

8.6.21 Anthrax 1094

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section 8 Infectious diseases 1094 Meningitis should be treated with an aminoglycoside in combination with chloramphenicol. Supportive care should be provided as appropriate; some patients may require intensive care with respiratory support should sepsis develop. Suppurating nodes should be drained. Prognosis Tularaemia responds well to antibiotic therapy, especially if started early in infection. The mortality rate of the more acute forms of the disease is reduced from 30% to 2% if the patient receives appropriate antibiotics. Most deaths are associated with pneumonic or typhoidal forms. Relapse can occur when antibiotic therapy is withdrawn (even with aminoglycosides or fluoroquinolones). Other issues Patients are not considered an infection risk and do not require isolation. Tularaemia is notifiable in some countries, although not in the United Kingdom. Autopsies should only be performed by personnel wearing respirators if death from tularaemia is suspected. Bodies should not be embalmed before burial. Likely future developments Work is under way to identify a vaccine against tularaemia that will be suitable for licensing. It is highly likely that progress will be made in this area in the next few years, although it can take many years to obtain approval. FURTHER READING Centers for Disease Control and Prevention. Emergency preparedness and response: tularaemia. <https://emergency.cdc.gov/agent/tularemia/index.asp> Dennis DT, et al. (2001). Tularemia as a biological weapon: medical and public health management. JAMA, 285, 2763–73. Health Protection Agency (2007). Tularemia. <http://webarchive.nationalarchives.gov.uk/20070129155246/http://www.dh.gov.uk/PolicyAndGuidance/EmergencyPlanning/DeliberateRelease/DeliberateReleaseTularemia/fs/en> Jacobs RF, Condrey YM, Yamauchi T (1985). Tularemia in adults and children: a changing presentation. Pediatrics, 75, 818–22. Mulligan MJ, et al. (2017). Tularemia vaccine: safety, reactogenicity, ‘take’ skin reactions and antibody responses following vaccination with a new lot of the Francisella tularensis live vaccine strain—a phase 2 randomized clinical trial. Vaccine, 35, 4730–7.

8.6.21 Anthrax Arthur E. Brown ESSENTIALS Anthrax is primarily a disease of herbivorous mammals, caused by the Gram-positive rod *Bacillus anthracis*, which causes human infection when its spores enter the body, most commonly from handling infected animals or animal products. The disease occurs in most countries of the world, but is only sporadic where the condition is controlled in livestock by vaccination programmes. Anthrax is a leading agent of biological warfare. Pathophysiology—after entry into the body, anthrax spores are phagocytosed by macrophages and carried to regional lymph nodes, where they germinate to produce vegetative bacilli that enter the blood stream. These produce anthrax toxins, which have effects including impairment of cellular water homeostasis and of many intracellular signalling pathways. Clinical features—anthrax occurs in four clinical forms based on the route of exposure.

(1) Cutaneous—lesions are usually found on exposed areas of skin; a small papule develops at the

site of infection, enlarges, and ulcerates, with the painless ulcer becoming covered with a black leathery eschar surrounded by nonpitting oedema before healing in 2 to 6 weeks; associated systemic symptoms are usually mild. (2) Gastrointestinal—acquired by eating Table 8.6.20.1 Differential diagnosis of tularaemia Tularaemia Differential diagnosis Ulceroglandular Pyogenic bacterial infection, orf, pasteurella infections, syphilis, chancroid, lymphogranuloma venereum, scrub typhus, streptococcal and staphylococcal cellulitis, mycobacterial infections (including tuberculosis), sporotrichosis, herpes simplex virus, anthrax Glandular Pyogenic bacterial infection, cat-scratch disease, toxoplasmosis, mycobacterial infections, sporotrichosis, streptococcal and staphylococcal adenitis, syphilis, plague Oropharyngeal Streptococcal pharyngitis, infectious mononucleosis, adenoviral infection, diphtheria Oculoglandular Pyogenic bacterial infection, cat-scratch disease, herpes simplex virus, syphilis, adenovirus Typhoidal Enteric fever, brucellosis, leptospirosis, malaria, Q fever, rickettsial infection, toxic shock syndrome, endocarditis Gastrointestinal Enterohaemorrhagic E. coli, GI anthrax, Clostridium perfringens, listeriosis Respiratory Q fever, other atypical bacterial pneumonias (mycoplasma, Chlamydia pneumoniae, legionnaires' disease, psittacosis), viral pneumonia (influenza, hantavirus, respiratory syncytial virus, cytomegalovirus), tuberculosis, pneumonic plague

