Cutaneous Anthrax: A Concise Review

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GOAL

To gain a complete and detailed understanding of anthrax

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Explain the mechanisms of action of *Bacillus anthracis.*
2. Discuss the clinical manifestations of cutaneous anthrax.
3. Describe the treatment options for patients with cutaneous anthrax.

CME Test on page 34.

This article has been peer reviewed and approved by Michael Fisher, MD, Professor of Medicine, Albert Einstein College of Medicine. Review date: December 2001.

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With the growing threat of bioterrorism, it has become important for clinicians to recognize the clinical manifestations of diseases spread in this manner. The aim of this article is to provide readers with a complete and detailed understanding of anthrax, with a specific concentration on the cutaneous manifestations and a concentrated review of the treatment and current information known about Bacillus anthracis.

Traditionally, anthrax was transmitted via contaminated soil, animals, or animal products such as skins or meat. The traditional pattern, which still occurs today, is that wherever there are cases of animal-borne anthrax, there will be an accompanying flux of human cases. The occurrence of human-to-human spread of this disease is very rare.[1-4]

A more untraditional way that humans can be exposed to anthrax is through biological warfare tactics in which spores are delivered to a target through some form of dispersal apparatus. An example of the possible horror that anthrax can cause if used as a weapon was seen following the accidental release of aerosolized spores in Ekaterinburg, Russia. The subsequent epidemic resulted in at least 66 deaths from a terminal form of the disease.[5] More recently, the disease has been transmitted through tainted mail in several locations in the United States.

A microbe identified as *Bacillus anthracis* causes the disease anthrax. *B anthracis* is an aerobic or facultatively anaerobic, gram-positive bacterium measuring 4×1 μm. *B anthracis* exists in 2 very different states, the vegetative or growing state and the spore form. When faced with an environmental stress, such as unfavorable pH, temperature, O_2 content, or

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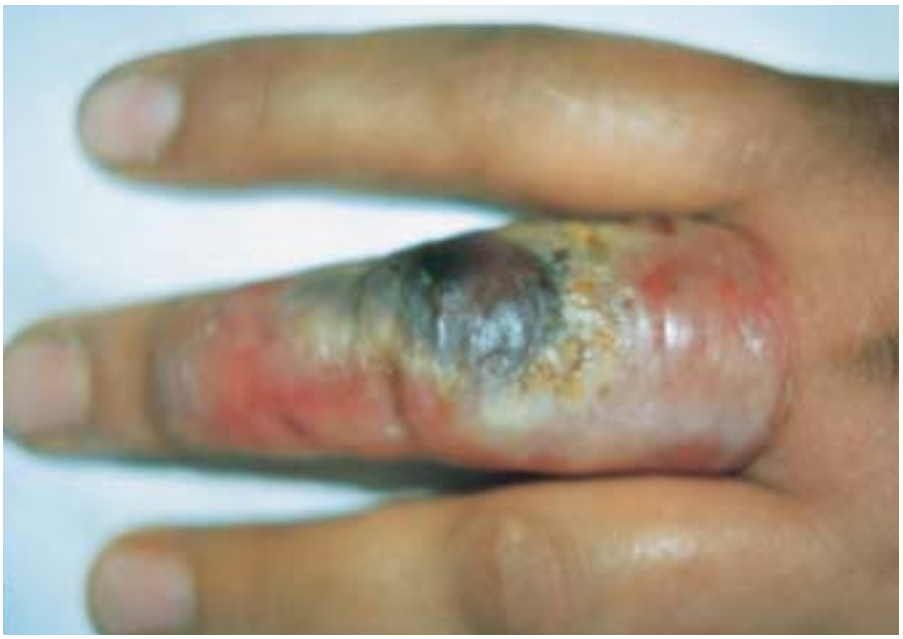

Figure 1. A necrotic lesion surrounded by hyperemia 3×8 cm in diameter with extensive edema on the dorsal face of the third finger of the left hand. (Photograph originally published in Çaksen H et al. *Cutis.* 2001;67:491.)

other factors, the vegetative cells will undergo sporulation.[6-8] These 2 states are very polarized. When *B anthracis* is in the vegetative state, it is one of the most fragile of all the *Bacillus* species. However, while it is in the spore state, *B anthracis* is very resistant to environmental extremes such as temperature, pH, irradiation, chemical substances like disinfectants and sporicides, and hosts of other stresses. In the spore form, *B anthracis* can remain viable in nature for up to 60 years.[6-9]

Pathogenesis of Disease

The virulence of this microbe resides in its poly-D-glutamic acid capsule and the 3 exogenous toxins that *B anthracis* produces: protective antigen (PA), lethal factor (LF), and edema factor (EF). The acid capsule allows the bacterium to escape phagocytosis by the host's immune cells. The exogenous toxins that the *Bacillus* produces work in concert with each other to cause the damaging effects of this disease.

