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An overview of anthrax infection including the recently identified form of disease in injection drug users

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Abstract

Purpose—*Bacillus anthracis* infection (anthrax) can be highly lethal. Two recent outbreaks related to contaminated mail in the USA and heroin in the UK and Europe and its potential as a bioterrorist weapon have greatly increased concerns over anthrax in the developed world.

Methods—This review summarizes the microbiology, pathogenesis, diagnosis, and management of anthrax.

Results and conclusions—Anthrax, a gram-positive bacterium, has typically been associated with three forms of infection: cutaneous, gastrointestinal, and inhalational. However, the anthrax outbreak among injection drug users has emphasized the importance of what is now considered a fourth disease form (i.e., injectional anthrax) that is characterized by severe soft tissue infection. While cutaneous anthrax is most common, its early stages are distinct and prompt appropriate treatment commonly produces a good outcome. However, early symptoms with the other three disease forms can be nonspecific and mistaken for less lethal conditions. As a result, patients with gastrointestinal, inhalational, or injectional anthrax may have advanced infection at presentation that can be highly lethal. Once anthrax is suspected, the diagnosis can usually be made with gram stain and culture from blood or tissue followed by confirmatory testing (e.g., PCR). While antibiotics are the mainstay of anthrax treatment, use of adjunctive therapies such as anthrax toxin antagonists are a consideration. Prompt surgical therapy appears to be important for successful management of injectional anthrax.

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Keywords

Bacillus anthracis; Anthrax; Pathogenesis; Diagnosis; Treatment

Introduction

Anthrax infection is caused by *Bacillus anthracis*, a large, aerobic, gram-positive, spore-forming bacterium that exists in either a dormant spore or actively replicating vegetative rod form; in clinical specimens, the bacteria appears encapsulated. The spore is found in soil around the world, although active disease is more common in warmer and wetter locations [1]. Infection occurs most commonly in herbivore mammals, either domestic or wild that ingest spores during grazing [2]. However, human contact with contaminated animal products can result in three forms of clinical infection referred to as either cutaneous, gastrointestinal (GI), or inhalational on the basis of the initial route of entry [3]. A new form of soft tissue infection associated with injection drug use and termed injectional anthrax has also been identified [4]. While the cutaneous form of anthrax is most common [5], the non-cutaneous forms typically result in more severe disease frequently requiring intensive care unit support [6, 7]. The risk of anthrax for bioterrorist use and the recent outbreak of injectional anthrax in more than 50 patients in the UK and Germany have increased awareness of this potentially lethal infection.

Anthrax in developed countries

Although cutaneous anthrax had long been recognized owing to the characteristic black eschar associated with it, naturally occurring inhalational anthrax was first formally described in the mid-1800s in British wool workers (i.e., woolsorter's disease). Improvements in industrial hygiene, decreases in the use of imported contaminated animal materials, and immunization of at-risk workers subsequently reduced the incidence of anthrax substantially in developed countries [2], although occasional cases still occur. Three recent cases of naturally occurring inhalational anthrax, one in the USA and two in the UK, were reported in drum makers using hides from infected animals [8–10]. There was also a very recent case of inhalational anthrax in an individual who had traveled through the midwest USA and was exposed to both animal products and dust [11]. Finally there was a case of gastrointestinal anthrax in a woman in the USA who is believed to have ingested aerosolized spores [12]. Anthrax continues to be enzootic in less developed areas of the world lacking stringent preventive measures [13].

Two notable instances of intentional anthrax (i.e., disease occurring from unnatural causes) highlight the bacteria's risk as a biological weapon. In 1979, an unusual anthrax epidemic occurred in the city of Sverdlovsk in the former Soviet Union. There were 68 confirmed deaths and it is the largest documented outbreak of human inhalational anthrax. Later investigation showed that this outbreak was likely due to widespread inhalation of anthrax spores accidentally released from a military facility [14, 15]. In 2001 an outbreak of anthrax infection occurred in the USA following the mailing of spore-containing envelopes to news and government offices [16]. Overall there were 11 inhalational and 11 cutaneous cases reported. All five patients who developed shock with inhalational disease died [16]. Prophylactic antibiotic treatment for many potentially exposed individuals likely mitigated a much higher fatality rate. The specific source of the contaminated envelopes is still debated [6].

The most recent outbreak of anthrax thought to be naturally occurring developed in injection drug users between December 2009 and December 2010 in Europe, primarily in the UK. There were 54 confirmed cases and 18 deaths overall [17]. Patients presented with soft

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tissue infections related to sites of heroin injection. There were several potential sources for contamination of this heroin. Most heroin sold in Europe originates in Afghanistan and is transported through Iran and Turkey—all countries where anthrax is enzootic [18, 19]. Moreover, heroin is routinely cut with substances that are frequently contaminated with pathogens [20].

Microbiology and pathogenesis

Bacillus anthracis is part of the *B. cereus* group of bacilli [21]. It is a gram-positive, nonmotile, aerobic, facultative anaerobic, large rod-shaped bacterium capable of forming dormant spores (Fig. 1) [1, 6, 22]. Under conditions of heat and high CO_2 the spore transforms into a rod-shaped vegetative form that then replicates, produces virulence factors, and causes disease. When the vegetative form is exposed to O_2 and cooler temperatures, the bacterium can again sporulate [1].