8.6.21 Anthrax 1095 contaminated food and comprising (a) oropharyngeal anthrax, presenting with fever, neck swelling, sore throat, oropharyngeal ulcer, and dysphagia, OR (b) terminal ileal/caecal anthrax, presenting with fever, nausea, vomiting, and abdominal pain, followed by rapidly developing ascites and bloody diarrhoea. (3) Inhalation—aerosol exposure leads to a nonspecific viral-type prodrome which progresses to a fulminant stage of severe respiratory distress, cyanosis, stridor, and profuse sweating; up to half of patients develop anthrax meningitis; shock and death typically follow in hours or days. (4) Injection—acquired by injection of heroin contaminated with anthrax spores. Symptoms range widely, but usually include inflammation and oedema at the injection site (no eschar), which may be complicated by compartment syndrome, necrotizing fasciitis, and sepsis. Diagnosis—may be very difficult in the absence of a known outbreak, particularly for inhalation anthrax where a clinical clue is widening of the mediastinum caused by lymphadenopathy. Confirmation is by laboratory identification of B. anthracis. Serological testing can be used for retrospective diagnosis. Treatment—this is with supportive care and antibiotics, which are effective against the multiplying (vegetative) form of B. anthracis, but not against the spore form. Mild cases of cutaneous anthrax are usually treated with oral penicillin. For gastrointestinal, inhalational, and meningeal anthrax, at least two antibiotics should be given intravenously; for example, ciprofloxacin or doxycycline along with another antimicrobial expected to be effective (penicillin, ampicillin, rifampin, vancomycin, chloramphenicol, imipenem, clindamycin, and clarithromycin). Prognosis—the mortality of untreated cutaneous anthrax is 10–20%, but fatalities are rare with appropriate antibiotic treatment. Almost all cases of inhalation anthrax and anthrax meningitis are fatal; initiation of treatment after the start of fulminant disease is rarely effective. Prevention—routine immunization of livestock should be instituted in endemic areas with continuing cases of animal anthrax. Carcasses of animals suspected of dying from anthrax must be disposed of appropriately. Anthrax vaccines should be offered to members of high-risk groups (those at occupational risk, laboratory workers, and some military groups). Postexposure prophylaxis should be given following suspected exposure to aerosolized anthrax spores (e.g. ciprofloxacin for 60 days). Introduction Anthrax is a zoonosis caused by Bacillus anthracis, a bacterium which can infect most species of mammals. Herbivores are particularly susceptible to

B. anthracis, acquiring the infection most often through contact with spores in the soil. The bacteria multiply rapidly to high concentrations in these animals which, upon death and spilling of blood and secretions, sporulate on the carcass and soil. Products from the spore-contaminated carcass provide the mode of *B. anthracis* exposure to humans. Thus, it is control of the infection in animals that is crucial to preventing anthrax in humans. Effective control relies on (1) vaccination of livestock and (2) proper disposal of infected animal carcasses. Anthrax occurs among animals in most countries of the world. It is still prevalent in epidemic or endemic form in many countries of Asia, Africa, and the Middle East. In North America and Australia anthrax has become rare. At the same time anthrax has gained in importance due to its potential as a biological weapon.

Appreciation of this threat has increased since 2001 and spurred development of improved methods of prevention, diagnosis, and treatment. Historical importance In agricultural settings, anthrax has been recognized for more than two thousand years. With industrialization, anthrax became a problem for workers processing animal products which originated in endemic/epidemic countries. Today, use of *B. anthracis* as a bio-weapon is perceived in developed countries as its major threat to the public health. Prominent reminders are the accidental release of *B. anthracis* spores from a Soviet military facility in 1979 and their deliberate release by letter in the United States of America in 2001. In the late 1800s, nonagricultural exposure to *B. anthracis* spores carried by animal hides and wool led to cases of cutaneous and inhalation anthrax ('woolsorters' disease') in industrializing countries. In Liverpool, a disinfection station was established where imported wool and other animal fibres were bathed in formaldehyde. This public health measure led to a marked decrease in cases in England, but the model was not followed elsewhere.

