ANTHRAX – NEGLIGIBLE OR DREADFUL? - A REVIEW.

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Summary

In the present review we have discussed the epidemiology of the diseases from 1500 AD various bacteriologists and microbiologists worked together the effective vaccines. Though anthrax is bacterial highly pathogenic is not mutagenic. The structure of bacilli spores of anthrax can be taken consideration for the drugs development. Hence the anthrax may be controllable but with negligence it would be dreadful disease with high mortality rate globally.

Keywords: Wool sorter's disease; Rag picker's disease; cutaneous anthrax; Inhalation anthrax; gastrointestinal anthrax.

Introduction

Anthrax is an acute disease caused by *Bacillus anthracis*. It affects both humans and animals and most forms of the disease are highly lethal. There are effective vaccines against anthrax and some forms of the disease respond well to antibiotic treatment. Like many other members of the genus *Bacillus*, *Bacillus anthracis* can form dormant spores that are able to survive in harsh conditions for extremely long periods of time even decades or centuries. Such spores can be found on all continents, even Antarctica. When spores are inhaled, ingested or come into contact with a skin lesion on a host they may reactivate and multiply rapidly.Anthrax commonly infects wild and domesticated herbivorous mammals which ingest or inhale the spores while browsing. In fact ingestion is thought to be the most common route by which herbivores contract anthrax. Carnivores living in the same environment may become infected by consuming infected animals. Diseased animals can spread anthrax to humans either by direct contact (e.g. inoculation of infected blood to broken skin) or consumption of diseased animals flesh. Anthrax spores can be produced in vitro and used as a biological weapon. Anthrax does not spread directly from one infected animal or person to another but spores can be transported by clothing or shoes and the body of an animal that died of anthrax can also be a source of anthrax spores.[1]

History [2, 3]

Table No 1: History of anthrax occurrence.

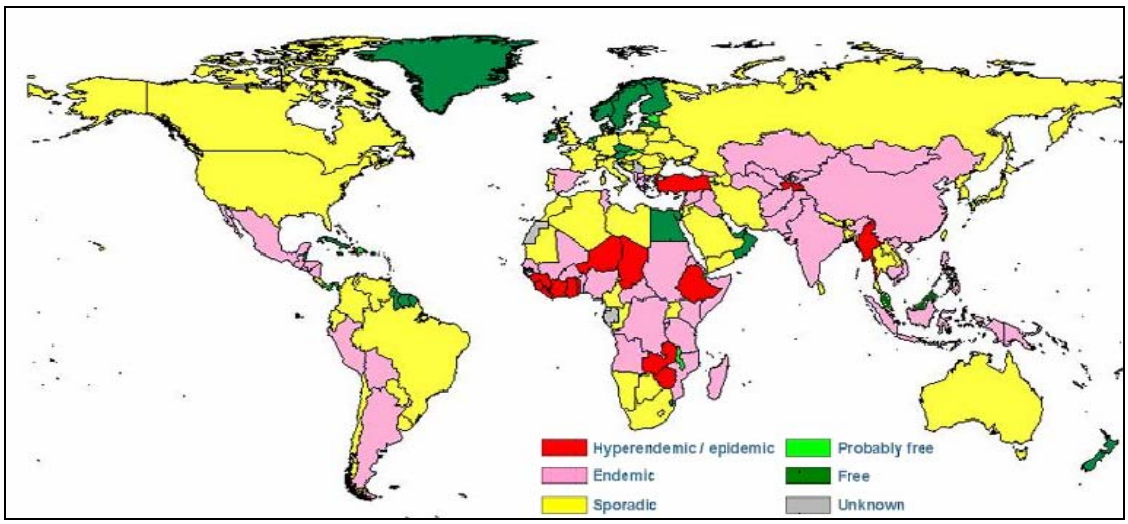
1500 A.D	A "plague of boils" in Egypt affected the Pharaoh's cattle. 'Boils' are symptomatic of anthrax
1600	The "Black Bane" thought to be anthrax, in Europe kills over 60,000 cattle.
1700	There are some accounts of human cases
Early 1800	The first human cases of cutaneous anthrax in the US and UK were reported in men who contracted the disease after having been in contact with infected livestock.
1868	The disease was called Wool Sorter's disease or Rag Picker's disease because it affected workers in those trades. Anthrax was observed under a microscope.
1876	German bacteriologist Robert Koch confirmed bacterial origin of anthrax.
1915	German agents injected horses, mules and cattle with anthrax during WWI. This was the first recorded use of anthrax as a biological weapon.
1937	Japan started a biological warfare program in Manchuria, including tests involving anthrax.
1942	UK demonstrated experiments using anthrax at Gruinard Island off the coast of Scotland
1943	United States began developing anthrax weapons.
1945	In Iran an anthrax outbreak killed more than 1 million sheep.
1950s and 60s	U.S. biological warfare program continues after WWII at Fort Detrick, Maryland
1969	President Nixon ended United States' offensive biological weapons program, but defensive work still continues.
1970	Anthrax vaccine for humans was approved by U.S. FDA.
1978-80	The world's largest outbreak of human anthrax via insect vectors or contaminated meat struck Zimbabwe, Africa where more than 10,000 cases were recorded and over 180 people died
1979	In Soviet Union, aerosolized anthrax spores were released accidentally at a military facility, affecting 94 and killing 64 people.
1991	About 150,000 U.S. troops were vaccinated for anthrax in preparation for Gulf War.
1990-93	The cult group, Aum Shinrikyo, released anthrax spores in Tokyo, fortunately no one was injured. On February 27, 2004, the leader of this group was given a sentence of death at a district court in Tokyo.
1995	Iraq produced 8,500 liters of concentrated anthrax as part of the biological weapon program under Saddam Hussein's administration.
2001	Letters containing anthrax spores were mailed too many places in the US such as NBC, New York Times, and Media in Miami. In Florida, a man died after inhaling anthrax at the office.