Three factors play a primary role in the pathogenesis of *B. anthracis*: a capsule; production of two exotoxins (lethal and edema); and the bacteria's ability to achieve high microbial concentrations in infected hosts [23]. The capsule enables the vegetative bacteria to evade phagocytosis by host cells [24]. Lethal (LT) and edema (ET) toxin are binary toxins, each made up of two proteins: protective antigen (PA) and lethal factor (LF) for LT and PA and edema factor (EF) for ET. Protective antigen mediates cell binding and uptake of LF and EF, the toxigenic components. Lethal factor is a zinc metallo-protease that selectively inactivates mitiogen-activated protein kinase kinases (MAPKK) 1–4, 6, and 7 [25]. Edema factor is a calmodulin-dependent adenyl cyclase that increases intracellular cAMP levels to very high levels [26]. Moayeri and Leppla [27] provide an excellent overview of the potential actions of LF and EF. Both toxins have been implicated in the production of shock and lethality, although the precise mechanisms underlying these effects are still unclear [17, 28–32]. However an increasing number of other bacterial components are being identified with potential pathogenic relevance for anthrax [17, 31].

Clinical forms

While cutaneous anthrax is typically recognized early and treatment is almost always effective, other forms (i.e., gastrointestinal, inhalational, and injectional) present with very nonspecific early symptoms. Thus, in the absence of a known outbreak, these other forms often progress to more advanced disease before they are recognized, and morbidity and mortality are relatively high.

Cutaneous anthrax

Ninety-five percent of reported anthrax cases are cutaneous and most occur in Africa, Asia, and eastern Europe where countermeasures such as animal and worker vaccination are limited [33]. There was recently a large outbreak of cutaneous anthrax reported in northwestern Bangladesh [34]. Disease typically results when pathogenic spores are introduced subcutaneously through a cut or abrasion in an exposed area of skin [6, 35]. The spores then germinate into vegetative forms that produce local edema. The primary skin lesion is usually a painless, pruritic papule that appears 3–5 days following initial infection. The lesion forms a vesicle that undergoes central necrosis and drying, leaving a characteristic black eschar surrounded by edema (Fig. 2) [35]. The eschar dries and sloughs in the next 1–2 weeks [36]. On histology, anthrax skin lesions show necrosis and massive edema with lymphocytic infiltrates. There is no liquefaction or abscess formation but focal points of hemorrhage are evident, with some thrombosis [37]. Antibiotic treatment is recommended for cutaneous anthrax to decrease the likelihood of systemic disease. Without such therapy, mortality due to malignant edema (characterized by severe edema, induration,

multiple bullae, and symptoms of shock) has been reported to be as high as 20 %. With appropriate antibiotic treatment, death due to cutaneous anthrax is uncommon [5].

Gastrointestinal anthrax

Most cases of GI anthrax are caused by ingestion of poorly cooked meat in which vegetative forms of the bacilli have developed and replicated [6]. Gastrointestinal anthrax occurs in oral-pharyngeal or lower GI forms. The oral-pharyngeal form is associated with development of an oral or esophageal ulcer followed by regional lymphadenopathy, edema, and sepsis [38]. The lower GI form manifests as primary intestinal lesions occurring predominantly in the terminal ileum or cecum. Patients with lower GI anthrax present initially with nausea, vomiting, and malaise, which then progresses rapidly to bloody diarrhea, an acute abdomen, or sepsis [39]. Ulceration of the gastrointestinal mucosa may result in hematemesis. Two to four days after the onset of symptoms, a clear to purulent ascites may develop that often grows *B. anthracis* on culture [40]. The lower GI tract demonstrates mucosal necrosis, extensive edema, and mesenteric lymphadenitis (Fig. 3) [12, 41]. Anthrax bacilli can be seen in the mucosal, submucosal, and lymphatic tissues, along with inflammatory infiltrates [42]. The mortality rate with GI anthrax can approach 100 % [43]. Morbidity is due to blood loss, fluid and electrolyte imbalances, and subsequent shock. Death results from intestinal perforation or anthrax toxemia. In survivors, most symptoms appear to subside in 10–14 days [40]. The only confirmed US case of GI anthrax was atypical in that it occurred in a person who likely swallowed aerosolized anthrax spores released from an animal-hide drum [10].

Inhalational anthrax

Inhalational anthrax occurs when anthrax spores less than 5 μm in size are inhaled and reach the lower respiratory tract [44]. Once there, alveolar macrophages phagocytose and transport the spores to the hilar and mediastinal lymph nodes where they germinate and produce bacterial toxins [6]. The clinical presentation of inhalational anthrax has been described as a two-stage illness. Initially, patients display flu-like symptoms with cough, fever, and fatigue that last from hours to a few days and then may briefly resolve [2]. The second fulminant stage is characterized by rising fever, dyspnea, diaphoresis, and shock. Hemorrhagic meningitis may complicate inhalational anthrax, resulting in patients presenting with meningismus, delirium, and obtundation. In patients presenting with advanced disease, cyanosis and hypotension progress rapidly and death can occur within hours [6]. Patients with progressive inhalational anthrax are typically found to have mediastinal adenopathy and hemorrhagic pleural effusions that can be detected on chest radiography (Fig. 4) [45–47]. Pathological examination usually shows a focus of necrotizing hemorrhagic pneumonitis at the portal of infection, with hemorrhage and necrosis of peribronchial and mediastinal lymph nodes [15]. Many patients also have gastrointestinal and leptomeningeal lesions due to hematogenous spread.

Data from the Sverdlovsk outbreak indicate a modal incubation time of approximately 10 days for inhalational anthrax. However, the onset of symptoms sometimes occurred up to 6 weeks after the exposure date suggesting that anthrax spores may remain viable in the lungs for many days [15]. Early diagnosis of inhalational anthrax is difficult and requires a high index of suspicion. Prior to the 2001 attacks, clinical information was limited to a series of 18 cases reported in the twentieth century and the limited data from Sverdlovsk [6]. In the twentieth century series of US cases, the mortality rate of occupationally acquired inhalational anthrax was 89 %, but the majority of these cases occurred before the development of critical care units and, in most cases, before the advent of antibiotics [2]. The mortality rate in patients in the 2001 US outbreak, while lower than in earlier cases, was still very high. Although retrospective, an extensive review of inhalational anthrax cases has

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suggested that earlier antibiotic treatment and the use of pleural drainage or toxin inhibitors may decrease mortality [45].

