooked tissues (e.g., meat) from an infected animal, although unusual sources (e.g., drumming on contaminated hides) have been reported. Person-to-person transmission of anthrax is very rare and has been seen only in cases of cutaneous anthrax. Apparent

infection of the fetus *in utero* was also reported in several historical anthrax cases, although some infected women did not transmit the organism to their fetuses.

B. anthracis has been weaponized and these agents have also been used in bioterrorism. Weaponized anthrax spores have been altered to form aerosols readily and are often inhaled; however, they can also cause skin lesions or gastrointestinal anthrax.

Bacillus cereus carrying anthrax-like plasmids

Little is known about the ecology of *B. cereus* isolates that carry pX01- and pX02-like plasmids. Most *B. cereus* are saprophytes and divide in the environment.

Disinfection

Anthrax spores are resistant to heat, sunlight, drying and many disinfectants. They can be killed with formaldehyde or glutaraldehyde; overnight soaking is recommended. Commercial hydrogen peroxide/ peracetic acid disinfectants, aqueous chlorine dioxide, sodium dichloroisocyanurate and high concentrations of hydrogen peroxide (26-50%) are also reported to be effective for some types of disinfection. A 10% NaOH or 5% formaldehyde solution can be used for stockyards, pens and equipment. Sodium hypochlorite has also been recommended for some purposes, if organic material is not present. The efficacy of hypochlorite solutions against *B. anthracis* spores depends on the pH and the concentration of free available chlorine. To become an effective sporicidal agent, household bleach must be diluted with water and adjusted to pH 7. Prolonged contact is recommended. Commercial sodium hypochlorite-based sporicidal wipes may be effective in contaminating small areas. Gaseous sterilization can be accomplished with agents such as chlorine dioxide, vapor-phase hydrogen peroxide and formaldehyde gas, under specific conditions of humidity and temperature. The possibility of inducing spore germination to generate less resistant vegetative cells has been proposed, but not yet evaluated for efficacy.

Anthrax spores can also be eliminated by autoclaving at 121°C (250°F) for at least 30 minutes. Gamma radiation has been used to decontaminate animal products, as well as mail from contaminated postal facilities. Exposed arms and hands can be washed with soap and hot water, then immersed for one minute in a disinfectant such as an organic iodine solution or a 1 ppm solution of mercuric perchloride. Alcohol-based disinfectants commonly used for hand cleaning are not effective against spores.

There is little information on the time and temperatures needed to destroy *B. anthracis* spores in food. One source indicates that, while these spores can be killed by 10 minutes "at boiling temperature," they can survive 98°C for 30 minutes.

Infections in Animals

Incubation Period

Reported incubation periods in animals range from one to 14 days. In herbivores inoculated orally, infections typically become apparent in 3-7 days. One source indicates that the incubation period in pigs is usually 1 to 2 weeks, while a laboratory experiment (oral inoculation) resulted in clinical signs after 1-8 days.

The incubation period for *B. cereus* biovar *anthraci*s and other anthrax-associated *B. cereus* is not known.

Clinical Signs

In animals, anthrax can be a peracute, acute, subacute or chronic disease. More susceptible species tend to develop peracute and acute illnesses, while subacute and chronic cases are more likely to be reported in resistant hosts.

