Injectational anthrax in human: A new face of the old disease

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Abstract

Unusual human behavior leads to the emergence of new forms of infectious diseases and new routes of infection. In recent years, a new form of anthrax, called injectational anthrax, emerged and was related to 2 human anthrax outbreaks in Europe. The infection was caused by heroin contaminated with anthrax spores. The new form of anthrax differs from the earlier known “natural” forms of the disease in symptoms, length of the incubation period and recommended treatment. Despite medical treatment, the mortality rate in injectational anthrax is about 35%. This article presents an overview of the forms of anthrax infection in humans, with focus on injectational anthrax syndrome, as well as actual recommendations for treatment, including antibiotic therapy, surgery and possibilities of administering anthrax antitoxin. As a source of contamination of heroin have not been identified and new cases of injectational anthrax might occur again in any country in the future.

Key words: treatment, anthrax, drug users, soft tissue infection

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Anthrax is an animal and human disease caused by *Bacillus anthracis* – a Gram-positive bacterium that produces spores extremely resistant to many (broad spectrum) physical and chemical factors, such as drying, heat, gamma radiation, ultraviolet light, various pH, and many disinfectants.^{1,2} Thus, the spores may remain viable and infectious in the environment for decades. Wilson and Russell proved that anthrax spores have been still able to germinate after 60 years of storage in soil samples under laboratory conditions.³ In the Kruger National Park, *B. anthracis* has been recovered from bones estimated to be approx. 200 years old.⁴ Germination of anthrax spores occurs usually within the infected host producing the vegetative forms of the bacteria. However, Saile and Koehler revealed that anthrax spores may germinate in the rhizosphere and around grass plants roots.⁵ Favorable conditions for anthrax spore germination might include soils rich in calcium and organic matter with a pH above 6.0 and temperature of soil above 15°C.⁶

Vegetative *B. anthracis* cells within the infected host multiply rapidly, eventually killing the host.¹ Concentration of anthrax cells in blood from carcasses can reach 10⁹ CFU/mL. The microorganisms enter soil and water during terminal hemorrhaging from the rectum, nostrils or mouth of the animal carcass or upon carcass destruction by scavenging carnivores.

The low CO₂ level in open air, when compared with the level in tissue, induces sporulation that enables transformation of *B. anthracis* vegetative cells into the highly resistant spores. The spores are an infective form of the bacterium. Consequently, human can be infected via contact with contaminated soil, infected animals and infected or contaminated animal products.^{1,2}

Apart from natural outbreaks, anthrax is considered to be “a bioterrorism agent.” Although natural anthrax outbreaks are rare in developed countries, bioterrorism events may currently occur at any time, in any form (e.g., anthrax letters in 2001). The rarity of the disease makes it difficult to diagnose anthrax cases by clinicians and in laboratory diagnostics conducted by clinical microbiologists.⁷

The detection of *B. anthracis* in clinical and environmental samples can be conducted using conventional and molecular tests. In blood or other body fluid samples (including fluid from cutaneous lesions), or tissue specimens, *B. anthracis* is readily visualized in capsule-stained smears and readily isolated in pure cultures. Cultured microorganisms are identified based on Gram stain, colony morphology, a motility test, a capsule production test, and a γ phage plaque assay. Also, matrix assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF) might be used to identify cultured *B. anthracis* provided that a database dedicated to bioterrorism agents is available. Molecular tests, such as polymerase chain reaction (PCR) and real-time PCR, can be used for anthrax detection in clinical and environmental samples as well as for cultured bacteria.^{1,7} Moreover, rapid tests

based on specific antibodies, such as lateral flow immunochromatographic (LFI) assay for anthrax detection, have been developed. But the sensitivity and specificity of the rapid tests are not satisfying.⁸ Recently, Cox et al. described modified LFI combined with γ phage amplification that might increase the sensitivity and specificity of the assay.⁹