Injectional

The first recognized case of injectional anthrax was in a 49-year-old HIV-negative heroin skin-popper who presented initially with a 4-day history of an infection in his right gluteal region [4]. Although the skin was erythematous, incision and drainage did not reveal pus and there was no eschar. The patient was discharged on oral dicloxacillin. The patient re-presented 4 days later in shock and coma. There was evidence of meningitis on lumbar puncture and his gluteal region, thigh, and lower abdominal wall were erythematous. There was still no eschar formation. Surgical exploration demonstrated extensive edema of muscles and subcutaneous tissue but no pus or necrosis. Despite treatment with high-dose penicillin, chloramphenicol, and dexamethasone the patient died within 3 days of admission. Cerebral spinal fluid and wound samples revealed *B. anthracis*. The absence of an eschar and the similarity of the case to ones reported after injection of anthrax-contaminated antibiotic in India and to disease noted in chimpanzees injected subcutaneously with the bacteria led to this form of the disease to be termed ‘injectional anthrax’ [48, 49].

There were no subsequent reports of injectional anthrax until December 10, 2009, when two hospitalized injection drug users from Glasgow in the UK were found to have blood cultures positive for *B. anthracis* [50]. Additional cases then began to appear. In a letter to *The Lancet*, the Health Protection Scotland Anthrax Clinical Network provided an overview of some of the earlier cases [51]. By the end of this outbreak in December 2010, there were 47 confirmed injectional anthrax cases with 13 deaths in Scotland and five cases with four deaths in England [48]. There were also two cases with one reported death in Germany. To date, 10 of these 52 cases have been published as case reports, although the level of data provided in each report has varied [20, 52–57] (Table 1). Nine of the ten cases presented with tissue swelling and evidence of soft tissue infection anywhere from 1 to 10 days after the injection of heroin, often at subcutaneous sites. Skin changes were noted in some but not all of these cases. Early skin changes with injectional anthrax can be fairly similar to other skin manifestations of injection drug use, and may have resulted in some of the patients in the UK presenting with more advanced disease (Fig. 5) [54, 55]. One patient presented with abdominal symptoms and evidence of peritonitis following groin injection. Diagnosis in cases was based on positive blood or tissue cultures and/or PCR analysis. Data regarding abnormal laboratory parameters, the presence or development of shock or organ failure, and antibiotic treatment were not consistently reported. In nine cases reporting the relevant data, patients required surgical debridement and/or fasciotomy. Repeated debridement was reported on in several cases. The patient with abdominal symptoms underwent repeat laparotomies. Findings at surgery varied, although excessive bleeding and edema were frequently noted (Fig. 5) [54, 55]. For the nine cases reporting the relevant data, three patients died, although one death may not have been related directly to anthrax. Notably distinct from cutaneous disease, these anthrax soft tissue infections were not associated with black eschar formation.

Diagnostic methods

In 2001, the US Center for Disease Control (CDC) developed interim case definitions for anthrax. A confirmed case was defined as a clinically compatible one that was laboratory confirmed by the isolation of *B. anthracis* from the patient, or by laboratory evidence based on at least two supportive tests employing non-culture detection methods [58] (Table 2). *B. anthracis* can be isolated from numerous clinical samples, including blood, skin lesion exudates, cerebrospinal fluid, pleural fluid, sputum, and feces. In systemic infections, organisms can often be cultured from the blood if the sample is collected prior to

antimicrobial therapy. Anthrax should immediately be considered if Gram's stain of specimens reveals high concentrations of gram-positive bacilli growing in chains [59]. Diagnoses of the cases encountered in the recent UK outbreak were based on culture and/or PCR testing of blood or excised tissues [20, 50, 52–57].

Management

Active infection

Antimicrobial therapy—Treatment of anthrax must be considered in the context of those patients with likely or diagnosed active disease and in those who have potentially been exposed but do not yet demonstrate clinical symptoms. Of those patients with diagnosed active disease, treatment recommendations differ depending on the clinical form.

For patients with inhalational anthrax, the CDC recommends treatment with ciprofloxacin or doxycycline and one or two additional antimicrobials for a period of no less than 60 days [60] (Table 3). Although penicillin shows good in vitro sensitivity for anthrax, initial treatment with non-penicillin agents until sensitivity patterns are known has been suggested since resistant anthrax strains may be engineered with relative ease [6]. Initial therapy should be intravenous (IV), with adjustment of the regimen to treatment with oral antimicrobials on the basis of the clinical course. For patients affected with severe inhalational disease (i.e., with shock and respiratory failure; stage 2), IV ciprofloxacin is recommended over doxycycline as the primary antimicrobial agent, unless ciprofloxacin use is contraindicated [61]. Treatment for severe cases should also include at least one agent with adequate CNS penetration (e.g., ampicillin or penicillin, meropenem, rifampin, or vancomycin) to cover possible meningeal involvement. Clindamycin is also recommended because of its potential ability to inhibit exotoxin production [61]. Sensitivity levels for 31 antibiotics against 32 strains of *B. anthracis* are provided in the literature [62].

Patients affected with localized or uncomplicated cases of naturally acquired cutaneous anthrax would be considered to have stage 1 disease, and should be treated with oral ciprofloxacin or doxycycline for 60 days accordingly [60]. Oral amoxicillin may be used following clinical improvement since penicillin has been shown to render cutaneous anthrax lesions culture-negative within 24 h [61]. For severe cases of cutaneous anthrax with signs of systemic involvement, extensive edema, or lesions on the head or neck, IV therapy using a multidrug approach is recommended [60].