In ruminants, peracute systemic disease is common, and sudden death is often the only sign. Staggering, trembling and dyspnea is sometimes noted shortly before death, followed by rapid collapse and, in some cases, terminal convulsions. Ruminants with the acute form of anthrax are ill for a short period (typically up to 2 days) before they die. Fever and excitement may be noted initially, but this is often followed by depression, stupor and anorexia. Other clinical signs may include disorientation, muscle tremors, dyspnea, hematuria, diarrhea, congested mucous membranes, and small scattered hemorrhages on the skin and mucous membranes. Pregnant cows may abort, and milk production can drop severely. The milk may also appear bloody or discolored with a yellow tinge. Bloody discharges from orifices such as the nose, mouth and anus are sometimes seen terminally. Some ruminants develop subcutaneous edematous swellings, often in the ventral neck, thorax and shoulders, but sometimes at other sites including the genitalia. Pulmonary anthrax, with a productive cough and an acute course, has been reported rarely. What appeared to be a cutaneous form of anthrax was seen in some previously vaccinated cattle during an outbreak in Canada. These animals did not seem to have any systemic signs, but they developed variable numbers of expanding areas of dark, necrotic skin, on one or both sides of the body. The affected skin eventually sloughed, leaving bloody, crusted areas that healed spontaneously in a few weeks. Anthrax mastitis, with clinical signs mainly limited to the udder, was also reported in a cow during this outbreak. The appearance of anthrax in wild herbivores varies with the species, but tends to resemble the disease in domesticated ruminants.

An acute course is common in horses. Frequently reported clinical signs in this species include fever, anorexia, depression, other signs of sepsis, severe colic and, in some cases, bloody diarrhea. Some horses have swellings on the neck, sternum, lower abdomen and genitalia. Swelling of the neck can cause dyspnea. Affected horses usually die within 3 days, but some can survive longer.

Septicemia and sudden death occur occasionally in pigs. More often, pigs have mild subacute to chronic cases characterized by localized swelling, fever and enlarged lymph nodes. The throat can swell rapidly in pigs that develop anthrax lesions in the oropharynx. These animals may have difficulty swallowing, can become dyspneic, and may suffocate. Intestinal involvement can result in anorexia, vomiting, diarrhea (which may be bloody) or constipation. One source also mentions black necrotizing papules on the skin and mucosa. Some pigs with anthrax recover. Recovered, asymptomatic animals may have active lesions in the tonsils and cervical lymph nodes at slaughter.

Naturally-acquired anthrax in dogs, cats and wild carnivores usually resembles the disease in pigs, with gastrointestinal and/or pharyngeal signs. One review of the published cases in dogs suggests that massive swelling of the head, neck and mediastinum is the most common sign in this species. In the published cases, death was usually the result of toxemia and shock, but swelling of the threat and suffocation could also have been a factor. Hemorrhagic gastroenteritis was reported in one dog, in addition to a swollen foreleg and ptyalism. Severe acute gastroenteritis has also been seen in other carnivores and omnivores. In some cases, carnivores have died of anthrax with few or no significant preceding clinical signs.

Anthrax in birds is reported to be an acute septicemic disease, with death occurring soon after the clinical signs appear.

B. cereus biovar anthracis

Free-living nonhuman primates infected with *B. cereus* biovar *anthracis* can die within hours after the first observed clinical signs. While this might indicate that the course is peracute, wild animals also hide signs of illness until the terminal stage.

Post Mortem Lesions

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Rigor mortis is usually absent, delayed or incomplete, and the carcass is typically bloated and decomposes rapidly. Dark, tarry blood sometimes oozes from the body orifices; however, some sources suggest this is not a common sign and oozing may not be extensive even if it occurs. Edema may be noted in some animals, particularly around the throat and neck. **Necropsies should be avoided, to prevent contamination of the surrounding area with spores.**

If a ruminant carcass is opened, signs of septicemia will be evident. The blood is dark, thick and does not clot readily. Blot clots also tend to appear gelatinous due to the abnormal clotting. Edematous, blood-tinged effusions may be seen in subcutaneous tissues, between skeletal muscles and under the serosa of organs. The spleen is usually enlarged and classically has a 'blackberry jam' consistency, although this appearance is not always observed, especially in small ruminants. Affected lymph nodes are usually swollen and congested, and often contain hemorrhages. Petechiae and ecchymoses are also common on various serosal surfaces, the epicardium and endocardium. Hemorrhages and ulcers may be noted in the intestinal mucosa. Peritonitis and excessive peritoneal fluid may be present, and the liver and kidneys may be swollen and congested. Similar internal lesions can be seen in some horses; in others, the lesions may be limited to edema and lesions in the neck and throat.

