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### **Anthrax: A Review For The Medical Officer**

G Vautier

#### **Introduction**

On the 2nd October 2001 a 63 year old picture editor for a tabloid newspaper awoke in a confused state (1). His wife rushed him to their local Emergency Department in Florida, where an initial diagnosis of bacterial meningitis was made. Three days later he was dead. The diagnosis of anthrax meningitis came to light from the Gram stain examination of his cerebro-spinal fluid. His exposure to the bacterial spores had come from mail sent to his office. Within six weeks four others had died; two were postal workers from Washington; a 61 year old Vietnamese hospital employee from New York; and a 94 year old lady from Oxford, a small town in Connecticut (2) (it remains a mystery as to how the latter two fatalities had been exposed to the bacillus). In total there were 21 victims of "the anthrax attack of 2001"; the murderer is unknown but it is alleged that the prime suspect had close connections with a United States government laboratory. *Bacillus anthracis* had had its debut as a weapon of terrorism.

The reader will be well aware that as part of force protection measures vaccination against anthrax is being offered to service personnel. As part of this voluntary procedure Medical Officers have been requested to provide information concerning anthrax and vaccination against the disease. This review is intended to outline significant aspects of the disease and provide a starting point for further information.

#### **Background**

Deriving its name from the black skin lesion seen in the cutaneous presentation, the organism has a worldwide distribution. Primarily it is an infection of herbivores in whom there is a high mortality, with death caused by bleeding from epithelia within the nose and gut. It is rarely seen in the developed world due to an active vaccination programme of susceptible livestock.

The *Bacillus* has a long celebrated history, it is suggested that accounts of infection date back to ancient Egypt (3) and may have been the cause of the "Fifth Plague" 1,500 years B.C (Exodus 9.3). It was Koch's study of the organism in 1877 that spawned his eponymous postulates. In 1878 a report in the Bradford Observer encouraged John Bell to scrutinize the deaths of woolsorters (4). His investigation led to the description of

inhalation anthrax, the most serious clinical manifestation of the infection in man. As a weapon the *Bacillus anthracis* has two previous recorded uses; in 1915 in the United States livestock destined for the Allied force in Europe were infected and it is alleged that a large number of military personnel were also affected; and the Japanese used anthrax against the Chinese during the Second World War. The only significant contemporary outbreak was in April and May 1979 in the city of Ekateringburg (previously known as Sverdlovsk) in the former Soviet Union (5). Information from this epidemic is scarce, but the evidence supports the theory that it was due to a windborne spread of an aerosol form of anthrax from a military research facility within the city. The number of deaths from this single exposure remains uncertain but is suggested to be of the order of 100 people.

#### **Pathogenesis**

The infamy of Gruinard Island provides one of the few commonly recalled facts, for example, that it can survive in its spore form under arduous conditions for many years. Having gained entry to its host, it is phagocytosed by scavenging macrophages that, in inhalational and gastrointestinal forms, transport the organism to regional lymph nodes (Figure 1) (6). Within the lymph node it germinates to its vegetative (replicative) form. Virulence of the bacterium centres upon the production of exotoxins, coded for on the plasmid pXO1; and the synthesis of a polyglutamyl capsule, coded for on the plasmid pXO2, that inhibits further phagocytosis. There are two dimeric exotoxins, both include a protective antigen (PA) that binds to host cells and is required for translocation of the other toxin component into the cell. The other moieties of the two toxins are lethal factor (LF) and oedema factor (EF). LF, a zinc metallo-proteinase that causes a hyperstimulation of macrophages. This results in an outburst of pro-inflammatory agents, in particular tumour necrosis factor and interleukin-1 $\beta$ , leading to the systemic vascular collapse of the victim. EF increases the intracellular levels of cAMP that in turn causes localised disturbance of water homeostasis. EF also inhibits neutrophil function.