Recommendations regarding the antibiotic treatment of injectional anthrax will be greatly aided when the full experience with patients in the 2009–2010 UK outbreak is analyzed and published. During the outbreak and on the basis of early cases, Health Protection Scotland published recommendations [63]. As presented in Table 3, in suspected cases of injectional anthrax with soft tissue infection empiric antibiotic treatment should be started to cover *B. anthracis*, as well as other more common causes of soft tissue infection. This treatment includes ciprofloxacillin and clindamycin intravenously, in combination with other antibiotics such as penicillin, flucloxacillin, and metronidazole (i.e., a five-drug regimen). As noted below, timely and aggressive tissue debridement is also a mainstay for such cases [63]. Injectional drug users suspected of having disseminated anthrax infection without evidence of soft tissue infection should be treated as for inhalational disease with possible meningeal involvement.

The recommended clinical management of anthrax, including the use of antimicrobial agents, is presently undergoing review and revision by the CDC based on the proceedings of an Affiliated Event of the 49th Annual Infectious Disease Society of American Annual Meeting held October 18 and 19, 2011.

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Anti-toxin therapies—Anti-toxin therapies for anthrax are still considered investigational. An immunoglobulin preparation derived from individuals previously vaccinated with anthrax vaccine adsorbed (AVA), known as anthrax immune globulin (AIG) (Emergent BioSolutions Inc., Rockville, MD, USA) is currently under investigation as part of a phase I/II clinical trial with the intention to treat patients with manifest symptoms of anthrax disease [64]. There is presently a supply of AIG available from the CDC under an Investigational New Drug protocol for the treatment of patients with confirmed life-threatening anthrax [65]. Recent inhalational, GI, and a number of the UK injectional cases were treated with this antibody [50]. The results of this combined experience have not yet been fully presented.

A human monoclonal antibody generated against recombinant PA, raxibacumab (ABthrax), and produced by Human Genome Sciences (HGS; Rockville, MD, USA) has shown efficacy against both lethal toxin and anthrax spore challenges in animal models [66, 67], and appears safe in uninfected humans [64]. In 2009, the US Government ordered 65,000 doses of raxibacumab for delivery to the US Strategic National Stockpile by the end of 2012 [68].

Other antibody-based preparations directed at PA, LF, and EF have also been proposed as potential anthrax treatments and are now under study [69–78]. There are also several non-antibody-based anti-toxin therapies under investigation that are reviewed elsewhere [79, 80].

Post-exposure prophylaxis

Prophylaxis following a potential anthrax exposure includes both antibiotics as well as vaccine treatment to accelerate host immunity. Anthrax vaccine adsorbed (AVA, BioThrax; BioPort Corporation, Lansing, MI, USA) is an aluminum hydroxide-precipitated preparation of PA from attenuated, non-encapsulated *B. anthracis* cultures of the Sterne strain that has been used in the USA [81]. The current UK licensed anthrax vaccine (anthrax vaccine precipitated, AVP) produced by the Health Protection Agency (HPA; Porton Down, UK) is similarly composed of alum-precipitated PA from the Sterne strain of *B. anthracis*, along with a much smaller amount of LF [82]. In a study of non-human primates challenged with high dose aerosolized *B. anthracis* spores, post-exposure vaccination with AVA enhanced protection from 14 days of antibiotic prophylaxis [83]. This data has suggested that post-exposure vaccination may shorten the duration of antibiotic prophylaxis required to protect against inhalational anthrax.

A CDC conference on anthrax post-exposure prophylaxis recommended treatment with ciprofloxacin and doxycycline as equivalent first-line antimicrobial agents following potential inhalation exposure to *B. anthracis* [61]. Antibiotic therapy should be continued for 60 days on the basis of this recommendation. The CDC also calls for treatment with a three-dose series of AVA administered first within 10 days of exposure and then 2 and 4 weeks after exposure [84]. This regimen has been recommended for children and pregnant or lactating women as well [85].

ICU therapies and special considerations

Patients presenting with anthrax infection and shock should be treated aggressively with the same type of hemodynamic support utilized for septic shock due to other types of bacterial infection [6, 17, 31, 80]. It must be noted, however, that it is currently unknown how the vascular effects of LT and ET might alter responsiveness to conventional hemodynamic support. Studies in rats found that, in contrast to *E. coli* and lipopolysaccharide (LPS) challenge, fluid support actually worsened outcome with LT challenge [86]. A more recent study investigating the efficacy of norepinephrine treatment also showed that while norepinephrine improved survival of rats challenged with LPS and increased blood pressure

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before the onset of lethality with LT, it did not improve survival with the latter [87]. In contrast to these rat studies, however, in a mechanically ventilated canine model, conventional hemodynamic support (i.e., fluids and norepinephrine titrated on the basis of intravascular hemodynamic measures) did improve outcome [88]. Interestingly, the protective effects of hemodynamic support were enhanced when combined with anti-PA directed monoclonal antibody.

Several lines of evidence suggest that continued chest drainage or intermittent thoracentesis might be important in the management of inhalational anthrax cases. This intervention appeared effective in patients during the 2001 inhalational anthrax outbreak [89] and in a more recent case [90]. In this latter case, analysis of serial samples showed high pleural fluid lethal toxin levels, and the case's positive outcome has been attributed in part to a combination of improved mechanical effects on respiration from fluid drainage as well a reduction in lethal toxin levels [90]. Evaluation of the treatment of inhalational anthrax cases from 1900 to 2005 has also suggested that pleural fluid drainage improves survival [45].

Glucocorticoids have also been considered as possible adjunctive therapy for patients with serious systemic illness due to inhalation anthrax, including anthrax patients with meningoencephalitis and patients with extensive edema involving the head and neck [91, 92]. A retrospective review of 70 cases of anthrax meningoencephalitis from 1966 to 2002 reported a 14 % decrease in overall mortality among patients treated with glucocorticoids as an adjunct to antimicrobial therapy [93]. It has also been shown that at very low concentrations, LT represses glucocorticoid receptor transactivation in both a cellular system and animal model, further suggesting that glucocorticoids may have therapeutic value in anthrax patients [94]. However in this latter study, dexamethasone treatment was not beneficial in toxin-challenged animals.