Omnivores and carnivores can have lesions consistent with septicemia, but this seems to be less common than regional involvement of the pharyngeal area or gastrointestinal tract. Affected portions of the digestive tract and nearby tissues are often edematous and severely inflamed, and they may contain hemorrhages, ulcers and necrotic areas. Peritonitis may also be seen. Some apparently healthy pigs can have anthrax lesions in the cervical lymph nodes and tonsils at slaughter. The lymph nodes in these cases are typically enlarged and have a mottled salmon to brick-red color on cut surface, or they may contain small greyish-yellow necrotic foci. The tonsils may be covered by diphtheritic membranes or ulcers.

There are few description of anthrax in birds. In ostriches, reported lesions include darkening of the skin, hyperemia and edema in the respiratory tract, and hemorrhagic-necrotizing foci in inner organs. Hemorrhagic enteritis was also seen in some birds.

B. cereus biovar anthracis

B. cereus biovar *anthracis* is reported to cause gross and microscopic lesions similar to those caused by *B. anthracis*.

Diagnostic Tests

Anthrax is often diagnosed by detecting *B. anthracis* in a blood sample from a carcass. Blood clots poorly in affected animals, and samples may be obtained by making a small cut in an ear vein, or by collecting it with a syringe from any available vein. Bacteremia is rare in pigs, and a small piece of affected lymphatic tissue is often collected aseptically instead. *B. anthracis* may also be found in tissue aspirates and pharyngeal swabs. Swabs or samples from the nasal turbinates can be useful in older carcasses (>3 days). Recovery can also be attempted from soil contaminated by terminal discharges if *B. anthracis* cannot be isolated from a decomposing carcass; however, this may be difficult.

A presumptive diagnosis can be made if the characteristic bacteria are found in blood, other body fluids or tissue smears. *Bacillus anthracis* is a large Gram positive rod that may occur singly, in pairs or in short chains in clinical samples (and in long chains in cultures). Air-dried, fixed smears should be stained with polychrome methylene blue (M'Fadyean's stain) or Giemsa. With M'Fadyean's stain, *B. anthracis* organisms are blue-black bacilli surrounded by a pink capsule. Unlike many bacilli, their ends often appear square. Giemsa stains the bacillus purple and the capsule reddish-mauve. Endospores are not found in host tissues unless they have been exposed to air. Antibiotic treatment may result in false negatives.

Bacterial culture, using a variety of media, may be employed for a definitive diagnosis. *B anthracis* is not hemolytic, and unlike the other members of the *B cereus*

group, it is not motile. While it does not form a capsule when grown aerobically *in vitro*, capsules can be induced with specialized culture methods (e.g., incubation in blood for several hours, or growth on nutrient agar with 0.7% sodium bicarbonate at 37ºC under CO_2). *B anthracis* can usually be identified by its susceptibility to specific bacteriophages known as the gamma bacteriophage. Most strains are sensitive to penicillin, and they also exhibit a characteristic 'string-of-pearls' formation when grown with this agent. Other methods, such as PCR, can also be used for bacterial identification. Culturing *B. anthracis* from environmental samples and processed animal products can be difficult, and may require specialized laboratory procedures.

PCR assays, which are generally based on the pX01 and pX02 plasmids, can diagnose anthrax directly in diagnostic samples. Loop-mediated isothermal amplification (LAMP) techniques have also been published. Although the existence of pathogenic *B. cereus* strains with pX01- and pX02-like plasmids (e.g., *B. cereus* biovar *anthracis*) can complicate the identification of *B. anthracis* by genetic methods, these organisms are rarely found in clinical cases outside tropical forests in Africa. Genetic techniques such as multilocus variable number of tandem repeats analysis (MLVA) can be used to trace outbreak strains. Mouse or guinea pig inoculation to confirm virulence has largely been replaced by PCR; however, animal tests may be considered if other diagnostic methods have failed.

