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ANTHRAX REVISITED
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ABSTRACT

***Background*: Anthrax is an ancient disease affecting animals and humans. Sporadic cases of anthrax and small epidemics have been seen from time to time in different parts of the world and in Africa. However many clinicians are not very familiar with the various presentations and management of anthrax. It is relevant for the health care workers to re-familiarise themselves with all aspects of anthrax, with the impending threat of bioterrorism.**

***Objetive*: To familiarise healthcare workers on all aspects of anthrax.**

***Study Selection:* To describe epidemiology pathogenesis, clinical features, management and prevention of anthrax including measures to take when weapons grade anthrax is suspected.**

***Data synthesis:* Three forms of the disease are recognised, cutaneous, inhalational and intestinal. Cutaneous anthrax is the most common form. Inhalation anthrax is the most severe form of anthrax. The treatment of anthrax in most cases is penicillin, however with the threat of bioterrorism, intentional releases of anthrax spores in the environment has caused much concern. Weapons grade anthrax of more virulent strain and resistant to commonly used antibiotics is possible.**

***Conclusion*: In view of the different clinical presentations and outcomes it is important that health care workers re-familiarise themselves with the disease and in the event of bioterrorism are able to take appropriate measures.**

HISTORICAL BACKGROUND

Anthrax is a very ancient disease caused by infection with a sporeforming gram positive organisms, *Bacillus anthracis*. It has been found in domestic animals and humans for thousands of years. Historical accounts of the disease are found in Greek, Roman, Hebrew and Hindu records(1). Earlier outbreaks of human anthrax occured in Rome and were attributed to consumption of contaminated meat and use of hides and hair of such animals. The exodus of Egyptian cattle described in the Holy Bible is thought to be due to anthrax(2).

Bacillus anthracis, the aetiologic agent of anthrax was first discovered in the blood of sheep by Rayer in 1850. The name anthrax was coined from the Greek word for coal. This description is based on the black eschar that is seen in cutaneous anthrax.

Sporadic cases of anthrax have been reported from all over the world. A large airborne epidemic of anthrax occured in Russia in 1979 due to an accident that happened near a military production facility in Sverd-Lovsk(3).

The incident was covered up and the cause attributed to faulty inspection of meat. It was not until 1988 when the truth was exposed by an American pathologist Walker who after examining pathological specimens of 64 people concluded that the people had died of airborne anthrax.

In Kenya sporadic cases of anthrax have been reported from all over the country, however the majority of the reported cases have been from Rift-Valley Province and some from Central Province(4).

In Uganda human anthrax was reported around Western Lakes after consumption of hippopotamus meat(5).

EPIDEMIOLOGY

Bacillus anthracis is a spore forming gram Positive organism. Anthrax endospores are very hardy and remain dormant in the soil for many years. They are resistant to extremes of climate, ultraviolet light, heat and many disinfectants.

Herbivorous animals acquire infection by grazing on land contaminated with spores. Cattle, sheep and goats are most susceptible but almost any species can be affected such as hippopotamuses, elephants, camels antelopes and even Ostriches(6). Infected animals bleed from gastro-intestinal tract, nose and contaminate the environment with vegetative forms which sporulate. In phosphate deficient areas of South Africa cattle may

also be infected by licking carcases of dead companions. Carnivores may be infected by eating dead animals containing large amount of vegetative forms of Anthrax.

Scavengers such as hyenas and vultures may spread the infection from village to village(7). Flies settle on infected carcasses with open wounds and also disseminate infection. Humans are less susceptible to anthrax than animals. Humans get infected with anthrax by handling infected animals or animal products and by inhalation or ingestion of animal products. Sometimes insect bites also transmit anthrax. Human to human transmission of anthrax is rare, however, in Gambia communal use of back scrubbing implements made from palm fibre have been found to be contaminated with spores of *Bacillus anthracis* and implicated in human to human transmission(8). Highly susceptible herbivorous animals can serve as sentinels.

More recently cases of anthrax have occured in United States of America through intentional delivery of spores of anthrax via mail. The first case was diagnosed on 2nd October 2001 in Palm Beach County in Florida when a patient presented with anthrax meningitis and later died. His co-worker was also diagnosed with pneumonia and was confirmed to have inhalational anthrax. More cases have been diagnosed since then in New York City(9). Bioterrorism was suspected.