B. anthracis played a central and interesting role in the birth of medical microbiology. In the 1870s, Robert Koch cultured the organism on artificial media, described the vegetative and spore phases of its life cycle, and demonstrated disease causality by fulfilling 'Koch's Postulates'. Louis Pasteur added extensively to the anthrax-based evidence for the germ theory of disease and studied the attenuation of the organism. In the early 1880s, Pasteur in France and Greenfield in England independently demonstrated that heat-attenuated strains of *B. anthracis* protected sheep, goats, and cows from anthrax. This disease of livestock was of enormous economic importance in Europe and in less than 20 years, millions of sheep and cattle had been given this first animal vaccine. But stable attenuation of strains so that they were both safe and immunogenic remained challenging. It was 40 years later that Max Sterne developed such a strain of *B. anthracis*. This live attenuated strain became and remains the basis for the anthrax vaccines used globally to protect livestock.

Aetiology *B. anthracis* combines a rapidly multiplying, vegetative phase in animals which resists phagocytosis and produces a lethal toxin-mediated disease with a spore phase which resides dormant in the environment. The vegetative phase is a large, nonmotile Gram-positive rod. In clinical specimens it has a large capsule and occurs singly or in short chains that appear as 'jointed bamboo' rods. The vegetative form sporulates when it is deprived of essential nutrients. The spore, the infectious form of the organism, consists of a compact core protected by multiple concentric shells (cortex, coat, exosporium; see Fig. 8.6.21.1). They resist heat, desiccation, ultraviolet light, gamma irradiation, and some disinfectants.

section 8 Infectious diseases 1096 *B. anthracis* is a highly clonal species with a genome consisting of a single circular chromosome (5.2 Mbp) and two plasmids, pX01 (182 Kbp) and pX02 (95 Kbp). The homogeneity of *B. anthracis* strains constrained studies of transmission and epidemiology in the past. But research, accelerated after the anthrax letters in the United States (2001), led to strain-distinguishing genetic techniques. Strains can now be typed and distinguished based on

single nucleotide polymorphisms (SNPs) and variable number tandem repeat (VNTR) markers. Strains of *B. anthracis* fall into three major lineages (A, B, C) with lineage A causing more than 90% of infections globally. The SNP and VNTR techniques allow further subdivision of the *B. anthracis* population into 12 subgroups and more than 220 unique genotypes. Future analyses of yet unstudied isolates and strains emerging in outbreaks due to long dormant spores are expected to further expand these numbers. Ecology Anthrax is a zoonosis with a life cycle passing through animals (primarily herbivores) and the environment (largely soil). *B. anthracis* spores infect a mammal where they germinate and multiply as vegetative bacilli. If the animal dies, these bacilli spill on the ground via blood and secretions, and start to sporulate upon exposure to air. Soil containing spores becomes a reservoir for subsequent exposure of other animals. New infections occur via ingestion of vegetation or soil, inhalation of dust, or bites of flies each of which could carry spores. Animals vary greatly in susceptibility to parenterally introduced spores with lethal doses (LD₅₀) ranging from less than 10 to more than 10⁷ spores. However, the LD₅₀ is some thousand-fold higher, even in susceptible animals, when the spores must overcome healthy and intact skin or mucosa. On the spectrum of susceptibility, herbivores are highly susceptible while humans are moderately so. The factors leading to animal outbreaks are complex and incompletely understood. The death of a bacteraemic animal is likely to lead to spore production when ambient temperature and humidity is high. Flies can transfer spores to nearby foliage, increasing the incidence of infection in other browsing animals ('case multipliers') or infect animals more remotely through biting ('space multipliers'). The blood and nutrients which enter the soil from the dead animal may produce more grass in that contaminated spot and attract other browsers to this risk area. Rains, while washing spores off nearby foliage, tend to drain in ways that concentrate spores in depressions which may become sites of outbreaks ('hot spots') years or decades later.

Epidemiology Forms of disease Anthrax in humans has traditionally been classified based on either occupation (agricultural vs. industrial) or route of infection (cutaneous, ingestion, inhalation). A more recent classification (see Table 8.6.21.1) also distinguishes deliberate release. Human cases in the agricultural setting (usually cutaneous form) result from direct contact with infected animal carcasses, generally by herders, butchers, and slaughterhouse workers. Industrial cases involve workers who have contact, either directly or via aerosol, with spore-contaminated animal products such as hides, goat's hair, wool, or bone. Gastrointestinal anthrax follows ingestion of *B. anthracis*-contaminated food, often by villagers who are not aware that the animal was sick and so do not insure that meat is well cooked. Gastrointestinal cases are underdiagnosed in endemic regions. Inhalation anthrax is caused by alveolar deposition of the 1–2 µm spores. Historically those working with herbivore hides in industrial mills were at risk, but naturally acquired inhalation anthrax is now rare.