Epidemiology

Anthrax is primarily disease of herbivores, especially sheep, goats, cattle and horses. It infects man rarely. The agent is found in soil and on vegetation upon which grazing animals become infected through injured mucous membrane, when spores are found on spiny or irritating vegetation. Spores are released in great numbers when the animal dies and decomposes, contaminating both the carcass and soil. The spores enter the soil where they are viable for decades. "Incubator areas" have alkaline or neutral calcareous soils in which the bacterium can multiply under favorable conditions. Outbreaks occur primarily in warmer seasons. Biting flies may transmit during epidemic but are thought to be of little importance. Humans are accidentally exposed via contaminated animals or animal products, a particular hazard for veterinarians and farmers. Products (often imported) made from infected animals have caused recent human infections in the U.S. including such diverse products as bone meal, shaving brush bristles, hair or wool in textiles (especially alpaca wool, goat's and even camel's hair), hides and leather goods, goatskin drums. Handicrafters and hobbyists working with leather, hairs and wools at risk if materials from endemic areas. Oil cake and tank age made from contaminated materials can transmit anthrax. There is considerable variation among species in susceptibility: Guinea Pig is highly susceptible and rats resistant. [4, 5]

Geographical Distribution

Figure No 1: 20,000-100,000 cases estimated globally/year



Anthrax has been endemic in southern Europe, parts of Africa, Australia, Asia and North and South America. It persists in arid deserts of Middle East, Asia, Africa, Australia and South America with the most cases reported from Iran, Turkey, Pakistan and Sudan. It is relatively rare in the US, but last year, 500+ cases in Texas were recorded in White Tailed Deer. It has occurred in livestock in South Dakota, Nebraska, Arkansas, Mississippi, Louisiana, and California as well.[6, 7]

Statistics Of Anthrax Occurrences [7]

Globally

- Approximately 2,000 - 20,000 cases of anthrax occur each year.
- Most cases are cutaneous with inhalation and gastrointestinal being less frequent.

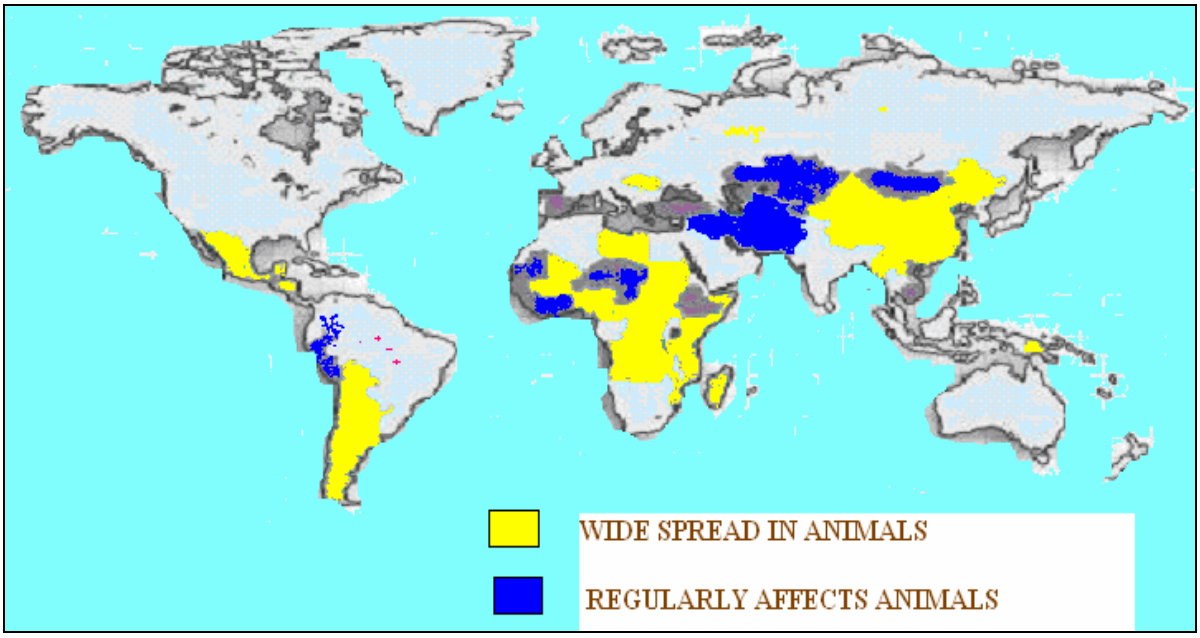
Human cases usually follow disease occurrences in ruminants and are most prevalent in Africa, the Middle East, and parts of Southeast Asia

Situation in India

Anthrax is enzootic in southern and eastern India but is less frequent in the northern Indian states. In the past years the anthrax cases have been reported from Andhra Pradesh, Jammu and Kashmir, Tamil Nadu, Orissa, Karnataka and West Bengal. Outbreaks of Anthrax have been reported from Karnataka (1999 and 2001), Orissa (2003 and 2005), and West Bengal (2000).