Forms of anthrax infection in human

Dependent upon the route of infection, 3 primary forms of human anthrax are recognized: cutaneous, pulmonary (inhalational) and gastrointestinal. Septicaemia and hemorrhagic meningitis may complicate all 3 forms. Cutaneous anthrax developed when anthrax spores get into the skin, usually through a scrape, cut, abrasion or insect bite. More than 90% of the lesions occur on exposed areas, such as the face, neck, arms or hands. Following the infection, the incubation period can range from 1 to 19 days but is usually 2–7 days. Lesion begins as a pruritic papule which enlarges and is surrounded by a ring of vesicles 2–4 days post infection. The vesicles may contain a hemorrhagic exudate. This area is also surrounded by a small ring of erythema and marked edema develops which can extend to some distance from the lesion. The lesion is usually 1–3 cm in diameter and remains round and regular. Rarely, a lesion may be larger and irregularly shaped. Unless a secondary infection occurs, there is no pus or local pain, although painful lymphadenitis may occur in the regional lymph nodes. Eventually, the vesicle or vesicular ring ruptures, discharging a clear fluid, and a central depressed black necrotic lesion, known as an eschar, is formed. The eschar begins to resolve about 10 days after the appearance of the initial papule. Resolution is slow (2–6 weeks), regardless of treatment.^{10–15} Cutaneous anthrax is the most common form of *B. anthracis* infection. The mortality rate of this form without medical treatment is estimated to be 20%. When appropriate treatment is applied, the mortality rate is reduced to 1%.¹ However, when the lesion is located on the face, neck or chest, clinical symptoms may be severe, toxic and fatal.^{1,2,10}

Inhalational anthrax occurs when a person inhales anthrax spores. This form is regarded as the most deadly form of anthrax. Only about 10–15% of patients with pulmonary anthrax survive without treatment. However, about 55% of patients survive with aggressive treatment.¹⁶ The incubation period of this form of the disease is generally considered to be 1–6 days. However, during the largest outbreak of inhalational anthrax in Sverdlovsk in 1979, a mean incubation period of approx. 10 days was reported with some cases taking up to 43 days.¹⁷ The initial symptoms are non-specific and with a clinical picture similar to that of a typical pneumonia from other causes and cardiovascular collapse with noninfectious causes. The symptoms begin with a mild fever, fatigue, malaise, myalgia, a non-productive

cough, and some chest or abdominal pain. The disease progresses rapidly, and within 2–3 days the second phase is characterized by high fever, toxemia, dyspnea, and cyanosis. Hypothermia and shock are the ultimate causes of death. In up to half of the patients, meningitis develops as a complication. In radiographic examination, mediastinal widening is a characteristic finding but is nonspecific for inhalation anthrax. Less specific findings include pleural effusions and parenchymal infiltrates.^{10,12–15}

Gastrointestinal form of anthrax is a result of consumption of contaminated food (usually meat) or drinking contaminated water. It can present clinically as either oropharyngeal or intestinal infection. Typically, the incubation period is 1–6 days. Oropharyngeal anthrax is characterized by sore throat, mucosal ulcerations, soft tissue edema, enlargement of cervical lymph nodes, and dysphagia. Intestinal anthrax is caused by infection of the bowel or stomach. The symptoms of intestinal anthrax are initially non-specific and include nausea, vomiting, anorexia, mild diarrhea, and fever. In some cases, the clinical picture may become more severe 24 h after the initiation of symptoms, and may include acute diarrhea, nausea, vomiting, and abdominal pain. With the progression of the illness, abdominal pain, hematemesis, bloody diarrhea, and massive ascites occur, and signs suggestive of acute abdomen appear. Toxemia, sepsis and shock then develop, followed by death.^{10,12–15} Without treatment, the mortality rate in this form is about 50%.¹⁵

All the above anthrax forms have been known to exist since ancient centuries and could be a result of natural infections as well as a bioterrorism related events. In the 21st century, a new form of anthrax appeared in humans – it has been called injectional anthrax.