PATHOGENESIS

The capsule of *Bacillus anthracis* is resistant to phagocytic effect. This mechanism for evading of phagocytosis facilitates rapid entry of the organism into the blood stream where rapid multiplication of the organism occurs and can be lethal. The vegetative anthrax bacilli secrete exotoxins which are responsible for manifestations of systemic anthrax.

Anthrax toxin consists of three different proteins; the protective antigen, lethal factor and oedema factor. The protective antigen binds to the plasma membranes of target cells and serves as specific receptor that mediate the entry of oedema factor and lethal factor into the target cells. The oedema toxin increases the intracellular cyclic AMP which in turn alters the water homeostasis resulting in massive oedema and inhibits polymorphonuclear leukocyte functions(10). Macrophages are the principal targets of lethal factor leading to intoxication of macrophages with the production of free oxygen radicals and cytokines such as interleukin and tumour necrosis factor resulting in shock and death.

CLINICAL FORMS OF ANTHRAX

Three forms of the disease anthrax are recognised; cutaneous, inhalational and intestinal.

Cutaneous anthraxx: This is the commonest form of anthrax(11). The primary lesion occurs on the exposed area of the skin at the site of abrasion or scratch. After a short incubation period of 1-2 days a small pruritic red macule developes which can be mistaken for an insect bite. With time extensive oedema usually develops in the tissues. A number of satellite vesicles containing clear fluid also develope. A characteristic central black eschar develops as a result of central necrosis. The skin lesion is usually painless except when there is secondary infection though the regional lymphglands may be tender. It is usually curable but rarely may become systemic when it can be fatal due to bacteraemia and toxoaemia. Mortality can be upto 20% in untreated cases. The Location of cutaneous lesion influences the extent of oedema and the severity of the disease. Both tend to be greater when the lesion is located in looser tissue, such as the neck, than in the firmer tissues of the limbs and the trunk. A few cases have been reported of temporal arteritis(12) associated with cutaneous anthrax infection and corneal scarring from palpebral cutaneous anthrax(13). *Bacillus anthracis* may be cultured from fluid from vesicles prior to antibiotic treatment. Antibiotic therapy clears the organisms but the skin lesion continues to progress to eschar formation despite early intervention(14). Corticosteroids are effective in reducing mortality and shortening recovery time in severe cases with extensive oedema.

Inhalation anthrax: Anthrax spores are 1-2 um in diameter, the size that is ideal for inhalation(15,16). Inhalation anthrax is the more severe form of anthrax which results from inhalation of anthrax spores contained in dust produced by industrial processing of contaminated products such as wool, hair and hides. The inhaled spores are engulfed by alveolar macrophages and transported to the tracheobronchial lymphglands, where rapid multiplication of bacteria occurs. Further multiplication of bacteria and spread via the lymphatics to the circulation results in bacteraemia and toxaemia(17). The incubation period is 1-7 days but host factors, size of innoculum and chemoprophylaxis may affect the duration of incubation period. In the Sverdlovsk outbreak in Russia the incubation period for inhalation anthrax was about ten days but in some the symptoms occured upto six weeks after exposure(18,19).

Anthrax is not considered to be a true pneumonia. Usually there is no or minimal lesion in the lungs. The principal lesions are acute mediastinitis and septicaemia(20).

The initial episode is a flu-like illness characterised by fever, muscle pains, cough and sensation of precordial oppression. A few days later the patient may improve transiently only to get suddenly worse with a more fulminant course characterised by acute respiratory distress, cyanosis and stridor(21).

Pulmonary oedema, haemorrhagic mediastinitis and pleural effusion are commonly seen. Death occurs within twenty four hours of these severe manifestations.

The diagnosis of anthrax may be difficult because of mild and non-specific early symptoms and rapid

fulminant course of the subsequent illness. Mediastinal changes can be detected early in the course of infection by chest x-ray(22).

Mediastinitis due to *Histoplasma capsulatum* can give similar radiological findings. The prognosis of inhalational anthrax is improved if early treatment is instituted on suspicion. Patients with systemic illness often die before blood culture can be obtained. Organisms can be identified from fluid in skin lesions, pleural fluid and from sputum.

Gastrointestinal anthrax: Gastrointestinal anthrax is caused by eating raw or partially cooked meat of animals dead or dying of anthrax(21). Clusters of cases occur. The incubation period of gastrointestinal anthrax is 1-7 days. An oropharyngeal and abdominal form of the disease have been described. After ingestion of contaminated meat the patient present with nausea, vomiting, abdominal pain, haemetemesis and bloody diarrhoea. Intestinal obstruction and perforation with clinical signs of peritonitis occur. Ascites often developes. The patients may develop severe toxaemia and eventually die. The mortality is between 25-60%.