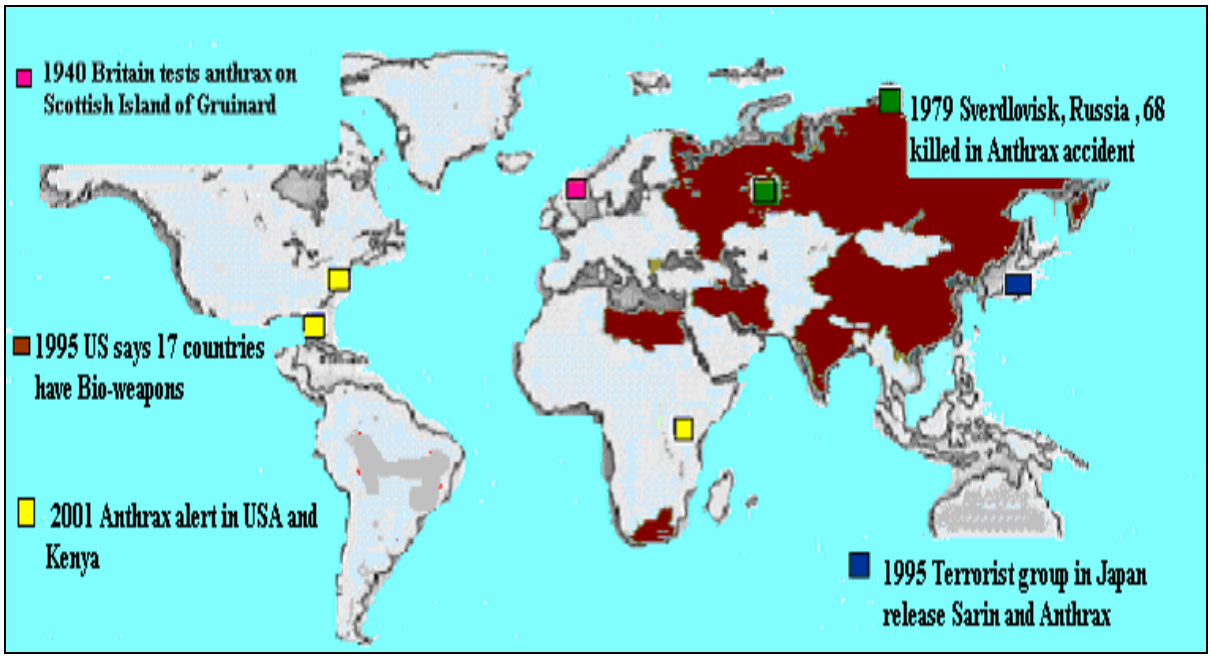
Naturally Occurring Anthrax Cases [7]

Figure No 2: Naturally Occurring Anthrax Cases



Biologic Warfare [7]

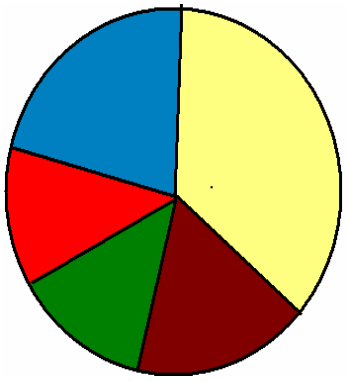
Figure No 3: Biological Weapons and Anthrax



Anthrax Attack In America [8]

Table No 2: Anthrax Attack In America

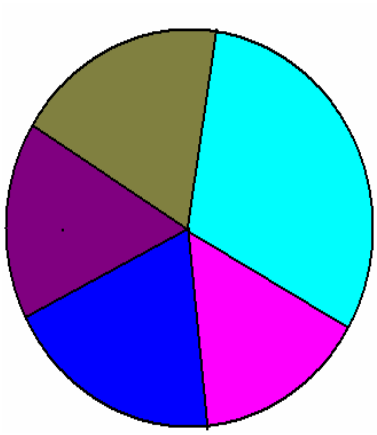
	Two cases of cutaneous anthrax
	Letter containing anthrax sent to Senator Tom Daschie.
	Letters To Daschie and NBC posted here.
	Journalist dies from respiratory anthrax and colleague contracts disease.
	Microsoft office receives letter from Malaysia containing anthrax.



Anthrax Cases In America [9]

Table No 3: Anthrax cases In America

	2 postal workers die from inhalation anthrax, 3 other were hospitalized.
	A hospital worker dies from inhalation anthrax. Four people were treated for the skin form of the disease.
	A postal worker is hospitalized for inhalation anthrax, 3 other people treated for skin anthrax.
	A journalist dies of inhalation anthrax; a colleague also contracts the disease but recovers.
	A 94- old woman from a rural community becomes the fifth person to die of inhalation anthrax.