Injectional anthrax syndrome

The term ‘injectional anthrax’ has been proposed by Ringertz et al., when the first case of heroin related anthrax was described.¹⁸ Injectional anthrax is presented by a severe soft tissue infection at the injection site, such as cellulitis, abscess or necrotizing fasciitis. The infection is very often complicated by septic shock and meningitis.^{18–20} Besides antibiotic treatment, a surgical debridement is often necessary in treating the infection.^{21,22} Despite medical treatment, the mortality rate of this form of anthrax is about 35%.^{19,23,24}

Important differences between injectional and cutaneous anthrax have included lack of black eschar formation typical for cutaneous form and an increased risk of shock along with a significantly higher mortality rate.^{16,20,24}

Injectional anthrax is transmitted by intravenous, subcutaneous or intramuscular injection of contaminated heroin. The incubation periods are estimated from a day (or less) to 10 days or more. But the incubation periods are only approximations because of the uncertainty about which dose of the drugs was contaminated. This was

estimated based on the timing of the last injection at an infected site. It must be kept in mind that the actual incubation periods might be longer by an unknown margin. The illness duration ranged from less than a day to over 28 days, and was calculated as the interval between the initial hospital admission and patients discharge home (or death). The longest duration of illness was related to necessity of expensive debridement of damaged tissue and its consequent reconstructive plastic surgery.²⁵

According to Interim Clinical Guidance for the Management of Suspected Anthrax in Drug Users, published by National Services Scotland and Health Protection Scotland, any drug user who presents with severe infection of soft tissue, signs of meningitis or severe sepsis (even without evidence of soft tissue infection), signs and symptoms of gastrointestinal or inhalational anthrax, should be considered as a possible case of anthrax.²⁶

Injectional anthrax cases in Europe

The first case of injectional anthrax was described in 2000 in Norway.¹⁹ The biggest outbreak of this new anthrax form started in December 2009 in Scotland. Between December 2009 and December 2010, a total of 119 cases were reported in Scotland, 5 cases in England and 2 cases in Germany. No further cases were documented until June 2012, when cases reemerged in Scotland, England, Germany, and were diagnosed for the first time in France, Wales and Denmark. Between June 2012 and April 2013, a total of 15 cases were recorded.^{23,25}

Non-injectional anthrax in heroin users

During the anthrax epidemic among heroin users in 2009–2013, cases of systemic anthrax were also noticed as a consequence of inhaling heroin. Snorting or smoking contaminated heroin would allow viable spores of *B. anthracis* to penetrate into the upper and lower respiratory tracts and into the gastrointestinal tract. Inhalation or ingestion of anthrax spores might result in systemic illness. Systemic anthrax had fulminant course and usually results in death.²⁵

Genetic relatedness of *B. anthracis* from heroin users

Genetic relatedness of *B. anthracis* from heroin users were investigated using high resolution genotypic methods: single nucleotide polymorphism (SNP) analysis and multilocus variable-number tandem repeat analysis (MLVA) for analysis of 22 and 31 markers, respectively. All strains isolated between 2000 and 2012 shared the same 22 SNPs.

Moreover, all the strains possessed the 2 highly distinctive „heroin-specific” SNPs, which differentiate the isolates from other investigated strains belonging to the same genetic group.^{19,27} MLVA typing of the isolates from heroine users revealed differences only in 2 markers: Bams30 and pXO2, which are highly mutable. No one of the isolates was different in both of the markers.¹⁹ Deviation in only 1 highly mutable marker are frequently observed among isolates originated from a defined endemic region.²⁸ In the putative evolutionary analysis such isolates are clustered into a single complexes. Such complexes of highly related genotypes can be regarded as the same outbreak strain based on the investigation of outbreak scenarios and analysis of epidemiological data.^{19,27} In the investigated outbreak, it was concluded that all the isolates from heroin users are of a single strain, originating from a single source of the infection. Moreover, this single source could be even a single infected animal.²⁵