Fig. 8.6.21.1 Transmission electron micrograph of *B. anthracis* spores showing core, surrounded by cortex, coat, and exosporium with filamentous 'hairy nap'. Courtesy of Joel Bozue, USAMRIID.

Table 8.6.21.1 Classification of human anthrax based on source of infection or mode of acquisition

Based on source of infection	Agricultural	Traditional	Industrial	Traditional	Grouping
Based on mode of acquisition	Cutaneous	Most common form	Gastrointestinal	Underappreciated in endemic areas	Inhalation
	Potentially important modern event	Based on mode of acquisition	Cutaneous	Most common form	Gastrointestinal
	Underappreciated in endemic areas	Inhalation	Likely due to deliberate release	Injection	European outbreak (contaminated heroin)

8.6.21 Anthrax 1097 Burden and distribution of disease The worldwide incidence of human anthrax is not known, but is estimated to be about 2000 cases annually, of which some 95% are cutaneous. Based on reporting of anthrax outbreaks in animals, the World Health Organization (WHO)

characterizes several countries in Africa, the Middle East, and Asia as hyperendemic or epidemic (see Fig. 8.6.21.2). Many other countries in these regions, as well as in southern Europe and the Americas, are considered endemic while most remaining countries have at least sporadic cases. The largest reported outbreak of agricultural anthrax in recent times occurred in Zimbabwe in the late 1970s during the civil war. Most of the estimated 10 000 human cases were cutaneous, while a small number were gastrointestinal. Disruption of veterinary health services, especially anthrax vaccination, led to outbreaks among cattle and other livestock, and an associated epidemic in humans. Outbreak examples An outbreak of the oropharyngeal form of anthrax occurred in Thailand in 1982 when 24 people developed anthrax after eating undercooked meat from infected cattle and water buffalo. In Switzerland in 1991, workers in one textile factory contracted anthrax (24 cutaneous and one inhalation case) from contaminated Pakistani goat hair. An unusual outbreak of inhalation anthrax occurred in 1979 among residents of Sverdlovsk in the former Soviet Union. Spores accidentally released into the atmosphere from a military laboratory were carried downwind and caused at least 77 cases of human inhalation anthrax (66 deaths) and the deaths of many animals. Since 2000, there have been deaths among drug users in Europe due to *B. anthracis*-contaminated heroin. Seventy laboratory-confirmed cases, including at least 26 deaths, have been reported from the United Kingdom, Denmark, France, and Germany. Clinical presentations lacked a typical recognizable pattern. Genetic studies suggested that *B. anthracis* in these cases was from two introductions of, similar strains. Deliberate release State-sponsored biological weapons programmes often selected anthrax as an ideal organism. It is easily obtained and cultured, spores are very stable and small enough to reach alveoli when aerosolized, and inhalation infections are usually fatal. In the early 1970s more than 140 countries signed or ratified the Biological Weapons Convention, agreeing to terminate offensive weapons programmes and destroy existing weapons stockpiles. Monitoring compliance of this convention remains problematic. Anthrax has also been favoured by terrorist groups. In the early 1990s, members of the Aum Shinrikyo cult dispersed aerosols of *B. anthracis* spores over a Japanese city. Fortunately there was no Hyperendemic/epidemic Probably free Free Unknown Endemic Sporadic Fig. 8.6.21.2 Global anthrax epidemiology by country. Status is colour coded (see key) on this map. Adapted from the World Anthrax Data Site a website at the Louisiana State University WHO Collaborating Center (data as of 2003).

section 8 Infectious diseases 1098 disease outbreak because the cult had used an avirulent (Sterne) strain. In 2001, at least five letters containing anthrax spores (the virulent Ames strain) were mailed in the United States to several government and news offices. This led to 11 cases of inhalation anthrax with five deaths, and another 11 suspected or confirmed cases of cutaneous anthrax. The outbreak made clear how efficiently *B. anthracis* spores could be aerosolized. Thus, while the threat of human anthrax due to natural exposure has lessened in most developed countries, the threat of its deliberate release has increased. Pathogenesis General Transmission of anthrax to humans is via spores entering the skin or gastrointestinal or respiratory tracts. Spores are phagocytosed by macrophages and dendritic cells, and germinate intracellularly either at the local site or in draining lymph nodes. Many genes are expressed in the resulting vegetative bacilli, including a set located on plasmids and responsible for virulence. Genes on plasmid pX02 code for a poly-D-glutamic acid which forms a capsule resistant to phagocytosis. Strains which lack this capsule are avirulent and form the basis of most anthrax vaccines. Genes expressed on the other plasmid (pX01) guide the synthesis of two exotoxins. Within hours of germination, vegetative bacilli start to synthesize the three proteins [protective factor (PA), lethal factor (LF, 85-kDa) and