Countries Storing Anthrax [10]

Table No 4: Countries Storing Anthrax

Countries	No. of Stores	Countries	No. of Stores
1.Canada	01	9.India	02
2. Mexico	03	10. China	02
3. Cuba	01	11.Thailand	03
4.Venezula	01	12.Singapore	01
5. Brazil	06	13. Japan	03
6. Argentina	03	14.New Zealand	01
7. Australia	05	15. UK	02
8. Iran	01		

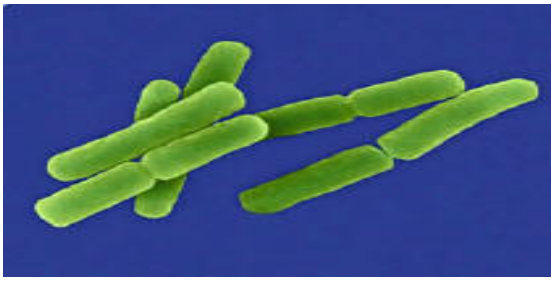
Causative agent

The causative organism *B.anthracis* is a gram-positive, non motile, non-haemolytic and spore-forming bacillus. The virulence of the organism is determined by the capsule and exotoxins; oedema toxin and lethal toxin. Anthrax is considered an important biological warfare agent because (i) it is highly fatal and when transmitted through inhalation is almost always fatal, (ii) Anthrax spores can remain viable for several decades and can be easily produced in large quantities at a very low cost, and (iii) it is easy to weaponize and disseminate anthrax as an odourless and invisible aerosol which can affect thousands of people at the same time. [11]

Pathology

In infected tissues, bacterial capsules remain intact, and the organisms become surrounded by large amount of proteinaceous fluid due to the toxins released. There are however few leukocytes in non-immune animals. The bacteria rapidly disseminate, and lymph nodes are a common site of bacterial growth, leading to enlarged, hemorrhagic nodes. The highly fatal inhalation form of the disease is due to such infested nodes in the space between the lungs, an area called the mediastinum. This hemorrhagic mediastinitis is commonly known as "wool sorters disease." From these infected nodes, the bacilli can easily reach blood. In resistant animals, massive accumulation of leukocytes keep infection localized. Chains of large Gm positive rods are easily distinguished by microscopic examination of a Gram stained smear of lesion pus.[12]

Figure No 4: *Bacillus anthracis*



Life Cycle

Bacillus anthracis is the bacteria that causes anthrax, an often fatal infection of the skin, respiratory system (inhalation anthrax), or gastrointestinal system. The disease affects almost any animal, but those most susceptible are large herbivores. Humans are affected through their interactions with these herbivores products derived from their corpses; inhalation anthrax is sometimes referred to as wool sorter's disease due to the prevalence of the infection among those who handle wool. While theoretically possible, there have been no cases of human to human anthrax transmission in the literature.[13]

Cutaneous anthrax is characterized by painless, black-ended necroses at the site of infection, along with edema of the surrounding tissues. It is the most common form of anthrax infection, accounting for 95% of reported cases in the United States. It is generally not a life threatening condition. [14]

Genome Structure [9]

1. Chromosome: 5.2 million bp, Ames strain sequenced.

2. Plasmids: px01 (184 kbp, Pathogenicity island): pX02 (95.3 kbp, Capsule)

Anthrax receptor: Occurs > than ten thousendfold on macrophage cell. ATR/TEM8 gene (Chromosome 4)