Although the management of injectional anthrax is evolving, aggressive surgery with debridement appears necessary when there is a clinical need to control soft tissue infection [63]. Drainage of extravascular fluid collections when present may also be important.

There are no data suggesting that patient-to-patient or person-to-person transmission of anthrax occurs. Therefore while standard barrier precautions are recommended for all hospitalized anthrax patients, the use of airborne protection measures is not indicated [95, 96]. Contact isolation precautions should be used for patients with draining cutaneous anthrax lesions [97]. Healthcare workers or household contacts should only receive post-exposure prophylaxis if it is determined that those persons were exposed to anthrax aerosol or surface contamination [6].

Dressings removed from draining cutaneous anthrax lesions should be disposed of as biohazardous waste. Individuals coming in direct contact with a substance alleged to contain *B. anthracis* should wash the exposed skin and clothing thoroughly with soap and water. For environmental surfaces contaminated with infected body fluids, a disinfectant such as hypochlorite, used for standard hospital infection control, isadequate [7]. Humanand animalremains infected with *B. anthracis* should be cremated rather than buried to prevent spread of disease [6].

Conclusion and future directions

Over 125 years ago, anthrax emerged as a damaging disease of domesticated animals and the farming economy [2]. In the early 1900s, improved industrial and animal husbandry hygiene, decreased use of potentially contaminated animal products, and vaccination of those at risk of occupational exposure resulted in a significant decline in anthrax in the developed world [7]. However, the 2001 US outbreak and the more recent UK experience

with injection drug users have once again shown that this infection, while rare in developed areas, is still a risk. Rapid diagnosis and treatment with antimicrobials and other adjuvant therapies are essential to minimize disease progression and death.

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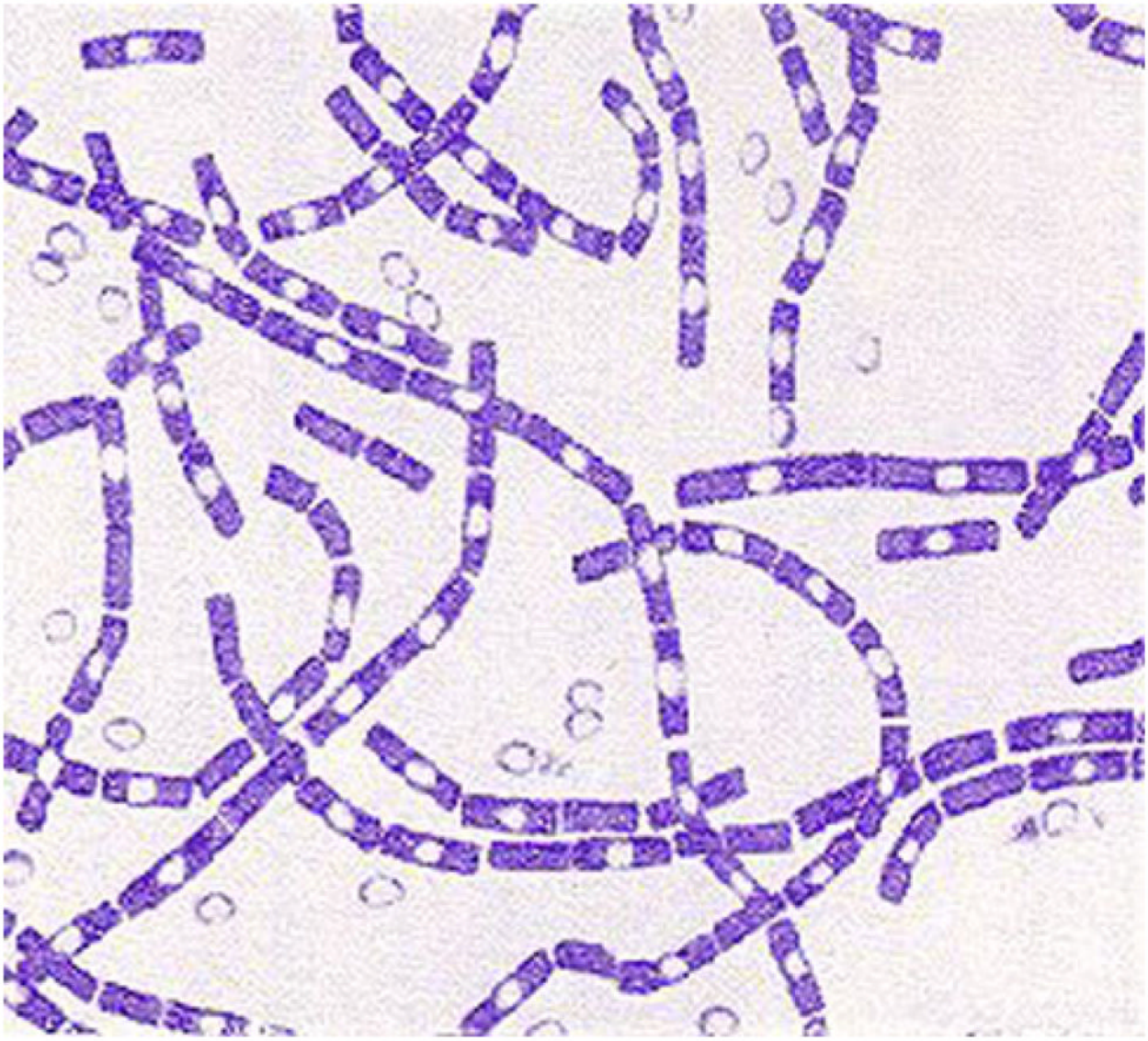