The anthrax immunochromatographic test (AICT) is a field test that detects a component of the anthrax toxin in blood. It is used in Australia to rapidly identify animals that have died recently of anthrax. The thermoprecipitin test (Ascoli test) is an older test that detects thermostable anthrax antigens in decomposed carcasses and animal products. The Ascoli test is not very specific, as other species of *Bacillus* can also produce such antigens. While it may still be employed in a few countries, the results should be interpreted with caution. Other immunoassays for toxins have also been published. Research laboratories may use immunofluorescence to detect *B. anthracis* in blood or tissues, but this method is not commonly used for diagnosis.

A skin hypersensitivity test using anthraxin (AnthraxinT) has been used in some countries, such as Russia, for the retrospective diagnosis of anthrax. Serology is mainly used in research, and rarely employed to diagnose anthrax in animals. Published serological tests include ELISAs, immunoblotting (Western blotting), and lateral flow immunochromatographic assays.

Bacillus cereus that carry anthrax plasmids

Standardized methods to diagnose these organisms have not been published. Many *B. cereus* that cause anthrax-like illnesses are motile, although some are not. Isolates of *B. cereus*, including *B. cereus* biovar *anthracis*, are not susceptible to gamma bacteriophage.

Treatment

Antibiotics may be effective if treatment is started early. Penicillins are generally used for *B. anthracis* infections in animals, although other drugs can also be employed. Streptomycin may be given to act synergistically with penicillin. Tetracyclines have also been recommended, but opinions on their efficacy in livestock with anthrax vary. Antitoxins are not available for animals in most countries, although they are reported to be used in the former Soviet Union. Supportive therapy may also be necessary in sick animals. Some countries do not allow animals with anthrax to be treated.

Control

Disease reporting

Veterinarians who encounter or suspect anthrax should follow their national and/or local guidelines for disease reporting. In the U.S., state and/or federal veterinarians should be informed of any suspected cases.

Prevention

In endemic areas, modified live vaccines can prevent anthrax in livestock. Animals are vaccinated annually, before the season when outbreaks generally occur. Livestock vaccines have also been used to protect cheetahs and endangered ruminants including black rhinoceros. Vaccines should be used with caution in miniature horses, as some animals developed immune-mediated vasculitis and died shortly after vaccination, during outbreaks in Canada. Young llama calves, which had concurrently received ivermectin and other biologics, developed vaccination-associated anthrax in a report from the 1980s.

Quarantines, effective carcass disposal techniques, and decontamination can help prevent dissemination during outbreaks. Sick animals should be isolated, and the rest of the herd should be kept away from contaminated areas. Contaminated feed should be removed. If a pet has been exposed to anthrax, the fur should be decontaminated by repeated bathing to mechanically remove the organism.

To prevent sporulation, carcasses should not be opened. The general consensus is that scavengers should be prevented from accessing the carcass. Various physical barriers are typically used, sometimes in conjunction with chemicals such as formaldehyde, which may also help destroy any bacteria shed from the carcass. One recent study found no effect of excluding scavengers on local contamination by spores. Insect repellents may help prevent flies from disseminating the organism. Local regulations determine carcass disposal; however, incineration is considered to be the most effective method for destroying *B. anthracis* in carcasses, contaminated manure, bedding and other materials. Deep burial is also used, but there is a possibility that buried carcasses might cause anthrax if they are later unearthed. Other methods, such as leaving a carcass in place but preventing access, are not desirable, but have sometimes been used during outbreaks where other options are unavailable (e.g., in Africa). Barns,

pens and equipment should be cleaned and disinfected. Once the soil has been contaminated by spores, it is very difficult to decontaminate; however, procedures such as soil removal and/or treatment with formaldehyde have sometimes been employed.

During an outbreak, prophylactic antibiotics can protect exposed and at-risk animals. Animals that are treated with antibiotics cannot be vaccinated at the same time because animal vaccines are live. However, they can be vaccinated afterward. Vaccination alone may be employed in some outbreaks, depending on the situation.