Usually there is associated ulceration and mucosal necrosis with massive oedema at the site of infection. Mesenteric lymphadenopathy occurs with demonstration of bacilli in the mucosal and submucosal lymphatic tissue.

Oropharyngeal disease is usually characterised by lesions at the base of the tongue, dysphagia, fever and regional lymphadenopathy. Respiratory problems and pseudomembrane formation in the oropharynx are known to occur.

Most of the symptoms of gastrointestinal anthrax subside within two weeks if the patients survive(23).

Anthrax meningitis: A haemorrhagic meningitis with extensive oedema and inflammatory infiltrates of meninges occurs in less than 5% of all cases of anthrax either alone or as a complication of the other three types(24). *B. anthracis* spreads to the meninges via the lymphatics or haematogenous route. The cerebrospinal fluid is haemmorhagic. This is a very severe form of disease and invariably fatal. Death usually occurs one to six days after the onset of illness despite vigorous therapy. A few patients have survived with the administration of steroids and antitoxin together with antibiotics.

Treatment of anthrax: Treatment should be started as early as possible. Bacillus anthracis organisms are highly sensitive to penicillin, however during biological warfare penicillin resistant strains may be deliberately used and penicillin may not be efficacious in such cases.

For cutaneous anthrax without systemic symptoms benzyl penicillin one mega unit 6 hourly for 48 hours followed by oral penicillin for one week is curative. The skin lesion is little influenced by the antibiotic treatment but systemic spread is prevented.

For other types of anthrax (Pulmonary, Gastrointestinal and meningeal infections) intravenous administration of high dose penicillin 18-24 million units per day are recommended and the treatment should be continued for 14 days after the symptoms abate. Combination of streptomycin and penicillin is synergistic. Doxycycline, chloramphenicol, erythromycin or ciprofloxacin can be administered to patients who are allergic to penicillin. Tetracycline is not recommended for pregnant women or children. For a favourable outcome it is recommended that more severely ill patients be treated in intensive care unit with good supportive care.

More recently the threat of bioterrorism and intentional release of anthrax spores in the environment has caused much concern. Weapons grade anthrax is specially prepared with particles less than five microns but larger than one micron. Larger particles cannot reach the respiratory tract and particals smaller than one micron may be exhaled easily. In addition spores of anthrax resistant to commonly used antibiotics or containing additional virulence factor could be released.

In the event of intentional release of weapons grade anthrax the prophylactic regimen suggested by CDC is Ciprofloloxacin 500mg twice a day for 60 days or doxycycline 100mg twice a day for 60 days.

For children Ciprofloxacin 10-15 mg/kg 12 hourly for 60 days (should not exceed 1 gram per day)or doxycycline can be used. Dosage-Doxycycline:

>8yrs and >45kg-100mg Bs
>8yrs and ≥45kg 2.2mg/kg/B.D
≤8yrs - 2.2mg/kg B.D.

Prevention of anthrax: Annual vaccination of domestic animals is effective preventive measure throughout Africa. During an outbreak, carcasses of infected animals must not be opened or skinned but must be burnt or buried deep under quick lime or covered with crude oil to discourage scavengers. Sick animals should be strictly quarantined for at least two weeks. Mass vaccination of animals should be carried out. Bone meal can be sterilised by autoclaving, wool and hair by soaking in soap and formaldehyde solution. Vaporised formaldehyde can be used for decontamination of environment. In humans occupational risk can be reduced by disinfecting the animal material and immunisation of individuals. A protective vaccine "anthrax vaccine absorbed" is available which cannot be used in emergency situations due to a prolonged regimen. The dose used is 0.5ml subcutaneous and repeated at two weeks, four weeks and then at 6,12 and 18 months(25,26) and boosters are given annually. Live attenuated endospore based vaccines are widely used in Russia for both humans and animals(27).

Asymptomatic patients with suspected exposure to anthrax spores should be on prophylaxis with ciprofloxacin and doxycycline for six weeks or longer if the exposure dose is higher particularly if weapons grade anthrax is suspected (28).

In view of the threat of bioterrorism world over it has now become relevant for healthcare workers to re-familiarise themselves with clinical features of anthrax and its management.

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