Fig. 1.
Gram stain of *B. anthracis* at ×1,500 magnification. In its vegetative form, *B. anthracis* is a gram-positive, nonmotile, large rod-shaped bacterium that actively replicates and produces virulence factors that cause disease. In its dormant state, *B. anthracis* exists as an ellipsoid-shaped spore that is highly refractive to light and resistant to staining [22]

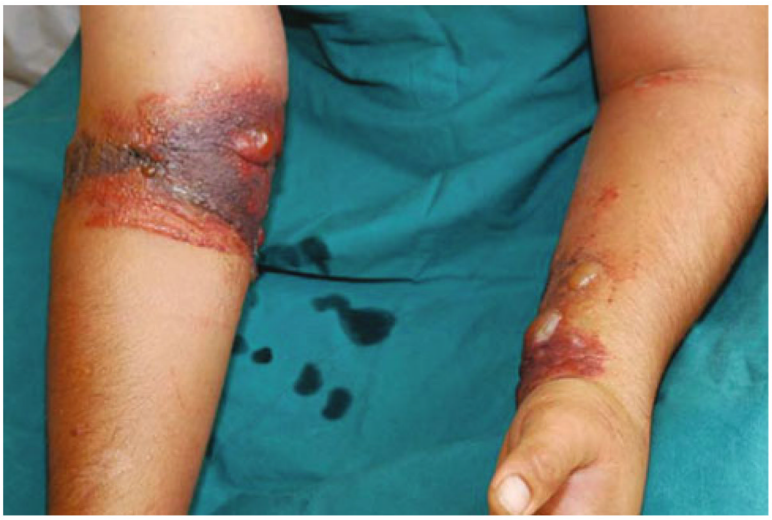

Fig. 2.
Cutaneous anthrax. These lesions appeared on the arms of a man who 6 days earlier had handled ill cattle. The extensive edema and hemorrhagic vesicles and bullae are typical of cutaneous anthrax and appear prior to the formation of a black eschar [35]. (Reprinted with permission of the American Thoracic Society. Copyright © 2012 American Thoracic Society [17])

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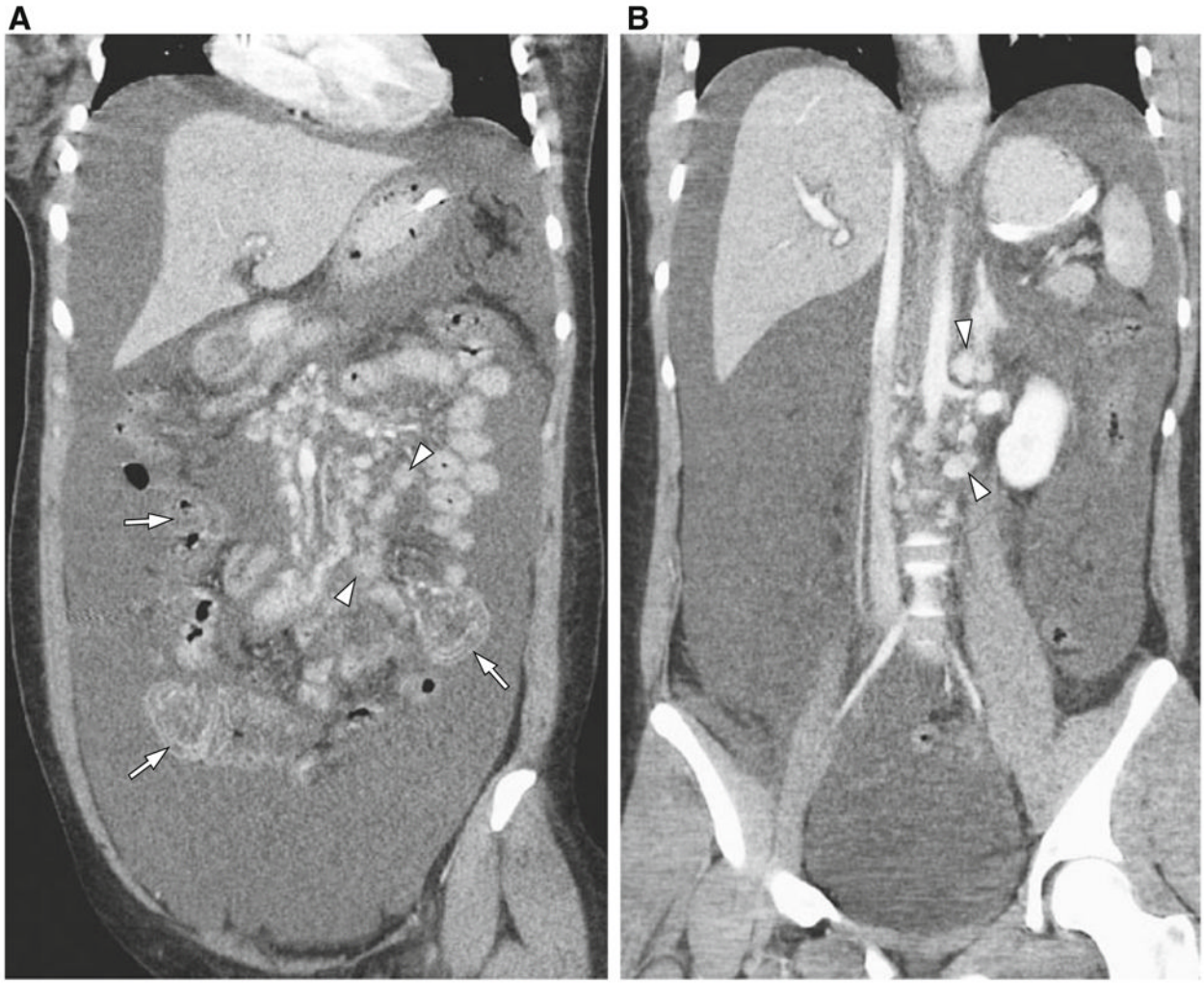

Fig. 3.