Morbidity and Mortality

Anthrax is a seasonal disease in many endemic areas, with a tendency to occur during warmer weather. In addition to sporadic cases, there may be periodic outbreaks affecting domesticated and/or wild animals. Some epizootics have been associated with drought, heavy rains or flooding. Outbreaks can predominantly affect one or a few species, causing only sporadic cases in other animals. Among wildlife, different species can be affected at different times of the year. For instance, elephants in one region of Namibia experience peak mortality at the beginning of the wet season, but plains ungulates tend to be affected most at the end of the wet season. In developed countries, domesticated animals in endemic foci are usually protected by vaccination, and outbreaks in these species have become uncommon. There are occasional reports of anthrax outside endemic regions, typically associated with contaminated supplemental feed, and often occurring in housed animals during cold weather.

Clinical cases tend to be seen more often in herbivores than omnivores and carnivores, and the case fatality rate is usually higher. However, there seem to be differences in susceptibility between species within these broad groups. For instance, kudu (*Tragelaphus strepsiceros*) and zebras (*Equus quagga*) are frequently killed by anthrax during outbreaks in Africa, while the mortality rate tends to be lower in some other herbivores. A significant percentage of African buffalo (*Syncerus caffer*) and wildebeest (*Connochaetes taurinus*) have antibodies to *B. anthracis*, indicating that they were exposed to this organism but survived. Likewise, many carnivores seem to feed on infected carcasses without significant mortality, but cheetahs (*Acinonyx jubatus*) often die after exposure, and very few cheetahs were seropositive in surveys. Periodic exposure to smaller amounts of organisms may help immunize some species: lions are reported to be fairly resistant to anthrax and tend to have high seroprevalence rates, but anthrax outbreaks have been reported in lions after a period of low prevalence in their prey. Among domesticated animals, clinical cases are usually fatal in domesticated ruminants and horses, while pigs often recover. Relatively few cases of anthrax have been documented in dogs, although fatal infections do occur.

Little is known about the *B. cereus* isolates that carry anthrax-like plasmids. However, *B. cereus* biovar *anthracis* seems to be a significant cause of mortality in tropical forests of Côte d'Ivoire, where it usually kills a range of mammals simultaneously. This organism appears to be highly virulent in nonhuman primates and Maxwell's duikers (*Cephalophus maxwellii*), based on the number of deaths and the absence of antibodies in populations exposed to this organism.

Infections in Humans

Incubation Period

The reported incubation period for cutaneous anthrax ranges from one to 20 days, but most clinical cases tend to develop within 7-10 days. Gastrointestinal anthrax has been seen 1-7 days after exposure, and injectional anthrax after 1-10 days. However, most cases of injectional anthrax occurred very soon after inoculation. The incubation period for inhalational anthrax is highly variable. While it was estimated to be 2-6 days in a limited number of cases, spores may remain viable in the lungs for several weeks (up to 100 days in nonhuman primate models), and these spores can germinate and cause inhalational anthrax during that time. After one accidental release of aerosolized spores in the Soviet Union, cases continued to appear in exposed people for up to 6 weeks.

Clinical Signs

Four forms of disease are seen in humans: cutaneous anthrax, injectional anthrax, gastrointestinal anthrax and inhalational anthrax. Any of these forms can develop into life-threatening septicemia or anthrax meningitis, but the frequency differs. Presumed anthrax sepsis has been reported in a newborn, and preterm labor was seen in some women with anthrax.