However, recently published results of whole genome analysis of *B. anthracis* isolates associated with injectional anthrax revealed 2 tight genetic clusters: one group (G-I) was exclusively associated with the 2009–2010 outbreak and located primary in Scotland, whereas the other (G-II) comprised more recent (2012–2013) cases but also a single Norwegian case from 2000. The level of genome variation between these 2 groups is frequently seen within a single country and could be indicative of a close geographic relationship for the 2 sources of contamination. Whether each group represents a single contamination or multiple contaminations from a single source is hard to determine. But the 10-year lapse in G-II injectional anthrax cases suggests that there is a single contaminating source for the G-II cases but that there have been 2 or more contamination events.²⁹

Source of contamination

It is highly speculative how the heroin was contaminated. At least 3 possibilities are mentioned: via addition of cutting agent derived from an animal, such as bone meal, via wrapping in animal hide contaminated with anthrax spores, or via contamination with soil during drug manufacturing and trafficking.^{25,29,30} At the beginning of the anthrax epidemic in Europe, it was suspected that the heroin contaminated with anthrax spores came from Afghanistan, where it was contaminated at the primary source, for example during raw heroin production, as Afghanistan produces 90% of the world's heroin.²⁹ However, the isolates from heroin users were excluded by genotyping from the Vollum branches strains commonly found in Afghanistan and Pakistan.²⁵ It was also shown that the heroin was not contaminated in the final destination (Scotland/UK/Europe). The investigation conducted by Price et al. revealed that *B. anthracis* strain from infected heroin users in different European countries is closely related

to anthrax isolates previously found in infected animals (goats) in Turkey.²⁹ Turkey is located on the Balkan Route, which is commonly used for trafficking heroin from Afghanistan into European countries. It is believed that Turkish laboratories play a significant role in the conversion of the morphine base into usable form of heroin.²⁹ Moreover, it is known that for transport of illegal heroin, animal skins (particularly goat skins) are frequently used. Contamination with *B. anthracis* spores from goat skin is, therefore, one of the possible explanations for the origin of the anthrax spores in the heroin.^{25,30} Thus, it was hypothesized that Turkey is a point of origin of the heroin contamination. But it must be kept in mind that isolates from several countries located on the major routes for trafficking heroin were not included in the conducted investigation. There is also a second route for trafficking heroin, called the Silk Route, which passes through many anthrax endemic countries where isolates, belonging to the same genetic group as *B. anthracis* from heroin users, have been found.²⁹ Nevertheless, molecular analyses provided evidence that a similar source of heroin contamination, resulting in injectional anthrax in heroin users, could have been active at least since the year 2000.^{19,30}

Treatment

Initiation of appropriate treatment, particularly administration of a combination of antimicrobial drugs, as soon as possible, is critical to improving the survival of the patient. Treatment recommendations differ depending on the clinical form of anthrax.

Uncomplicated cutaneous anthrax should be treated with fluoroquinolones (ciprofloxacin, levofloxacin or moxifloxacin) or doxycycline orally. Clindamycin is an alternative option if fluoroquinolones and doxycycline are contraindicated or unavailable. Also, treatment with penicillin or amoxicillin is an option, but only if the isolate is known to be susceptible to penicillin. Moreover, adequate dosages must be used because of the potential for developing drug resistance during treatment with subtherapeutic dosing. Typically, if naturally acquired, cutaneous anthrax is treated for 7–10 days. However, if bioterrorism-related or an aerosol exposure is suspected, patients should be treated for 60 days. This is because the patients are likely to have also inhaled spores and a potential for reactivation of latent infection may exist. It must be kept in mind that cutaneous anthrax with extensive edema, lesions on the head or neck, or signs of systemic involvement require intravenous therapy, a multidrug approach is recommended.^{13,31,32}

In severe soft tissue infections in injectional form of anthrax, timely surgical debridement, to remove dead or devitalized tissue, is the most important treatment because it would enable the removal of the primary source of toxin production. When extravascular fluid collections

are present, drainage may also be important. Empiric antibiotic treatment should be started to cover *B. anthracis*, as well as other microbiological agents commonly causing soft tissue infection. This treatment includes clindamycin and ciprofloxacin intravenously in combination with other antibiotics, such as metronidazole, penicillin and flucloxacillin (i.e., a 5 drug combination).^{13,26}