Maj Guy Vautier BM  
BSc MRCP RAMC

Consultant Physician  
Royal Hospital Haslar,  
Gosport, PO12 2AA.  
E-mail: guy.vaut@dscs.mod.uk

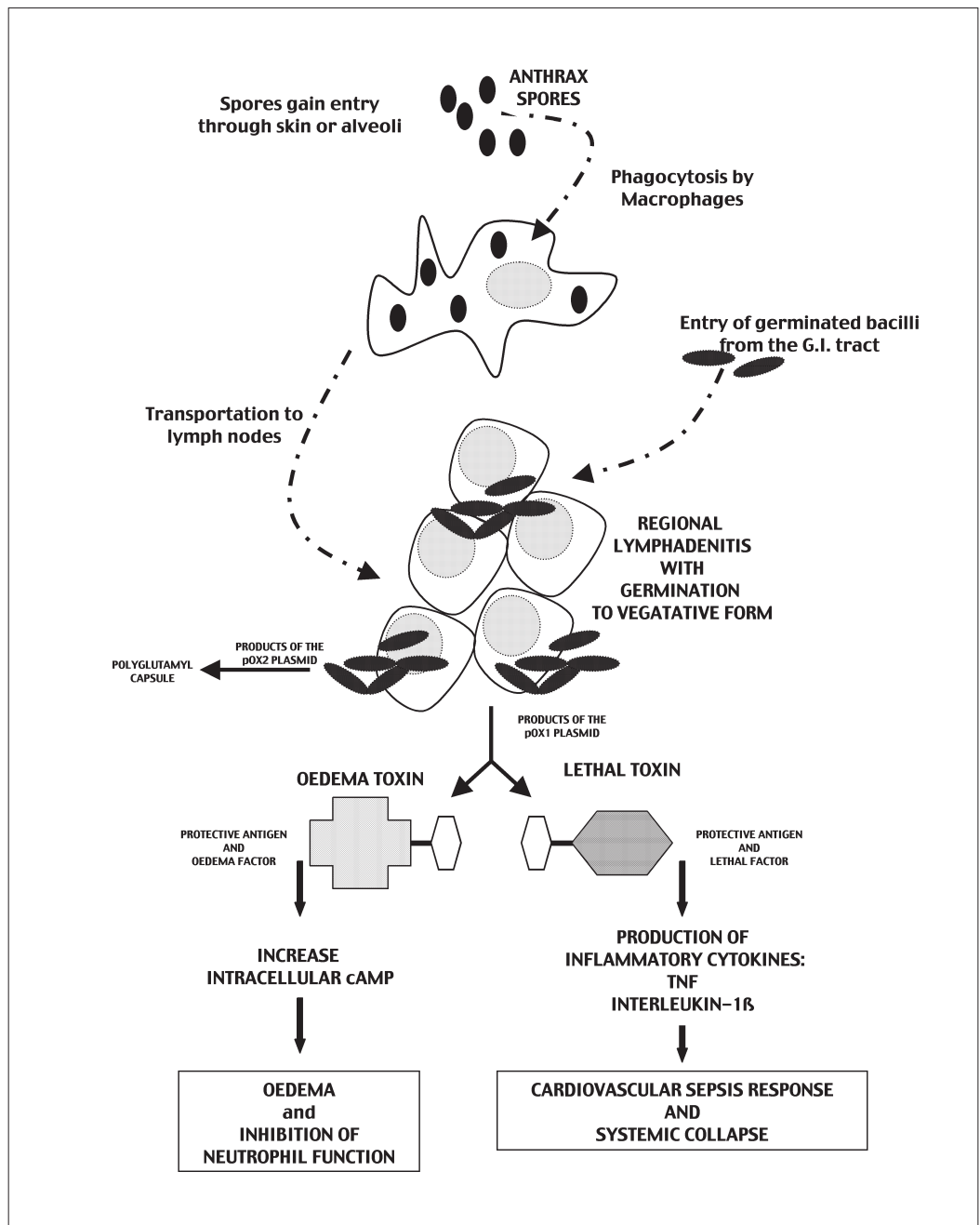


Fig 1. Schematic illustration of the pathogenesis of *Bacillus anthracis*.

### Cutaneous Anthrax

Three to five days after the spores enter the skin, probably through minor wounds, a painless itchy papule appears (6). A vesicle then develops, from which the organism may be identified. After approximately one week the vesicle undergoes extensive central necrosis with the production of the pathognomonic eschar. The cutaneous form is largely held to be localised and self-limiting. By two to three weeks the eschar heals and sloughs away. However, there is a small risk of systemic involvement hence the recommendation to offer antibiotic treatment. It is also important to remember the possible local complications of oedema depending upon the initial site of skin entry, for example, the neck or upper thorax resulting in upper airway compromise.