Cutaneous anthrax

Cutaneous anthrax initially appears as a papule, which may become surrounded by small fluid-filled vesicles that release clear or sanguineous discharge. The central papule quickly forms a vesicle or bulla, ulcerates, dries and develops into an eschar, which appears as a firmly adherent, depressed black scab. The satellite vesicles may also form ulcers. Cutaneous anthrax lesions are usually painless, but they are typically surrounded by significant edema, and may be accompanied by regional lymphadenopathy. Lesions on the eyelids are edematous, but a central black eschar is occasionally absent. An uncommon bullous form of cutaneous anthrax has also been described. It appears as a group of vesicles or bullae, which become hemorrhagic and necrotic. Coinfections with other organisms, including dermatophytes, can result in cutaneous anthrax cases with an atypical appearance. Pus is not usually seen in anthrax lesions unless they are secondarily infected. Low grade fever, malaise and headache may be apparent in more severe cases. Swelling on the face or neck can result in occlusion of the airways.

Cutaneous anthrax often resolves spontaneously; however, the organisms can sometimes disseminate and cause life-threatening illnesses including septicemia and meningitis. Face and neck lesions are more likely to spread to the CNS than lesions in other parts of the body. Resolution of uncomplicated cutaneous anthrax may take weeks, even

when the infection has been successfully treated with antibiotics. Small lesions usually heal with minimal scarring, but large lesions can leave significant damage. If the eyelids are affected, even smaller lesions may result in complications such as entropion.

Injectional anthrax

Injectional anthrax results from the subcutaneous inoculation of *B. anthracis*. The cases reported to date have mostly been associated with contaminated heroin. Extensive soft tissue swelling or edema was the most commonly reported sign, although it was not invariably present. Some patients also had erythema, pain, and vesicles or necrotic areas on the skin; however, the classical eschars of cutaneous anthrax were usually absent, and the pain or discomfort often appeared disproportionately mild in relation to the clinical signs. Unusual presentations were also seen. For instance, one case resembled impetigo. Debridement of the lesions sometimes resulted in disproportionate bleeding, requiring massive transfusions in some cases.

Systemic signs in some cases included fever and/or gastrointestinal signs such as nausea, vomiting and abdominal pain. Two people developed peritonitis after injecting contaminated heroin into the groin. Some cases progressed to sepsis, pulmonary signs and meningitis.

Gastrointestinal (including oropharyngeal) anthrax

Gastrointestinal anthrax usually develops after eating contaminated, undercooked animal tissues including meat. Germinating spores can cause inflammation wherever they localize, and may, in severe cases, result in hemorrhages, obstruction or perforation. While any part of the gastrointestinal tract can be affected, the ileum and colon are often involved in the abdominal form, while oropharyngeal anthrax is characterized by clinical signs localized to that region.

The initial symptoms of the abdominal form may be mild and can include malaise, a low fever and mild gastrointestinal signs such as nausea, vomiting, diarrhea and anorexia. In some cases, this is followed by the acute onset of severe abdominal pain, hematemesis and bloody diarrhea. Massive ascites may be present. Some patients have a high fever. There may also be dyspnea, cyanosis, disorientation and other signs of septicemia. Meningitis is also possible. Severe cases progress rapidly to shock, coma and death. However, abdominal anthrax may not always be severe. In one outbreak in Thailand, 7 of 74 people with gastrointestinal anthrax had severe symptoms, but acute diarrhea was the only sign in the others.

The initial symptoms in the oropharyngeal form can include fever, a sore throat, dysphagia, hoarseness, and swelling of the neck from edema and cervical lymphadenopathy. Neck swelling can result in airway compromise. Lesions may seen on the mucosa of the oropharyngeal region, including on the tonsils, pharynx and hard palate. In one report, these lesions initially appeared as areas of edema and congestion. A central whitish area, caused by necrosis and ulceration, developed by the end of the first week. During the second week, a pseudomembrane formed over the ulcer.

Inhalational anthrax

Inhalational anthrax occurs after inhaling spores. The symptoms are nonspecific and may develop gradually. Early, vague signs can include fever, chills, tiredness and malaise, as well as a nonproductive cough and mild chest pain in some cases. These symptoms sometimes improve for several hours to a few days; however, this prodromal period ends with the acute onset of severe respiratory distress, tachycardia, diaphoresis, stridor and cyanosis, followed by fatal septicemia and shock within a day or two. Hematogenous spread of *B. anthracis* after inhalation can cause gastrointestinal lesions and signs.