Figure No 5: Life cycle of Anthrax

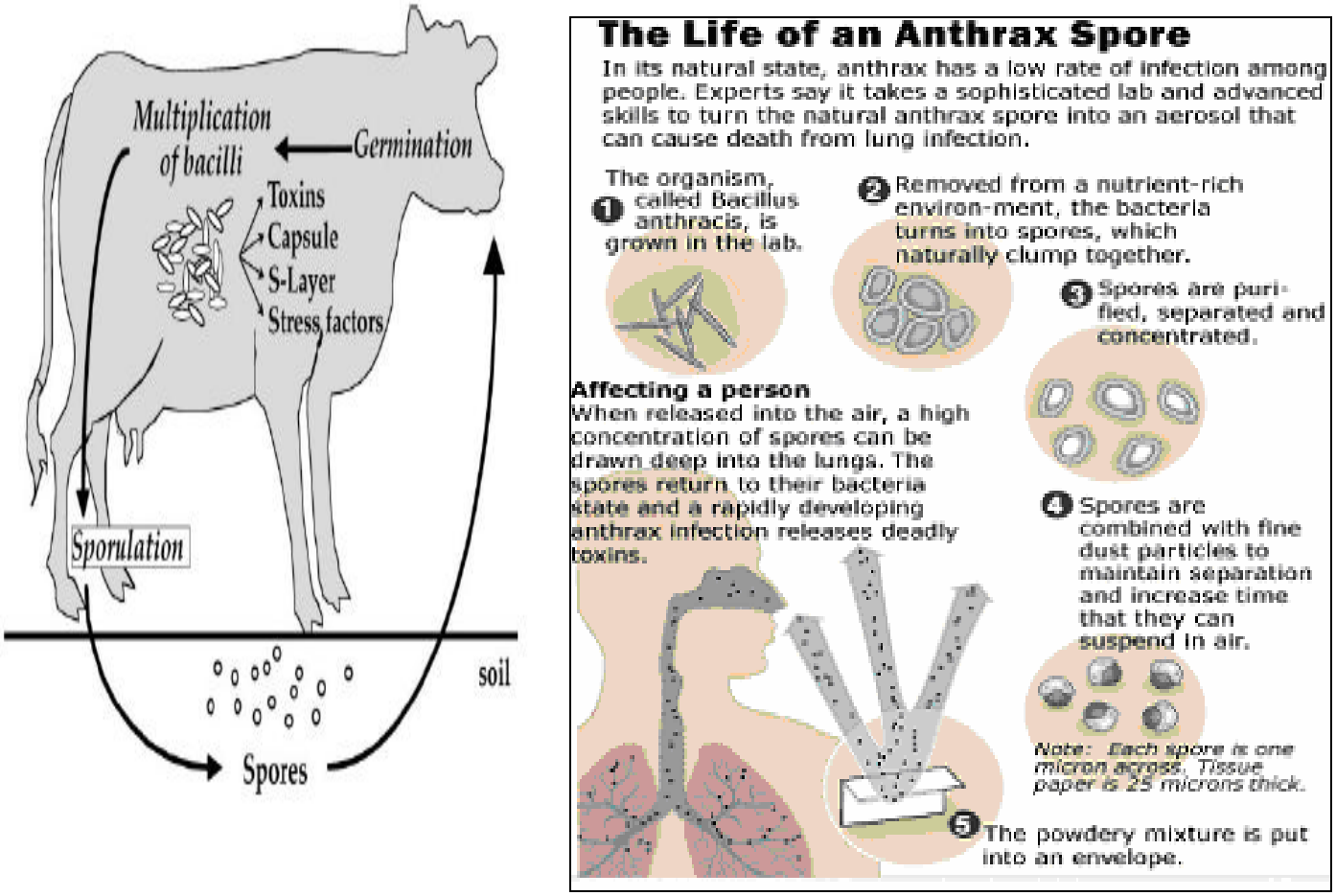
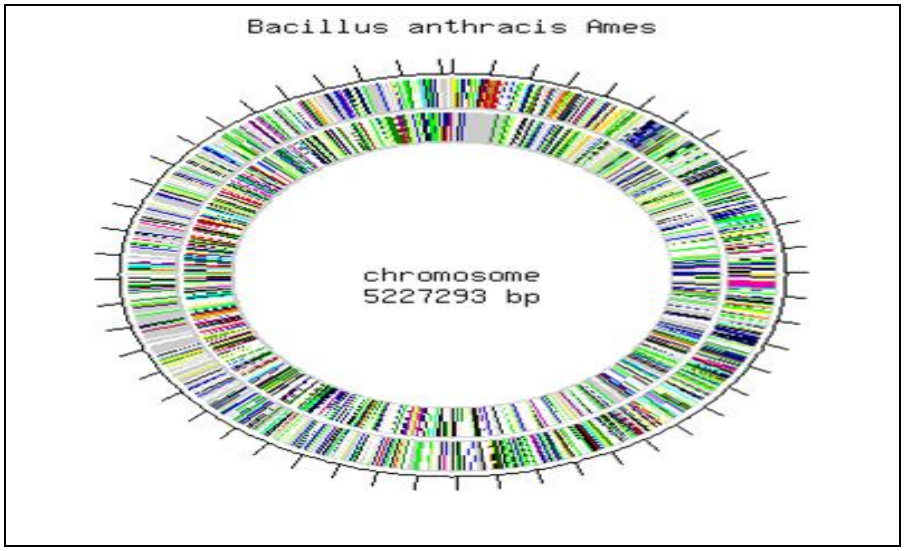