oedema factor (EF, 89-kDa)] which combine to form the anthrax toxins: lethal toxin (LT; PA + LF) and oedema toxin (ET; PA + EF). These exotoxins interfere with neutrophil and macrophage function. Thus, early on the combined effect of the capsule and exotoxins is to weaken the protective response of the innate immune system and allow rapid expansion of the *B. anthracis* population. The infection may become systemic with bacteraemia reaching 10⁷–10⁸ bacilli/ml. In the late stage of disease, the high levels of toxæmia produced by the large biomass of bacilli cause multiorgan damage with particular targeting by LT of the cardiovascular system (heart and vasculature) and by ET of the liver. The biology of the anthrax toxins and their cellular effects are complex. Soluble PA binds to cell surface receptors where it is cleaved by a furin protease. The larger C-terminal fragment (PA₆₃) remains bound and forms oligomers on cell surface lipid rafts where multiple copies of EF and/or LF bind. The whole complex is internalized through endocytosis and EF/LF are released into the cytoplasm through a channel within the PA oligomer. EF augments the conversion of adenosine triphosphate (ATP) to cAMP while LF inactivates key protein kinase pathways. The metabolic consequences include immune compromise, massive oedema, and the organ failure of severe anthrax.

Organ-specific When spores of *B. anthracis* are introduced cutaneously, they germinate, multiply, and produce exotoxins resulting in local tissue necrosis, oedema, and a paucity of leucocytes. Spread to draining lymph nodes results in haemorrhagic, oedematous, and necrotic lymphadenitis. Gastrointestinal anthrax follows ingestion of food contaminated with *B. anthracis* spores. Localization, germination, and multiplication of bacilli in the oropharynx and regional lymph nodes causes oropharyngeal ulcers, localized oedema, and neck swelling. Spores carried further tend to localize in the ileum or caecum and cause mucosal inflammation, ulcers, and ascites. These bacteria drain to mesenteric lymph nodes causing haemorrhagic adenitis. Inhalation anthrax follows deposition of spores in alveoli, phagocytosis, transport to tracheobronchial and mediastinal lymph nodes, and intracellular germination. In the mediastinum, haemorrhage, oedema, and necrotic lymphadenitis develop. Since this is not a pneumonia, sputum examination does not reveal the organism. Injection anthrax occurs a few days after injection of heroin contaminated with *B. anthracis* spores. It is characterized by massive local oedema which may be associated with local complications, dissemination and/or sepsis. All primary forms of anthrax can be complicated by septicaemia and, less often, haemorrhagic meningitis. These complications are especially frequent with inhalation anthrax and should be assumed for treatment decisions.

Criteria for diagnosis The diagnosis of anthrax may be suspected on clinical and epidemiological grounds, and is confirmed by laboratory identification of *B. anthracis*. Clinical specimens containing large Gram-positive rods, singly and in short chains of 2–4 cells, should be interpreted as possible *Bacillus* species. Demonstration of encapsulation of these bacilli by India ink, Giemsa's, or polychrome methylene blue stains leads to a presumptive identification of *B. anthracis*. Culture isolates have classic morphological characteristics: Gram-positive, broad spore-forming rods; intracellular oval spores which do not swell the vegetative cell; nonmotile; 'ground-glass' colonies which are (nearly always) nonhaemolytic on sheep blood agar. Standard confirmatory tests include lysis by specific γ -bacteriophage and direct immunofluorescent assays for cell wall or capsular antigens on the vegetative cells. Serological testing is not helpful at the onset of symptoms but can be used for retrospective diagnosis. Specific antibodies are detectable by enzyme-linked immunosorbent assay (ELISA), with testing of paired samples preferred. Polymerase chain reaction tests for the PA gene has been used but is not yet standardized. Delayed-type hypersensitivity assessed by antigen skin test (anthraxin) was developed in Russia for detection of prior infection or vaccination. Other technologies include immunohistochemistry for PA and capsule antigens, and genetic sequencing.