Anthrax meningitis

Anthrax meningitis can be a complication of any of the other four forms of disease. After a prodromal period of 1-6 days, typical signs of meningoencephalitis develop rapidly. Patients quickly lose consciousness and die, many within 24 hours. Blood is often found in the cerebrospinal fluid.

Bacillus cereus carrying anthrax-like plasmids

B. cereus isolates have caused a few cases of life-threatening, anthrax-like pulmonary disease, as well as syndromes that resembled cutaneous anthrax.

Diagnostic Tests

Anthrax can be diagnosed by observing typical organisms in stained clinical samples, by PCR, and by isolating *B. anthracis* in culture, as in animals. Immunohistochemistry may be available in reference laboratories. A wide variety of clinical samples can be collected, depending on the form of the illness. They may include blood, fluid from skin lesions, aspirates of lymph nodes or the spleen, ascitic fluid, respiratory secretions, pleural fluid, cerebrospinal fluid (in cases of meningitis), vomitus and feces. As in animals, antibiotic treatment may prevent isolation of the organism.

Antibodies develop late in the course of the disease, and serology (ELISAs or other assays) is only useful for retrospective diagnosis. Both acute and convalescent sera should be taken. Some patients with cutaneous anthrax may not become seropositive. A skin hypersensitivity test using anthraxin (AnthraxinT) is used to help diagnose anthrax in some countries. It may be helpful when a case cannot be confirmed by bacteriology and/or serology, and it can also be employed for retrospective diagnosis.

Treatment

Anthrax is treated with antibiotics. Naturally-occurring strains of *B. anthracis* are usually susceptible to penicillin and some other antimicrobials. Strains used in bioterrorist attacks are more likely to be antibiotic resistant. Guidelines in developed countries often recommend that antibiotics other than penicillin be used initially, particularly for systemic

disease, until the susceptibility of the isolate has been determined. However, penicillin is employed successfully in some countries, especially in cases of cutaneous anthrax. Early antibiotic treatment in a systemic illness significantly increases the probability that the patient will survive.

Antibiotics are effective only against the vegetative stage of *B. anthracis*, and do not destroy the spores. Treatment for at least 60 days has been recommended in inhalational anthrax, as spores might remain dormant in the lungs and germinate during that time. A few recent experiments in animal models have questioned whether continued treatment is necessary once immunity develops to *B. anthracis*, but until more definitive evidence is available, most sources continue to recommend 60 days for this form. Other types of anthrax are usually treated for much shorter periods, as residual spores are not a concern.

Anthrax toxins can cause damage even after the bacteria have been eliminated. Recently developed antitoxins seem to improve survival in animal models, especially when treatment is delayed. These antitoxins have been recommended for systemic anthrax, and they have also been used in some cases of injectional anthrax. In most countries, clinical experience with these agents is currently limited. However, older antitoxins have been used more extensively in some nations, such as Russia. Symptomatic and supportive therapy may also be necessary in some anthrax cases.

Guidelines for the treatment of anthrax, including guidelines specifically for children, have been published.

Control

People normally acquire anthrax from infected animals or their tissues; thus, humans can be protected by preventing animals from getting anthrax. Veterinary supervision of animal slaughter acts as an additional safeguard. In some cases, trade restrictions may be placed on certain animal products from countries where anthrax is common and uncontrolled. Improvements in industry standards have reduced occupational exposure for people exposed to hides, wool, bone meal and other animal products. However, low levels of contamination are still reported in some facilities, even in areas where anthrax is not endemic. The use of face masks seems to significantly reduce exposure among people who process contaminated wool and goat hair. In laboratories, good safety practices, including the use of biological safety cabinets, should be employed. Veterinarians should use protective clothing and equipment when examining sick animals. They should also avoid opening the carcasses of suspected cases. Vaccines are available for people at a high risk of infection.