Figure No 6: Genome Structure



Exposure

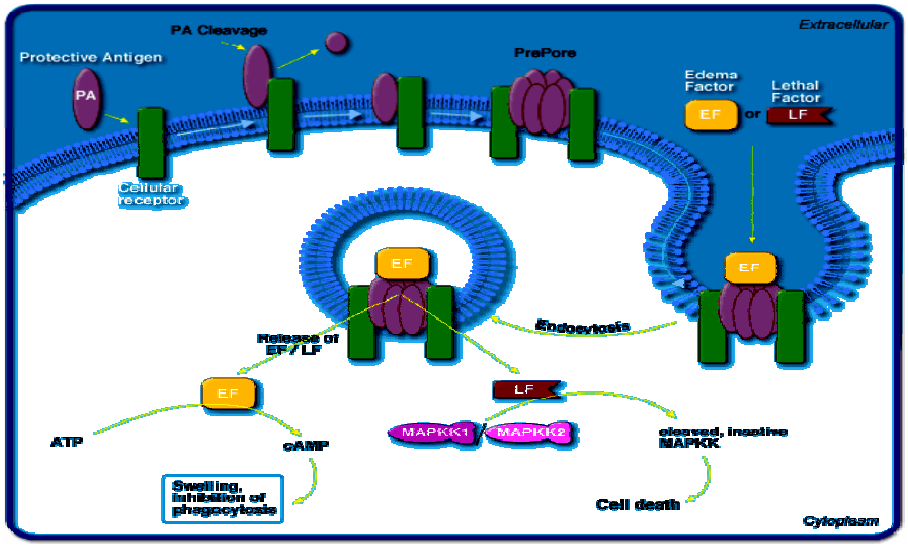
Occupational exposure to infected animals or their products (such as skin wool and meat) is the usual pathway of exposure for humans. Workers who are exposed to dead animals and animal products are at the highest risk, especially in countries where anthrax is more common. Anthrax in livestock grazing on open range where they mix with wild animals still occasionally occurs in the United States and elsewhere. Many workers who deal with wool and animal hides are routinely exposed to low levels of anthrax spores but most exposures are not sufficient to develop anthrax infections. Presumably, the body's natural defenses can destroy low levels of exposure. These people usually contract cutaneous anthrax if they catch anything. Historically, the most dangerous form of inhalational anthrax was called Woolsorters' disease because it was an occupational hazard for people who sorted wool. Today this form of infection is extremely rare, as almost no infected animals remain. The last fatal case of natural inhalational anthrax in the United States occurred in California in 1976, when a home weaver died after working with infected wool imported from Pakistan. The autopsy was done at UCLA hospital. To minimize the chance of spreading the disease, the disease was transported to UCLA in a sealed plastic body bag within a sealed metal container.[15]

Infection

Humans are moderately resistant to the disease, with 20,000 to 100,000 cases per year worldwide. Infection acquired via one of three routes, through the skin, by inhalation or by ingestion. Cutaneous infections constitute 95% of infections, and are acquired through minor abrasion, injured skin or at pressure point of contaminated hide against skin. Rarely, it is contracted by inhalation of spores, causing "Wool sorter's disease," (often through the processing contaminated goat hair). According the to Merck Manual, "Inhaling spores under adverse conditions (e.g. the presence of an acute respiratory infection) may result in pulmonary anthrax which is often fatal." Infections due to ingestion are rare in humans. It is not communicable from person to person. The incubation period is generally 3-5 days. Spores germinate in tissue at site of entry, lead to gelatinous edema. The pathogens spread by the lymphatics to blood stream shortly before (and after) death. It can be spread among animals via biting flies, insects and vultures, but this mode of transmission is thought to be rare.[16, 17]

Mechanism of Infection [18]

Figure No 7: Mechanism of Infection

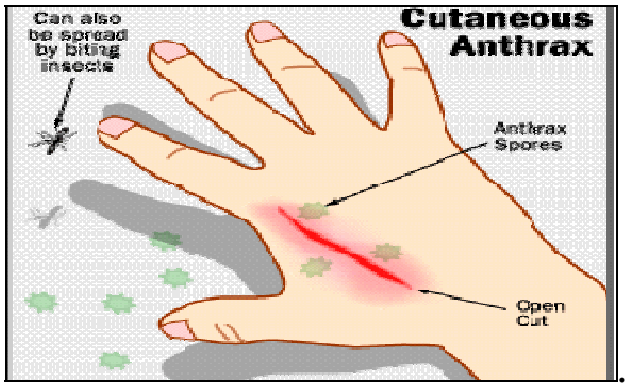


Mode Of Infection

1. Cutaneous

Cutaneous (on the skin) anthrax infection in humans shows up as a boil-like skin lesion that eventually forms an ulcer with a black center (eschar). The black eschar often shows up as a large, painless necrotic ulcer (beginning as an irritating and itchy skin lesion or blister that is dark and usually concentrated as a black dot, somewhat resembling bread mold) at the site of infection. Cutaneous infections generally form within the site of spore penetration between 2 and 5 days after exposure. Unlike bruises or most other lesions, cutaneous anthrax infections normally do not cause pain. Cutaneous anthrax is rarely fatal if treated, but without treatment about 20% of cutaneous skin infection cases progress to toxemia and death. [19]

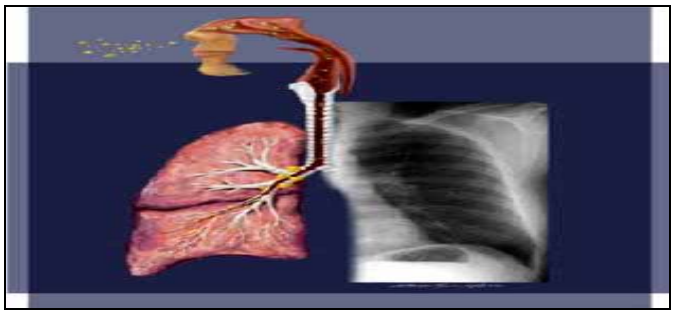
FigureNo 8: Cutaneous infections



2. Inhalation

Respiratory infection in humans initially presents with cold or flu-like symptoms for several days, followed by severe (and often fatal) respiratory collapse. Historical mortality was 92%, but when treated early (seen in the 2001 anthrax attacks) observed mortality was 45%. Illness progressing to the fulminant phase has a 97% mortality regardless of treatment.A lethal infection is reported to result from inhalation of about 10,000–20,000 spores, though this dose varies amongst host species. Like all diseases there is probably a wide variation to susceptibility with evidence that some people may die from much lower exposures; there is little documented evidence to verify the exact or average number of spores needed for infection. Inhalational anthrax is also known as woolsorters' or ragpickers' disease as these professions were more susceptible to the disease due to their exposure to infected animal products. Other practices associated with exposure include the slicing up of animal horns for the manufacture of buttons, the handling of hair bristles used for the manufacturing of brushes, and the handling of animal skins. Whether these animal skins came from animals that died of the disease or from animals that had simply laid on ground that had spores on it is unknown. This mode of infection is used as a bioweapon.[19]