Gastrointestinal anthrax. Coronal reconstruction images from a CT scan of the abdomen and pelvis after the administration of intravenous contrast material show a large amount of ascites and concentric wall thickening of a long segment of the distal small bowel (**a**, *arrows*). Numerous slightly enlarged lymph nodes are enhanced with intravenous contrast material and are seen at the root of the small bowel mesentery (**a**, *arrowheads*) and in the retroperitoneum (**b**, *arrowheads*) [12]. (Reprinted with permission of the American Thoracic Society. Copyright © 2012 American Thoracic Society [17])

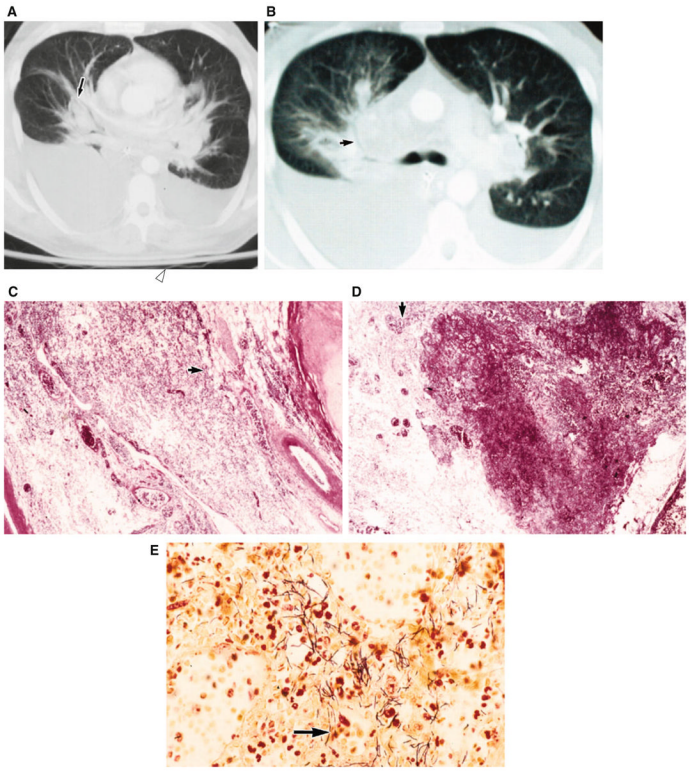

Fig. 4.

Inhalational anthrax. The contrast-enhanced chest CT scans (**a**, **b**) from a patient with inhalational anthrax show perihilar parenchymal lung disease (*arrow*, **a**), widening mediastinum, hilar adenopathy, pleural effusions, and peribronchial infiltrates as well as patchy peribronchial air-space disease, especially on the right (*arrow*, **b**). Photomicrographs of histopathologic specimens of hilar soft tissue (**c**–**e**) from the same patient at autopsy show perivascular and peribronchial hemorrhage (*arrow*, **c**; H & E, ×10), and necrosis (*arrow*, **d**; H & E, ×20) and abundant gram-positive bacilli (*arrow*, **e**; Brown–Brenn, ×100) [47]. (Reprinted with permission of the American Thoracic Society. Copyright © 2012 American Thoracic Society [17])

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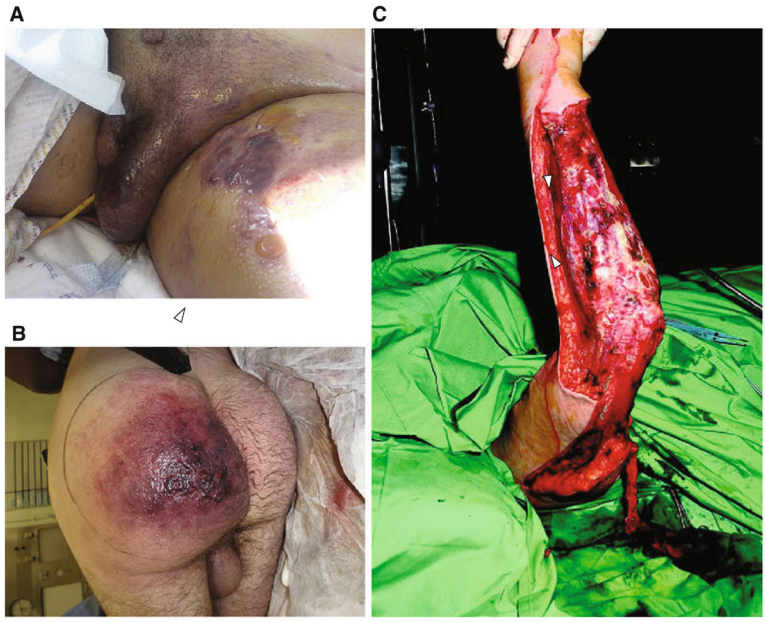

Fig. 5.

Injectional anthrax. Preoperative photographs of a woman (**a**) with skin necrosis involving the medial aspect of her left thigh and labia majora and a man (**b**) with swelling of his scrotum and skin necrosis involving his buttock [54]. Surgical debridement of necrotic skin and fascia of a patient with injectional anthrax and compartment syndrome of the right arm (**c**) [55]. (Reprinted with permission of the American Thoracic Society. Copyright © 2012 American Thoracic Society [17])

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Table 1

Summary of published UK injectional anthrax reported cases

First author (reference)	Age (years)	Sex	Presenting complaint	Surgical interventions described	Outcome
Radun [52]	42	Male	Leg swelling after popliteal injection	Debridement	Death
Beaumont [53]	23	Male	Forearm swelling 2 days after injection	NR	Survived
Jallali [54]	53	Female	Swollen leg, malaise 10 days after injection	Debridement, fasciotomy	Death[a]
Jallali [54]	32	Male	Swollen genital and gluteal region 6 days after gluteal injection	Debridement	Survived
Parcell [55]	28	Female	Swollen shoulder 5 days after injection	Debridement	Survived
Powell [20]	32	Male	Swollen leg and groin sinus drainage with chronic groin injection	Soft tissue exploration	Survived
Knox [56]	44	Male	Swollen and painful arm 10 days after injection	Debridement, fasciotomy	Survived
Knox [56]	36	Female	Swollen forearm and hand 3 days after injection	Fasciotomy	Survived
Knox [56]	32	Male	Swollen leg with spreading cellulitis not respsonsive to 2 days PO flucloxacillin	Debridement	NR
Johns [57]	24	Male	Abdominal pain, chills, rigors, nausea 2 days after groin injection	Laparotomy	Death