While culture loses much utility after the start of antibiotics, toxin-based assays may remain positive for up to another six days. Clinical features Cutaneous anthrax Anthrax acquired its name from the Greek description of the skin lesion's characteristic eschar as being the colour of coal (Greek

8.6.21 Anthrax 1099 anthrakos = coal). These cutaneous lesions (Fig. 8.6.21.3) are usually found on exposed areas of skin, such as the face, neck, arms, or hands, and may be single or multiple depending on the extent of exposure. The incubation period is usually 2–5 days. The lesion starts as a small papule at the site of infection and then enlarges and ulcerates. The depressed ulcer becomes covered with a black leathery eschar surrounded by nonpitting oedema that is occasionally massive ('malignant oedema'). Established lesions are characteristically painless and may be hypoaesthetic. (Pain suggests secondary infection.) Small satellite vesicles, containing many organisms and few white cells, may surround the original lesion. Regional lymphadenitis is common while systemic symptoms are usually mild. Lesions heal slowly (2–6 weeks) without scarring. In 10–20% of untreated patients the disease becomes systemic, with bacteraemia and toxæmia. Gastrointestinal anthrax Gastrointestinal anthrax is acquired by eating contaminated and inadequately cooked meat from an infected animal, and thus often occurs in social or familial clusters. The disease has an incubation period of 2–5 days and occurs in two forms. Oropharyngeal anthrax follows deposition of bacteria in the oropharynx. Patients present with fever, neck swelling, sore throat, and dysphagia. The neck swelling is caused by enlargement of the jugular lymph nodes together with subcutaneous oedema as in diphtheria. Enlarged nodes and local oedema may obstruct the airway. The mucosal lesion starts as an area of inflammation, progressing through necrosis and ulceration. A pseudomembrane (but no eschar) forms over the ulcer (see Fig. 8.6.21.4). Subcutaneous oedema may extend to the anterior chest wall and axilla, with inflammation of the overlying skin. In the more common form of gastrointestinal anthrax, *B. anthracis* organisms are deposited in the terminal ileum or caecum, occasionally in more proximal parts of the gastrointestinal tract. Disease onset is nonspecific with fever, nausea, vomiting, and abdominal pain, followed by rapidly developing ascites and bloody diarrhoea. Haematemesis, melaena, haematochezia, and/or profuse watery diarrhoea may occur. Presentation may be that of an acute abdomen. In severe cases, toxæmia, shock, and death follow. Early diagnosis is difficult, except when suspected due to the epidemiological setting, and the disease is likely underreported. Inhalation anthrax Inhalation anthrax results from the deposition of aerosolized spores in pulmonary alveoli. The incubation period ranges from 1 to 5 days, with modelling suggesting it is inversely related to (a) (b) (c) Fig. 8.6.21.3 Cutaneous anthrax. (a) Early ulcerated skin lesion with forming eschar. (b) Large lesion with extensive eschar on a Nigerian patient who carried an infected carcass on his shoulder. (c) Ulcer with satellite lesions on a Thai patient. Copyright D. A. Warrell. Fig. 8.6.21.4 Oropharyngeal anthrax in a Thai man showing extensive lesion in posterior pharynx with pseudomembrane. From Sirisanthana T, et al. (1984). Outbreak of oral-pharyngeal anthrax: an unusual manifestation of human infection with *Bacillus anthracis*. *Am J Trop Med Hyg*, 33, 144–50.

section 8 Infectious diseases 1100 dose. The prodrome is nonspecific with malaise, myalgia, fever, and nonproductive cough—similar to that of viral respiratory diseases. Some patients improve transiently after 2 to 4 days of symptoms. A fulminant stage then follows, bringing severe respiratory distress, cyanosis, stridor, and profuse sweating. Subcutaneous oedema of the chest and neck may develop. A characteristic radiographic finding is mediastinal widening with clear

lung fields. By advanced imaging techniques (CT or MRI), nearly all patients have mediastinal lymphadenopathy as well as pleural effusions (Fig. 8.6.21.5). Inhalation anthrax becomes systemic and commonly involves the central nervous system—about half of patients develop meningitis. Shock and death typically occur less than 24 h into the fulminant phase. Autopsies of persons dying of inhalation anthrax revealed serosanguinous pleural effusions and haemorrhagic oedema in the mediastinum where lymph nodes had haemorrhagic necrosis. About half of cases had cerebral oedema and about 20% had ascites.