Postexposure antibiotic prophylaxis, continued for at least 60 days, and vaccination are recommended for people who were exposed to aerosolized anthrax spores. Humans can usually be vaccinated while they are taking antibiotics, as most countries only use killed anthrax vaccines. However, a few countries may still employ live vaccines, which cannot be used simultaneous with antibiotics. Postexposure antibiotic prophylaxis, for a shorter period, may also be needed for people who have eaten contaminated meat. It is not generally recommended after cutaneous exposure; however, any exposed areas should be washed immediately, and the skin should be monitored for early signs of infection. Cutaneous anthrax lesions should be covered until antibiotics have been administered for 24-48 hours.

Morbidity and Mortality

Anthrax is still a significant disease in some countries, and outbreaks are seen occasionally in humans. In Africa, estimates suggest that each cow with anthrax can result in up to ten human cases. However, the incidence of anthrax has declined sharply in developed nations. In many countries, this disease now occurs infrequently and sporadically, mainly as an occupational hazard among veterinarians, agricultural workers, and people who process hides, hair, wool and bone products. Humans seem to be moderately resistant to *B. anthracis*, and antibodies can be found in some people who have no history of this disease. Individual resistance may vary. In rare cases, people have had more than one episode of cutaneous anthrax.

The cutaneous form accounts for at least 90-95% of the natural cases of anthrax. Gastrointestinal anthrax seems to be uncommon, but outbreaks sometimes affect dozens of people who ate the same food. Natural cases of inhalational anthrax are rare; however, aerosolized biological weapons would be expected to produce a high percentage of this form. In 2001, weaponized anthrax spores sent in contaminated letters caused 11 cases of inhalational anthrax and 11 cases of cutaneous anthrax in the U.S. Injectional anthrax also seems to be rare; however, a number of cases have been reported recently in Europe, associated with contaminated heroin.

The mortality rate varies with the form of the disease. Cutaneous anthrax is estimated to be fatal in 5-30% of untreated cases, but in less than 1% of patients treated with antibiotics. Mortality is higher when there are large, multiple or extensive skin lesions, or they involve the head, neck and upper torso. Relatively few outbreaks of gastrointestinal anthrax have been described in the literature. The reported case fatality rates ranged from 4% to 60-75% in the abdominal form, and from 12% to 50% in the oropharyngeal form. Effective treatment is likely to have contributed to the low mortality in some incidents; however, severe illnesses were sometimes much less common than mild cases. In at least one report, fatalities were more likely in children. Injectional anthrax associated with contaminated heroin had an overall case fatality rate of 33%, but some hospitals reported few or no deaths.

Mortality can be high in inhalational anthrax, unless treatment begins very early. Earlier estimates suggested that the case-fatality rate for this form approached 90-100%, but newer, more intensive treatment regimens may be more effective. In the 2001 mail-associated bioterrorist attack, the case fatality rate in patients with inhalational anthrax was 45%. However, once a patient reaches the fulminant stage, one study suggests that the mortality rate is > 90% regardless of treatment. Anthrax meningoencephalitis is also deadly, with an estimated case fatality rate of 92%.

Internet Resources

American Academy of Pediatrics/ Centers for Disease Control and Prevention (CDC). Pediatric Anthrax Clinical Management

Centers for Disease Control and Prevention (CDC). Anthrax

European Centre for Disease Prevention and Control. Anthrax

Food and Agriculture Organization of the United Nations. Manual on Meat Inspection for Developing Countries

Public Health Agency of Canada. Pathogen Safety Data Sheets

The Merck Manual

The Merck Veterinary Manual

World Health Organization. Anthrax

World Health Organization. Anthrax in Humans and Animals, 4th edition

World Organization for Animal Health (WOAH)

WOAH Manual of Diagnostic Tests and Vaccines for Terrestrial Animals

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* Link is defunct