NR not reported

[a]Not due directly to anthrax infection

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Table 2

Summary of diagnostic and supportive tests employed to confirm the diagnosis of anthrax in clinically compatible cases

Test	Description
Routine culture	Morphology, hemolysis, motility, and sporulation are evaluated after plating suspected *B. anthracis* cells on standard 5 % sheep blood or chocolate agar. *B. anthracis* colonies will be 2–5 mm in diameter with irregularly round borders and a ground glass appearance, are non-hemolytic and nonmotile, and should sporulate 18–24 h after incubation at 35–37 °C in a non-CO_2 environment
Immunohistochemical staining (gram stain)	Detection of *B. anthracis* cells in formalin-fixed tissues using antibodies specific for cell wall or capsule antigens
Real-time PCR	Targets three distinct loci on the *B. anthracis* chromosome and each of the two virulence plasmids
Capsule staining	India ink, McFadyean staining, or direct fluorescence assay (DFA) may be used to visualize encapsulated *B. anthracis* either in culture or directly in clinical specimens
Susceptibility to gamma phage lysis	Gamma phage specifically lyses *B. anthracis* vegetative cells and can be used to confirm diagnosis for isolates with a concomitant positive capsule stain
Time-resolved fluorescence (TRF)	Anti-PA assay similar to ELISA, but that uses detector antibodies labeled with fluorescing lanthanide chelates instead of enzymes and pulses of excitation energy to measure fluorescence
Immunochromatography (RedLine Alert)	A lateral flow immunoassay containing a monoclonal antibody that is specific for the presence of a cell surface protein found in *B. anthracis* vegetative cells and used for rapid presumptive identification of *B. anthracis* from non-hemolytic *Bacillus* colonies cultured on sheep blood agar plates
Direct fluorescent assay (DFA)	Two-component assay that uses fluorescein-labeled monoclonal antibodies to detect the galactose/*N*-acetylglucosamaine cell-wall-associated polysaccharide and capsule produced by *B. anthracis* vegetative cells either in culture or directly in clinical specimens
Immunochromatography (RedLine Alert)	A lateral flow immunoassay containing a monoclonal antibody that is specific for the presence of a cell surface protein found in *B. anthracis* vegetative cells and used for rapid presumptive identification of *B. anthracis* from non-hemolytic *Bacillus* colonies cultured on sheep blood agar plates
Fluorescence resonance energy transfer assay (FRET)	Fluorogenic peptide-based assay used to screen for *B. anthracis* lethal factor (LF) protease activity
Europium nanoparticle-based immunoassay (ENIA)	Nanoparticle-based detection of antibody response against the protective antigen (PA) anthrax toxin protein
Electrophoretic immunotransblot (EITB) reaction	Measures antibody protective antigen and/or lethal factor bands in serum from patients with suspected *B. anthracis* infection
Quantitative human anti-PA IgG enzyme-linked immunosorbent assay (ELISA)	Enzyme-based colorimetric detection of antibody response against the protective antigen (PA) anthrax toxin protein
Time-resolved fluorescence (TRF)	Anti-PA assay similar to ELISA, but that uses detector antibodies labeled with fluorescing lanthanide chelates instead of enzymes and pulses of excitation energy to measure fluorescence
Molecular characterization	Multi-locus variable-number tandem repeat analysis (MLVA) and sequencing of genes coding for 16S ribosomal RNA may be conducted for species identification and molecular characterization *B. anthracis* isolates

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Table 3

Antibiotic management for adults with anthrax infection

Clinical syndrome	Initial therapy[a,b,c]	Comments
Cutaneous (uncomplicated)	Ciprofloxacin 500 mg PO twice daily or doxycycline 100 mg PO twice daily 9–60 days	Oral amoxicillin may be used following clinical improvement because penicillin has been shown to render lesions culture-negative within 24 h
Inhalational, gastrointestinal, or complicated cutaneous disease with systemic involvement	Ciprofloxacin 400 mg IV q 8 h or doxycycline 100 mg IV q 12 h in combination with 1–2 additional agents (i.e., clindamycin 600 mg IV q 8 h or penicillin G 4 MU q 4–6 h or meropenem 1 g IV q 6–8 h or rifampin 300 mg q 12 h)	Clindamycin use strongly recommended for role in preventing toxin production. In cases of severe disease, ciprofloxacin is favored over doxycycline and either penicillin or rifampin should be administered to cover potential meningeal involvement
Injectional	Ciprofloxacin 400 mg IV q 8 h and clindamycin 600 mg IV q 8 h in combination with other antibiotics such as penicillin G 4 MU q 4–6 h, flucloxacillin 1 g q 6 h, and metronidazole 500 mg q 12 h (i.e., a five-drug combination).	Timely surgical debridement and/or I & D is essential to remove devitalized tissue and the nidus of infection

I & D incision and drainage

[a] Treatment for 60 days is recommended to avoid relapse or breakthrough of incubating disease. If initial therapy is IV, continue for minimum 10–14 days, then convert to PO (either ciprofloxacin or doxycycline) when clinically indicated

[b] Steroids may be considered as an adjunct therapy for patients with severe edema and for meningitis

[c] Avoid doxycycline in pregnant women; start with ciprofloxacin and switch to oral penicillin once susceptibilities are known