Injection anthrax Injection anthrax is caused by the injection of heroin which is contaminated with spores of *B. anthracis*. Clinical presentations are diverse and inconsistent, and thus quite challenging. Most common are erythema and oedema near the injection site, occurring within 1–3 days of injection. Eschars are not found. Infection of the arm can lead to compartment syndrome or necrotizing fasciitis; pain may be very severe. The infection often becomes systemic with toxæmia, sepsis, and a rapid death.

Meningeal anthrax Meningoencephalitis, associated with *B. anthracis* bacteraemia, may complicate any primary form of anthrax. (Anthrax meningitis without a known primary site occurs but rarely.) Within a few days of the primary lesion the patient suddenly develops confusion, loss of consciousness, and/or focal neurological signs. The cerebrospinal fluid contains a high concentration of organisms and may be haemorrhagic.

Differential diagnosis The differential diagnosis of anthrax varies by type. For cutaneous anthrax, the differential diagnosis includes staphylococcal or streptococcal skin infections, ulceroglandular tularemia, bubonic plague, bites of brown recluse spiders, orf, rickettsial pox, and scrub typhus. For oropharyngeal anthrax, the differential diagnosis includes diphtheria and peritonsillar abscess. For inhalation anthrax, the differential diagnosis includes pneumonic plague, histoplasmosis, sarcoidosis, tuberculosis, and lymphoma.

Clinical investigations Only one anthrax vaccine has been tested in a controlled, human efficacy trial. This was in the 1960s with a product similar to today's Anthrax Vaccine Adsorbed. The trial showed the vaccine to be efficacious. Vaccines since have been studied for safety and immunogenicity in humans, and efficacy in animals. For practical and ethical reasons human efficacy studies are unlikely. There is a similar challenge for the evaluation of passive immune therapies. Prior to the development of penicillin, anthrax antiserum was given as treatment for anthrax. Since 2001, human polyclonal anthrax immune globulin (collected from human vaccinees) has been stockpiled in the United States and used in a handful of cases. A monoclonal anti-PA antibody has been developed and also stockpiled. Neither of these antitoxin therapies has been evaluated in controlled, human efficacy trials.

Treatment Antibiotics are effective against the multiplying (vegetative) form of *B. anthracis*, but not against the spore form. At least two should be used in combination for all severe anthrax disease. To counter the toxæmia, it is recommended that the combination include an inhibitor of protein synthesis. Severe disease will also require intensive supportive care. Cutaneous anthrax has been treated successfully with penicillin through much of the world. But while penicillin sensitivity is the norm, the organism possesses an inducible β -lactamase. Thus, alternatives to penicillin-based drugs should be used (1) in severe or systemic disease; (2) in outbreaks where the drug has been given to at-risk animals; and (3) when deliberate release is suspected. Given those caveats, cases of nonsystemic cutaneous anthrax can be treated with penicillin for 7–10 days (orally with penicillin VK 250 mg every 6 h or parenterally with penicillin G 2 million units every 6 h). Ciprofloxacin, erythromycin, doxycycline, or chloramphenicol can be used in penicillin-sensitive patients. Antibiotics decrease the likelihood of systemic disease and thus mortality, but the time to resolution of skin lesions is unchanged.

Skin lesions

Fig. 8.6.21.5 CT image of an American adult with inhalation anthrax showing mediastinal enlargement secondary to lymphadenopathy. Note small bilateral pleural effusions and nearly clear

lung fields. From Jernigan JA, et al. (2001). Bioterrorism-related inhalational anthrax: the first 10 cases reported in the United States. *Emerg Infect Dis*, 7, 933–44.