It is worth underlining that surgery might be contraindicated or indicated, depending on the form of anthrax. For example, in cutaneous anthrax, surgery can lead to the dissemination and poor outcome. On the other hand, surgery may be indicated for gastrointestinal anthrax to identify and address potentially fatal complications, such as bowel ischemia, necrosis, and perforation.³²

Disseminated anthrax, such as inhalational anthrax with meningitis, should be treated with clindamycin and ciprofloxacin intravenously in combination with at least 1 other active drug with adequate central nervous system (CNS) penetration, e.g., penicillin, vancomycin, rifampicin, imipenem, meropenem, chloramphenicol or gentamycin.²⁵ Moxifloxacin and levofloxacin are considered equivalent alternatives to ciprofloxacin. Clindamycin is recommended because of its potential ability to inhibit exotoxin production. Another protein synthesis inhibitor is linezolid. If clindamycin or linezolid are unavailable, rifampin has been widely used. Although rifampin is not a protein synthesis inhibitor, it reveals synergistic effect with a primary drug. Chloramphenicol is also a protein synthesis inhibitor that penetrates CNS and has historically been used to treat anthrax successfully. If meningitis is suspected, doxycycline should not be used because it does not adequately penetrate the CNS. Center for Disease Control and Prevention (CDC) recommends that intravenous combination treatment for systemic anthrax with possible meningitis should be provided for 2–3 weeks or until the patient is clinically stable, whichever is longer.³² During the anthrax outbreak among injecting drug users in Scotland in 2009–2010, patients who have survived severe/systemic illness have been on appropriate antimicrobials for 3–4 weeks, initially intravenously (with 3 agents) and then orally with ciprofloxacin and clindamycin.²⁶

Because toxin-mediated morbidity is a major complication of anthrax systemic infections, for inhalational anthrax associated with respiratory compromise, extensive edema, and meningitis, corticosteroids have been suggested as adjunct therapy.³¹ Also, the role of anthrax antitoxin in treatment for systemic anthrax is worth mentioning. However, the therapy is still considered investigational. CDC recommends adding an antitoxin to the combination antimicrobial drug treatment for any patient for whom systemic anthrax is highly clinically suspicious. Whereas antimicrobials kill anthrax bacteria, the antitoxin neutralizes anthrax toxin circulating in the body, responsible for the severe illness. There are currently 2 antitoxins in the CDC Strategic National Stockpile: raxibacumab (Glaxo-SmithKline, London, UK) and Anthrax Immune Globulin

Intravenous (AIGIV) (Cangene Corporation, Winnipeg, Manitoba, Canada). Raxibacumab is approved by Food and Drug Administration (FDA) for postexposure prophylaxis and treatment for anthrax under the Animal Rule Summary. AIGIV is not FDA-approved and could be made available under an Investigational New Drug protocol or an Emergency Use Authorization during a declared emergency.³²

Conclusions

Unusual human behavior enabled the development of a new form of the disease known from the ancient times. Interestingly, cases of injectional anthrax occurred at time intervals in 2000, 2009–2010 and 2012–2013. Molecular investigation suggested a similar source of anthrax contamination of heroin in all cases. Nevertheless, the source was not identified and destroyed. For these reasons, a new case of injectional anthrax might occur in the future in any country. Heroin exposure routes which are risk factors of injectional anthrax include: injection intravenously, injection intramuscularly, injection subcutaneously, smoking, snorting. However, people with anthrax infection brought on by smoking or snoring contaminated heroin developed generalized symptoms and not the local symptoms typical for injectional anthrax. Moreover, some cases exposed to contaminated heroin by injection presented with little or no localized signs of infection but with generalized symptoms indicating toxemia and disseminated infection.²⁵ For these reasons, in any drug user who presents severe soft tissue infection or signs of systemic disease, anthrax infection should be considered.

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