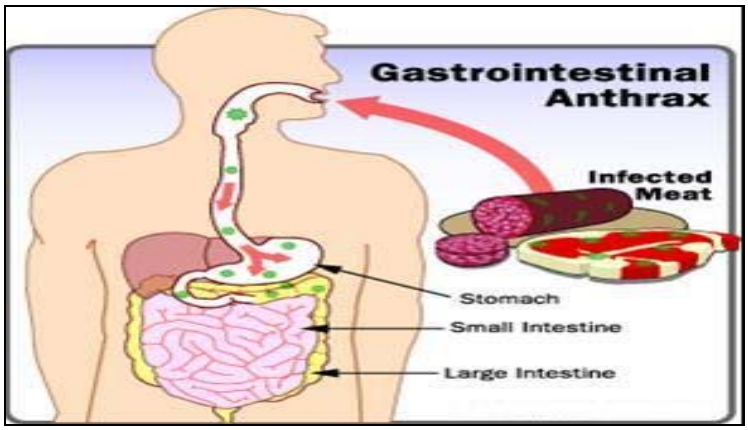
Figure No 9 : Inhalation infection



3. Gastrointestinal Anthrax

Gastrointestinal infection in humans is most often caused by eating anthrax-infected meat and is characterized by serious gastrointestinal difficulty, vomiting of blood, severe diarrhea, acute inflammation of the intestinal tract, and loss of appetite. Some lesions have been found in the intestines and in the mouth and throat. After the bacteria invade the bowel system, it spreads through the bloodstream throughout the body, making even more toxins on the way. Gastrointestinal infections can be treated but usually result in fatality rates of 25% to 60%, depending upon how soon treatment commences.[20]

Figure No. 10: Gastrointestinal infection.



Transmission

Anthrax does typically not spread from animal to animal or from person to person. The bacteria produce spores on contact with oxygen. These spores are extremely resistant and survive for years in soil, or on wool or hair of infected animals. Then if ingested or inhaled by an animal, or on entering through cuts in the skin, they can germinate and cause disease. Because the blood of infected animals sometimes fails. [21]

Exams And Tests

The tests to diagnose anthrax depend on the type of disease suspected.

Tests may include:

1. Culture of skin sore to test for cutaneous anthrax
2. Chest x-ray
3. Sputum culture
4. Spinal taps to check your spinal fluid for infection
5. Gram stain (staining a sample of tissue and looking at it under a microscope for the bacteria that cause anthrax infection) [22]

Incubation

The period of incubation is uncertain. The exact time of infection cannot be fixed as in cases of traumatic cutaneous anthrax. No case of pulmonary anthrax has been recorded which was due to only one exposure to infection. Sorters of noxious materials may work exposed to the risk of infection almost daily for years without any noticeable effect from it. It is only when the virus gains access to the blood stream through some accidentally open gateway that serious illness follows. Judging from what takes place in cutaneous cases we may presume that when the spores pass the respiratory epithelial barrier they will produce some local specific effect within twenty-four hours. Infective material may be present on the skin or the mucous membranes several days before it gains access to the blood and produces any noticeable effect. [23]

Treatment

Penicillin is the antibiotic of choice. For patients who are allergic to penicillin, many other antibiotics are effective, including erythromycin, tetracycline and chloramphenicol. The typical treatment for cutaneous anthrax is a 7 day course of Penicillin G, 600,000 U IM. Ciprofloxacin (Cipro) is being widely touted and there has been a stampede to buy it up by the frightened public. This broad-spectrum antibiotic is very expensive and has serious possible side effects. It is an illogical choice to treat anthrax, especially when simple penicillin G is effective and readily available. Furthermore, doctors should not be prescribing antibiotics for patients in the absence of indications. It only contributes to the appearance of antibiotic resistant bacteria. Because the anthrax bacterium has had little exposure to penicillin it is likely to be sensitive to it (as opposed to many other common bacterial infections). Indeed, widespread use of Cipro against this anthrax is unwise because it will favor development of resistance in common pathogens. As always, no antibiotics should be taken without clear indication of bacteria infection. Basic polypeptides kill anthrax, including polylysine. [5, 24]

Control

Herds at risk should be vaccinated, and animals infected should be culled immediately, and all anthrax-infected carcasses should be burned or buried in deep lime pits. It is difficult to eradicate due to long-lived spores in soil, with no easy method of disinfecting soil. [24]