8.6.21 Anthrax 1101 should be covered with sterile dressings and used dressings should be decontaminated. In gastrointestinal, inhalational, and meningeal anthrax, at least two high-dose intravenous antibiotics should be given. If naturally acquired, penicillin G (4 million units every 4 h) has been the drug of choice; ciprofloxacin (400 mg every 12 h) or doxycycline (100 mg every 12 h) are currently recommended in the United States. All cases of systemic anthrax should be considered as high risk for developing meningitis. Thus, only drugs with good penetration of the central nervous system should be used. Anthrax caused by a deliberate release will generally be acquired by inhalation. In this setting, drug resistance due to genetic modification is of concern and drug sensitivity testing of the organism is imperative. Treatment should begin intravenously with ciprofloxacin or doxycycline, along with one or two other antimicrobials expected to be effective. Rifampicin, vancomycin, chloramphenicol, imipenem, clindamycin, and clarithromycin are candidates. Prognosis The mortality of untreated cutaneous anthrax is 10–20%. With appropriate antibiotic treatment, fatalities become rare (<1%). Mortality of oropharyngeal anthrax is about 15% in treated patients; mortality of the more common form of gastrointestinal anthrax is uncertain, but estimated at about 40%. Nearly all cases of inhalation anthrax have been fatal. An exception to this general experience occurred with the anthrax letter cases (United States in 2001) in which mortality was about 50%. Survival in that setting was found to be associated with three factors: initiation of multidrug treatment during the prodromal stage, repeated drainage of pleural effusions and extensive supportive measures. Despite these improvements, inhalation anthrax which progresses to the fulminant phase is nearly 100% fatal, as it is for those who develop meningo-encephalitis. Prevention Control of anthrax in animals decreases the likelihood of human exposure and is the key public health measure for preventing human disease. Immunization of livestock should be instituted in endemic areas with continuing cases of animal anthrax. The basis for nearly all animal (nonhuman) vaccines against anthrax is a live attenuated (nonencapsulated) strain of *B. anthracis* developed in South Africa by Max Sterne in the 1930s. This was a huge public health advance and converted a scourge of man and animals into an occasional problem. Cases of animal and human anthrax should be reported to the appropriate authorities. Carcasses of animals, domestic or wild, suspected of dying from anthrax should be incinerated along with the nearby vegetation, in a manner that also sterilizes the underlying soil. If this is not possible, the carcass should be buried intact to a depth of six feet or more to decrease the likelihood of scavenger animals digging it up and opening the body. Gastrointestinal anthrax of humans can be prevented by avoidance, ideally, of meat from sick animals or at least proper cooking when contamination is suspected. Anthrax vaccines should be offered to members of high-risk occupational groups, such as laboratory workers and some veterinary and military groups. Current anthrax vaccines for humans are all produced from attenuated strains of *B. anthracis* and do not use live bacilli. The United Kingdom and the US vaccines are made from cell-free culture filtrates and induce antitoxin immunity. PA is the sufficient and seemingly necessary antigen in these vaccines, and hence its name. The licensed vaccine in the United States is Anthrax Vaccine Adsorbed (AVA); it is given intramuscularly at 0, 1, 6, 12, and 18 months. More than 95% of vaccinees are seropositive after the first three doses. The licensed vaccine in the United Kingdom is Anthrax Vaccine Precipitated (AVP); it is given intramuscularly at 0, 3, 6, and 26 weeks. The Russian vaccine is a suspension of live spores of attenuated strain STI-1 and was first licensed in 1953. It is given either by scarification through a drop of vaccine or subcutaneously at 0 and 3 weeks. The Chinese vaccine is a spore suspension of attenuated strain A16R and has been in use

since the 1960s. It is given by scarification and boosted at 6 to 12 months. All these vaccines require booster doses (usually annually) to maintain protective immunity. Drawbacks of the current cell-free vaccines (AVA and AVP) are the incomplete characterization of the vaccine and the complex, lengthy immunization schedules. These drawbacks, along with the increased possibility of a deliberate release, have renewed efforts to validate shorter, simpler immunization regimens, and to develop alternative vaccines. A recombinant PA vaccine has progressed to clinical testing. Additional antigens and adjuvants are being explored, as are new approaches which include live vaccines, DNA, and carrier vectors. Postexposure prophylaxis is given to those with suspected exposure to aerosolized anthrax spores (deliberate release). Oral ciprofloxacin, levofloxacin, doxycycline, and penicillin G procaine have been approved for this indication in the United States. For pregnant and lactating women and for children, amoxicillin is recommended. A lengthy (60-day) course of antibiotics is used because they are not effective until spores germinate and the organism becomes metabolically active. Effective antibiotics limit multiplication of *B. anthracis*, but success here removes the stimulus for protective immune responses. Therefore, disease may occur after cessation of antibiotics, when postexposure prophylaxis compliance is poor, or if the *B. anthracis* strain is drug resistant. For these reasons, concurrent vaccination (3 SC doses of AVA given at 2-week intervals) is recommended along with antibiotics as postexposure prophylaxis in the United States. Special circumstances The WHO has estimated that 50 kg of *B. anthracis* spores released over a city of 5 million people would infect 250 000 people, killing 40% of them. Numbers would be influenced by the quality of the aerosol, dispersal method, and weather conditions. Cases would be largely inhalation and the intensive medical care required would overwhelm the medical surge capacity of most cities. Antibiotics and vaccine for postexposure prophylaxis would be

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