### Gastrointestinal Anthrax

It is suggested that due to the rapid gut transit time anthrax spores would be cleared prior to having the opportunity to gain entry through the intestinal mucosa. Thus it is suggested that meat contaminated with the vegetative form is the cause of the gastrointestinal form of the illness. However, this remains a contentious issue (6,7). The organism is transferred to local lymph nodes and an extensive haemorrhagic lymphadenitis ensues. The gut becomes ulcerated. It is unknown if the ulceration is associated with the point of entry of the organism or is a regional effect of the toxins. Massive mucosal oedema occurs and the gut becomes necrotic. The victim frequently develops blood-stained ascites. Death is due to a combination of gastrointestinal blood loss,

gut perforation, the complications of fluid loss, or the systemic effects of toxins. The patient presents with an acute abdominal emergency and rapidly dies so that the diagnosis invariably only comes to light at a post-mortem examination. Of interest, 39 of the 42 available autopsy reports from the Sverdlosk incident of inhalation anthrax demonstrated pathology within the gut.

### Anthrax Pneumonia

This is the most feared form of the disease, with a mortality of 100% for untreated disease (8). The spores need to be aerosolised. The ideal particle size is less than 5µm in size, any larger and they may be cleared from the upper airway but can still cause pneumonic disease. The minimal dose of spores required to cause a significant clinical illness is not known. Studies estimate that for humans the dose to kill at least half of those exposed (the LD<sub>50</sub>) is of the order of 8,000 to 10,000 spores. Between three to six days after inhalation the victim will have non-specific features of headache, myalgia/arthralgia, fever, dry cough and occasionally retrosternal discomfort. During this time the organism is undergoing germination and transformation to the vegetative form in regional mediastinal lymph nodes. It is this process that causes the very typical widening of the mediastinum seen on the chest X-ray. Other X-ray features include pleural effusions, or pulmonary infiltrates (as seen in the recent cases) but until the terminal phase the lung fields may appear unaffected. The mediastinal lymph node enlargement can lead to large airway obstruction and stridor. Classically there ensues a short period, less than 24 hours, of resolution prior to the catastrophic respiratory distress and vascular collapse of the victim. This terminal phase of the illness is brought about by the release of vast concentrations of anthrax toxins.

### Anthrax Meningitis

Approximately 50% of victims of inhalation anthrax will suffer central nervous system involvement and it is a rare complication of the dermatological form of the illness (6). The pathology is of a haemorrhagic

meningitis with oedema and a marked inflammatory infiltrate. The bacillus can be isolated from the cerebrospinal fluid that is often heavily blood stained, and the sub-arachnoid haemorrhage found at post-mortem is the cardinal's cap sign. The presentation is that of a rapidly progressive neurological deterioration, and is invariably fatal.

### Diagnosis

From the clinical descriptions above it is apparent that early diagnosis is required in order to offer any form of a favourable prognosis to a patient. Thus clinical awareness and a high index of suspicion are needed. Microbiological confirmation is obtained by Gram stain smear of skin vesicle fluid or eschar, cerebrospinal fluid or occasionally direct staining of blood smears (7). Punch biopsy of skin lesions is also feasible. Blood cultures, (ideally taken before any antibiotics have been administered) may not become positive until after the patient has died. Blood cultures, cerebro-spinal fluid (if obtained) and dry nasal swabs should be sent to a designated reference laboratory (for the United Kingdom this is currently at Porton Down) for confirmatory analysis. Serological testing for antibodies to the protective antigen is available, but currently this remains a mainly retrospective diagnostic tool. Ongoing research, for more rapid diagnostic confirmation, is exploring the use of direct serological, and polymerase chain reaction analysis of samples, including nasal swabs from inhalation victims.

### Management

An outline of current anti-microbial recommendations for the treatment of inhalation anthrax is given in Table 1 (7,9). The prolonged treatment period is required as spores can remain viable within the host for many days. Wild type strains appear to remain sensitive to single agents, there appears to have been but a single report of a naturally occurring penicillin resistant strain (10). However, there is a serious concern that strains may be genetically engineered to have

PATIENT	ANTIBIOTIC	DURATION
Adult	Ciprofloxacin, 400 mg, IV, every 12 hours or Doxycycline, 100 mg, IV every 12 hours and One or possibly two other agents until sensitivity confirmed.	After initial IV treatment, and as long as there is clinical improvement then switch to oral therapy:  Ciprofloxacin, 500 mg, bd; or Doxycycline, 100 mg, bd for up to 60 days.
<16 years of age	Ciprofloxacin, 10-15 mg.kg-1, IV, every 12 hours. (NB risk of arthropathy with fluoroquinolones). or Doxycycline, 2.2 mg.kg-1 (up to maximum 100 mg), of IV, every 12 hours and One or possibly two other agents until sensitivity confirmed.	After initial IV treatment, and as long as there is clinical improvement then switch to oral therapy:  Same dose regime as initial IV therapy, for up to 60 days.