First Vaccination

In May 1881 Louis Pasteur performed a public experiment to demonstrate his concept of vaccination. He prepared two groups of 25 sheep, one goat and several cows. The animals of one group were injected with an anti-anthrax vaccine prepared by Pasteur twice, at an interval of 15 days; the control group was left unvaccinated. Thirty days after the first injection both groups were injected with a culture of live anthrax bacteria. All the animals in the non-vaccinated group died, while all of the animals in the vaccinated group survived. After mastering method of vaccination Pasteur applied the concept to rabies. He went on to develop vaccines against small pox, cholera, and swine erysipelas.The human vaccine for anthrax became available in 1954. This was a cell-free vaccine instead of the live-cell Pasteur-style vaccine used for veterinary purposes. An improved cell-free vaccine became available in 1970. [25]

Table No 5: Treatment for anthrax

Category	Initial IV Therapy	Duration
Adults	Ciprofloxacin 400 mg every12 hr OR Doxycycline 100mg every 12 hr AND Additional 1 or 2 antibiotics	When clinically appropriate switch to oral therapy: Ciprofloxacin 500mg 2x daily OR Doxycycline 100 mg 2x daily Continue oral OR IV therapy for 60 days
Children*	Ciprofloxacin 10-15 mg/kg ever 12 hr OR Doxycycline: >8y and > 45kg: 100mg every 12 hr >8y and ≤ 45kg: 2.2 mg/kg every 12 hr <8y 2.2mg/kg every 12 hr AND 1 or 2 additional antibiotics	Switch to oral when clinically appropriate Ciprofloxacin 10-15 mg/kg every 12 hr OR Doxycycline: >8y and > 45kg: 100mg 2x daily >8y and ≤ 45kg: 2.2 mg/kg 2x daily <8y 2.2mg/kg 2x daily Continue oral or IV for 60 days
Pregnant Women*	Same for non-pregnant adults	Same for non-pregnant adults

*Although ciprofloxacin and certain tetracycline are not recommended for children and/or pregnant women, in life threatening circumstances their use would be warranted.

Anthrax Vaccines

An anthrax vaccine licensed by the U.S. Food and Drug Administration (FDA) and produced from one non-virulent strain of the anthrax bacterium, is manufactured by BioPort Corporation, subsidiary of Emergent BioSolutions. The trade name is BioThrax, although it is commonly called Anthrax Vaccine Adsorbed (AVA). It is administered in a six-dose primary series at 0, 2, 4 weeks and 6, 12, 18 months; annual booster injections are required thereafter to maintain immunity.Unlike NATO countries, the Soviets developed and used a live spore anthrax vaccine, known as the STI vaccine, produced in Tbilisi, Georgia. Its serious side effects restrict use to healthy adults. [26]

Prevention

A study on anthrax ecology published in 1971 suggested that an effective means of controlling the disease was vaccinating livestock in order to cut off the disease's likely host. However, recently anthrax has entered the post 9/11 world's consciousness as a potential biological weapon. One report claims that 50 kg of aerosolized *B. anthracis* spores dispersed by airplane two kilometers upwind of a major population center would kill over 95,000 people. For this reason, human prophylaxis is increasingly sought after. Luckily, human vaccines do exist. Anthrax was actually the first disease in which a bacterial vaccine was found to be effective. This was a live, attenuated vaccine, obtained by Louis Pasteur. While still used for veterinary purposes, though not considered safe for humans due to residual virulence. The most common current vaccine is chemical, and consists mostly of purified protective antigen coupled with an adjuvant. However, the therapy has its drawbacks, as several boosters are required, and cases reactogenicities. Live spore vaccines appear to provide more protection against lethal challenges in animal models.[24]

Prognosis

When treated with antibiotics, cutaneous anthrax is likely to get better. However, up to 20% of people who do not get treatment may die due to anthrax-related blood infections. People with second-stage inhalation anthrax have a poor outlook, even with antibiotic therapy. Up to 90% of cases in the second stage are fatal. Gastrointestinal anthrax infection can spread to the bloodstream, and may result in death. [22]

Future Directions

The consensus that anthrax is essentially caused by poisoning by anthrax toxins points in the direction of an anti-toxin therapy that could be useful either as a vaccine or as a therapy after infection. In most cases, animals with protective immunity against anthrax lethal toxin (LeTx) affords protection from spore challenge, and animals injected with large doses of LeTx die in a manner very similar to those challenged with live endospores. Fortunately, the discovery that LeTx acts a zinc metalloprotease is fairly recent, and may pave the way for therapies that can directly counteract the effects of the toxin *in vivo.*[27]

Conclusion

All the bacterial infections are cured by sulfa drugs. However due to its intensity of disease, anthrax is commonly treated with Quinolones type of antibiotics especially with Ciprofloxacin and other antibiotics is Doxycycline. Penicillin G is also effective for control of anthrax. Anthrax which effects respiratory functioning leads to impairments of lungs. Anthrax is still considered an opportunistic infection and dreadful. Extensive work is still to be required to get the effective antibacterial agent. In the present review we have given all the silent features of anthrax, its incubation and mode of transmission, growth and effective treatment. The review has considered all the major observation of anthrax globally. Hence it may be under control if not causes the high mortality rate.

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