The PA binds to the host's target cell first. Subsequently, a protease on the cell's surface cleaves off part of the PA, which results in the exposure of its factor binding site. When this occurs, the LF and EF are able to compete for the binding site. After formation of either an LF-PA or EF-PA complex, the PA-factor complex is endocytosed into the cell. However, it is not until the PA-factor complex is released from the endosome into the cell's cytosol that the toxin complex starts to unleash havoc and destruction on the host cell.[4,10]

EF causes edema through its enzymatic ability to form cyclic adenosine monophosphate (cAMP) in affected cells. Although the resultant cellular edema from this mechanism is not deleterious to the cells, it has been shown to be disruptive enough to cause an overall cytostatic effect. Further research has shown that this factor will disrupt proper functioning of neutrophils, further crippling the victim's immune response to the disease.[4,10] LF is deleterious to any cell that endocytoses one of these complexes. This factor is a specific endopeptidase that has the ability to cleave the amino terminus of multiple mitogen–activated protein kinase kinases. The resultant destruction of these enzymes leads to cell death.[11,12] In murine models, when the factor complex is endocytosed by macrophages, it results in a mass production of interleukin 1 and tumor necrosis factor from the dying cells. It is believed that this is the probable mechanism that leads to the ability of this disease to cause toxic shock in extreme cases.[10]

Vascular endothelial cells are another type of cell that is susceptible to this toxin. Again, susceptibility to the entrance of the toxin complex is synonymous with cell lysis. This leads to a breakdown of all vascular and lymphatic vessels affected. Subsequently, the breakdown leads to hemorrhage, which may be terminal if the vascular damage is substantial enough. In addition, the breakdown of the retaining capability of the reticuloendothelial system's vessels and organs leads to a loss of this system's ability to quarantine the *Bacillus*. This collapse leads to systemic sepsis.[4,10] However, and perhaps more importantly, it is not the presence of the organism in the victim that causes the

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Figure 2. Necrotic lesions surrounded by hyperemia 0.5×0.5 cm and 1.5×1.5 cm in diameters on the dorsal surfaces of the second and third fingers of the right hand, respectively. (Photograph originally published in Çaksen H et al. *Cutis.* 2001;67:491.)

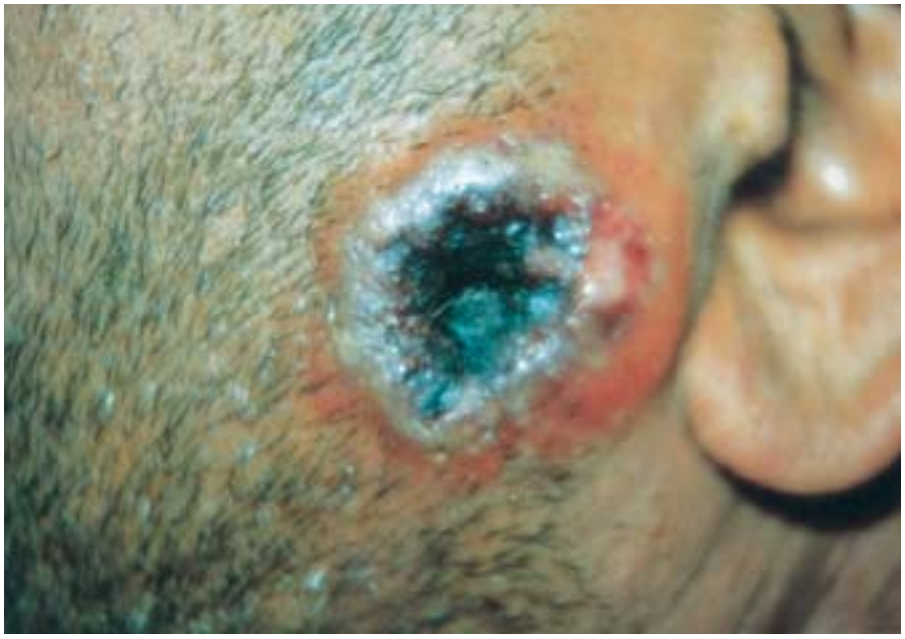

Figure 3. A black necrotic central eschar surrounded by vesicles 2×2 cm in diameter on the anterior region of the left auricle. (Photograph originally published in Çaksen H et al. *Cutis.* 2001;67:491.)

morbidity and mortality of this disease. The factors that are released by the organism cause the suffering and death from anthrax.[13]

Epidemiology

The latest epidemiological information from the World Health Organization states that although there has been a decrease in worldwide cases of this disease, there are still many regions were the disease still exists, including countries in sub-Sahelian Africa and Asia, many southern European countries, and certain areas of Australia. In the western hemisphere, anthrax is found in naturally occurring pockets in North America, specifically parts of Canada, South Dakota, Oklahoma, Nebraska, and Texas. In Central America, anthrax occurs at constant levels in Mexico and Guatemala with inconclusive reports coming from the rest of the countries in the region. The disease also is found in Haiti, Peru, Bolivia, and Venezuela.[14,15] Finally, constant resilient levels of the disease in Afghanistan, Iran, Turkey, western Africa, and western Asia caused them to be classified as areas of endemic anthrax.[16]

Table 1.