Table 1. Current recommendation for the antibiotic management of inhalation anthrax.

anti-microbial resistance. Hence the recent switch to offering multiple agents until antibiotic sensitivity is confirmed. Other antibiotics to consider include; rifampicin, vancomycin, penicillin, ampicillin, imipenem, clindamycin and clarithromycin.

Cutaneous anthrax may be treated with oral antibiotics. A fluoroquinolone or doxycycline is suggested, for a treatment period of up to 60 days. In cases whereby localised oedema of a cutaneous lesion presents a clinical threat (eg. a compromised airway) the treatment schedule as per inhalation anthrax is suggested. Topical treatment is not indicated. Skin lesions may be infectious so careful wound management is required, especially avoiding direct skin to skin contact.

The chance of person to person spread of inhalation anthrax is negligible, patients do not require isolation (11). However, care must be taken to decontaminate an affected individual (and their effects) as there is a high risk of spore carriage. Surface decontamination with 0.5% hypochlorite solution is used (one part household bleach to nine parts water). The movement of individuals into and out of a potentially contaminated area needs assiduous control, and collective protection procedures need to be planned and practised.

For those who may have been exposed (and as a mass casualty strategy) a 60 day oral regime of either Ciprofloxacin 500 mg twice each day, Doxycycline 100 mg twice each day or Amoxycillin 500 mg three times each day is recommended. Post-exposure vaccination should also be offered.

### Vaccination

There is a live nonencapsulated, nonvirulent strain of the *Bacillus* that is an extremely effective vaccine for livestock. In the former Soviet Union and in China live strain vaccines for humans are used. However, fear concerning retained virulence has led to the development of antigen extracts that are the basis of the vaccines offered in the United States (US) and the United Kingdom (UK). The vaccine used in the UK is from the same strain used for the preparation of the animal vaccine (12). A filtrate is produced containing mainly PA but also small amounts of LF and EF, but no live organism. The vaccine offered in the US (anthrax vaccine absorbed, AVA) is prepared in a similar fashion but contains very much less (if any) EF and LF (13). As the reader is probably aware immunisation in the UK consists of an initial three doses followed by a further dose at six months, and yearly thereafter. AVA has an initial four dose regime followed by further doses at twelve and eighteen months and annual boosters thereafter. Both vaccines in animal trials are reported to have very good efficacy. Concern has been raised about vaccine resistant

strains, the data is somewhat limited but it suggested that the AVA vaccine does offer protection to rabbits and primates exposed to such strains (13). The UK vaccine appears to cause a far greater rate of adverse reactions in comparison to the AVA vaccine. Eighteen per cent of UK service personnel suffered reactions severe enough to interfere with work, whereas in the US the reported equivalent rate is approximately 8% (14,15). This difference is believed to be due to the UK vaccine's EF and LF content. The US Department of Defence has had a mandatory vaccination programme since 1997 and has a continuing surveillance programme. By April 2000 nearly 425,976 personnel had received 1,620,793 doses of the AVA vaccine. A reviewing panel had not identified any unexpected patterns of adverse reaction reporting (14). There is no such large-scale experience reported with the UK vaccine. There is no information concerning any effect that either vaccine might have on fertility. A study of over 4,000 US Army women at Fort Stewart did not demonstrate an adverse effect on pregnancy, but was too small to detect adverse birth outcomes (16). Currently there are two areas of interest for future vaccines; firstly the genetic engineering of PA so that it may be expressed in pure forms in harmless bacteria. Secondly, various groups are attempting to identify other proteins coded for on the two virulence empowering plasmids that could be bonded to PA (11). Differing systems for delivery of the vaccine are being considered including oral and intranasal routes.

### Conclusion

Anthrax is a good biological weapon; it is relatively easy to produce and store; aerial release of spores is straightforward, and it has been estimated that 100 kilogrammes released over an urban population would be sufficient to kill between 130,000 and 3 million people. Inhalation anthrax has a rapid clinical progression, such that the only chance of survival comes from early recognition, necessitating a high index of suspicion. The current vaccines based upon the Protective Antigen, given the experience in the US, appear to be safe and effective. The vaccine offered in the UK causes a high rate of resolving adverse effects, though it is argued that this provides a broader base of protection against the bacillus. It is hoped that within the current UK programme proactive surveillance is in place similar to that running for the US Defence Department.

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