Treatment for Cutaneous Anthrax Patients Without Systemic Symptoms and Not Located on the Head or Neck and Not With Extensive Edema[26] and Not in Children Younger Than 2 Years[27]

Category	Initial Oral Therapy	Duration
Adults*	Ciprofloxacin 500 mg twice/d *or* Doxycycline 100 mg twice/d	60 d†
Children*	Ciprofloxacin 15 mg/kg every 12 hours (not to exceed 1g/d)‡ *or* Doxycycline§: >8 years and >45 kg: 100 mg every 12 h All other children: 2.2 mg/kg every 12 h	60 d†
Pregnant women*‖	Ciprofloxacin 500 mg twice/d (preferred) *or* Doxycycline 100 mg twice/d (Current recommendations favor ciprofloxacin over doxycycline in pregnant women when susceptibilities are unknown.)	60 d†
Immunocompromised persons*	Same as for immunocompetent persons and children	60 d†

*Cutaneous anthrax with signs of systemic involvement, extensive edema, or lesions on the head or neck require intravenous therapy, and a multidrug approach is recommended (see Table 2).

†Previous guidelines have suggested treating cutaneous anthrax for 7 to 14 days, but 60 days is recommended in the setting of this attack, given the likelihood of simultaneous exposure to aerosolized *Bacillus anthracis*.

‡Ciprofloxacin or doxycycline should be considered first-line therapy. Amoxicillin 500 mg orally 3 times a day for adults or 80 mg/kg per day divided every 8 hours for children is an option for completion of therapy after clinical improvement. Oral amoxicillin dose is based on the need to achieve appropriate minimum inhibitory concentration levels.

§The American Academy of Pediatrics recommends treatment of young children with tetracyclines for serious infections (eg, Rocky Mountain spotted fever).

‖Although tetracyclines or ciprofloxacin are not recommended during pregnancy, their use may be indicated for life-threatening illness. Adverse effects on developing teeth and bones are dose-related; therefore, doxycycline might be used for a short time (7–14 days) before 6 months of gestation.

Table adapted with permission from the American Academy of Dermatology Cutaneous Anthrax Management Algorithm. Available at: http://www.aad.org/BioInfo/Biomessage2.html. Accessed: November 19, 2001.

Clinical Manifestations

There are 3 main manifestations of anthrax. These are cutaneous, gastrointestinal, and inhalation forms. Ninety-five percent of all worldwide cases of anthrax are caused by the cutaneous form.[15,17,18] Approximately 80% of cutaneous cases will resolve spontaneously within a few weeks from onset of disease without any complication[19]; however, 10% to 20% of cutaneous cases will progress to fatality without treatment.[20-22] Of those who seek treatment, less than 1% of cutaneous infections are fatal.[20-23]

Epidemiologic data from the World Health Organization suggests that in the natural setting, there is a 10% chance of contracting cutaneous anthrax from a single contaminated carcass.[15] In the case of cutaneous anthrax, the spores must find a break in the skin to enter or they cannot infect the

Table 2.

Treatment of Cutaneous Anthrax Patients With Systemic Symptoms or Extensive Edema or Involving the Head or Neck or Children Younger Than 2 Years (Same as for Inhalation Anthrax Exposure)*[26]

Category	Intravenous Therapy†‡	Duration
Adults	Ciprofloxacin 400 mg every 12 h *or* Doxycycline 100 mg every 12 h *and* 1 or 2 additional antimicrobials‡	IV treatment initially.§ Switch to oral antimicrobial therapy when clinically appropriate (see Table 1 for oral therapy). Continue for 60 d (IV and po combined)‖
Children	Ciprofloxacin 10 mg/kg every 12 h (not to exceed 1 g/d)¶ *or* Doxycycline#: >8 years and >45 kg: 100 mg every 12 h All other children: 2.2 mg/kg every 12 h *and* 1 or 2 additional antimicrobials‡	IV treatment initially.§ Switch to oral antimicrobial therapy when clinically appropriate (see Table 1 for oral therapy). Continue for 60 d (IV and po combined)‖
Pregnant women**	Same as for nonpregnant adults (the high death rate from the infection outweighs the risk posed by the antimicrobial agent).Current recommendations favor ciprofloxacin over doxycycline in pregnant women when susceptibilities are unknown.	IV treatment initially.§ Switch to oral antimicrobial therapy when clinically appropriate (see Table 1 for oral therapy). Continue for 60 d (IV and po combined)‖
Immuno-compromised persons	Same as for immunocompetent persons and children	Same as for immunocompetent persons and children

*IV indicates intravenously; po, periorally.

†Steroids may be considered as an adjunct therapy for patients with severe edema and for meningitis based on experience with bacterial meningitis of other etiologies.

‡Other agents with in vitro activity include rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, and clarithromycin. Because of concerns of constitutive and inducible β-lactamases in *Bacillus anthracis*, penicillin and ampicillin should not be used alone. Consultation with an infectious disease specialist is advised.

§Initial therapy may be altered based on the clinical course of the patient; 1 or 2 antimicrobial agents (eg, ciprofloxacin or doxycycline) may be adequate as the patient improves.

‖Because of the potential persistence of spores after an aerosol exposure, antimicrobial therapy should be continued for 60 days.

¶If intravenous ciprofloxacin is not available, oral ciprofloxacin may be acceptable because it is rapidly and well absorbed from the gastrointestinal tract with no substantial loss by first-pass metabolism. Maximum serum concentrations are attained 1 to 2 hours after oral dosing but may not be achieved if vomiting or ileus are present.

#The American Academy of Pediatrics recommends treatment of young children with tetracyclines for serious infections (eg, Rocky Mountain spotted fever).

**Although tetracyclines or ciprofloxacin are not recommended during pregnancy, their use may be indicated for life-threatening illness. Adverse effects on developing teeth and bones are dose related; therefore, doxycycline might be used for a short time (7–14 days) before 6 months of gestation.

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person. Hence the first-line of defense against this form of the disease is wearing appropriate barriers to cover areas at risk of coming in contact with the spores (ie, using gloves to cover hands, properly dressing and sealing wounds, using standardized proper hygienic practices). Barrier and hygiene protection are vastly important because, unlike the 8000 to 10,000 inhaled spores that are believed to be required to cause inhalation anthrax, it takes very few spores to cause the cutaneous manifestation of this disease.[5]

After a person becomes infected with cutaneous anthrax, the disease will generally incubate from 2 to 7 days before the initial manifestation of the illness occurs. The overall documented range for presentation of the disease can be anywhere from 9 hours to 8 weeks after infection.[15] After the disease process is initiated, cutaneous anthrax follows a somewhat general trend.

The initial cutaneous manifestation is usually a small erythematous painless macule. This macule then evolves into a papule approximately 48 to 72 hours later. Within the following 24 to 48 hours, multiple vesicles and edema surround the lesion. These vesicles may weep, and, if the patient has not received treatment, anthrax bacilli can be cultured from the fluid. Further, even if the patient has not received treatment at this point, there should be no pain or purulence associated with this lesion unless there is a super-infection occurring.[15,21] Depending on the location and severity of the disease, the edema may be extensive. The patient is especially at risk of extensive and sometimes life-threatening edema if the lesion is located on the chest, neck, or face.[21] The patient may have painful lymphadenitis in the region's draining lymph nodes. Subsequently, 1 to 3 days after the vesicles appear, the papule will rupture and ulcerate. This leaves the characteristic brown or black eschar classically measuring 1 to 5 cm in diameter (Figures 1, 2, and 3). It is at this point that the symptomatology of a more severe infection of *B anthracis* may present itself, in the form of a high fever, toxemia, mass edema, and more severe regional lymphadenitis. If steps are not taken in these cases, shock and death have a great likelihood of occurring.[15] A few days after the eschar is formed, the lesion will begin the long process of healing, which may take up to 6 weeks. Finally, although proper treatment will reduce the chance of fatality and limit the size of the anthrax lesion, therapy will have very little bearing on the time to healing.[23]

Therapy

B anthracis is easily subdued by many antibiotics. In most of the world, the gold standard of treatment for anthrax is penicillin because of its low cost and vast availability. Globally, other antimicrobials that can be used if the patient is unable to take penicillin are aminoglycosides such as gentamicin, macrolides such as erythromycin, quinolones such as ciprofloxacin, and tetracyclines such as doxycycline and even chloramphenicol. Tests in animals have indicated that doxycycline is very effective for treatment and that the quinolone ciprofloxacin also may be suitable for prophylaxis and treatment.[24] Further, studies showed in vitro susceptibility of 22 separate strains of *B anthracis* to 27 antimicrobial agents.[25] Specific therapeutic regimes for penicillin, doxycycline, and ciprofloxacin are reviewed in Tables 1 and 2.

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