BIOTERRORISM: ESSENTIAL INFORMATION FOR THE PRACTISING PHYSICIAN

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SUMMARY

The recent anthrax cases in the USA have raised awareness of the bioterrorist threat worldwide. Many biological agents could be used as weapons and the potential methods of infection include aerosol inhalation, contamination of food and water supplies, direct contact and spread by insects and other vectors. Aerosol inhalation probably has the greatest potential to cause mass casualties. The four most feared diseases are anthrax, smallpox, plague and botulism. We describe the important features of these diseases, which every practising physician needs to know.

Keywords: anthrax, bioterrorism, botulism, plague, smallpox

INTRODUCTION

The recent deliberate use of anthrax as a biological weapon has caused much concern among the general public in the USA. Although there have been only a few clinical cases, there has already been substantial disruption to society due to the large numbers of false alarms and hoaxes. Raising awareness of bioterrorism facilitates early detection of cases and may prevent many avoidable deaths. However it may also cause unnecessary anxiety, and disruption of the normal functioning of the health and emergency services. This review provides information regarding the most feared biological weapons: anthrax, smallpox, plague and botulism. It aims to help physicians identify potential cases of these diseases and to be able to provide reassurance to patients who are unlikely to be suffering from them.

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ANTHRAX[1]

Anthrax is caused by the spore-forming Gram-positive rod, *Bacillus anthracis*. Anthrax spores can contaminate soil and natural disease is usually acquired by contact with animals. Three different forms of this disease occur: cutaneous, gastrointestinal and inhalational. Cutaneous disease is the commonest and generally least severe form. It is usually acquired by handling infected animal carcasses and presents as a painless, depressed black eschar surrounded by local vesicles and oedema. With antibiotic treatment, the case fatality rate is less than 1%. Gastrointestinal anthrax occurs after ingestion of contaminated, undercooked meat and causes abdominal pain, haematemesis, dysentery and haemorrhagic ascites. The case fatality rate is 25-60%. The inhalational form is called wool-sorters' disease as it previously occurred among those working with wool from infected sheep and goats. The inhalational form of the disease is the most likely one to be caused by a deliberate terrorist act. Even with antibiotic therapy case fatality exceeds 80%.

The typical incubation period for inhalational anthrax was two to fourteen days following a major accidental anthrax release in the USSR. However,

some cases occurred more than forty days after exposure, probably due to the late germination of spores. Patients initially develop non-specific influenza-like symptoms including fever, malaise, cough and chest discomfort. There may then be a short asymptomatic period or the patient may progress directly to fulminant disease characterised by severe breathlessness, stridor, septic shock and death.

Inhalational anthrax does not cause pneumonia. The organism spreads to the mediastinal lymph nodes and causes haemorrhagic lymphadenitis and haemorrhagic mediastinitis. One third of patients also develop haemorrhagic meningitis. A severely unwell, previously healthy patient who has a chest X-ray showing a widened mediastinum with clear lung fields should be assumed to have inhalational anthrax until proven otherwise. This presentation is almost pathognomonic of inhalational anthrax and the Ministry of Health should be immediately alerted to the possibility of the diagnosis.

Diagnosis of anthrax is confirmed by culture of the organism from blood or affected tissues. It is essential to discuss any potential anthrax case or other suspected bioterrorist agent with the microbiologist. Up to ten percent of positive blood cultures may grow Bacillus species, which are common contaminants. If the laboratory is not aware anthrax is being considered, diagnostic delay is likely and the correct diagnosis may even be missed.

The initial recommended treatment for anthrax is ciprofloxacin 400mg bd intravenously (IV). This antibiotic is chosen because of concerns that terrorists would use penicillin and tetracycline resistant strains. Following confirmation of *in vitro* susceptibilities, patients should be switched to a daily dose of twenty-four million units of IV penicillin G, administered every two to four hours or IV doxycycline 100mg bd. Sixty days of therapy is required but antibiotics can be given by the oral route once the patient's condition improves. Person-to-person transmission does not occur and respiratory isolation is not required.

Following a deliberate anthrax release, persons who have been exposed to anthrax will be identified by public health officials. These persons will initially be given ciprofloxacin 500mg bd orally and this should be changed to amoxicillin 500mg tds or doxycycline 100mg bd once susceptibilities are known. Sixty days prophylaxis is required.

Currently, no case of deliberate anthrax exposure has occurred in Singapore. The family practitioner is most likely to be asked about anthrax by patients who have a low probability of exposure, eg. a recent visit to the USA. The patient may be understandably anxious because the initial presentation of anthrax is non-specific. Providing the patient does not have specific clinical symptoms suggestive of anthrax, he or she should be reassured that the disease is extremely unlikely in those without a definite history of exposure. Unfortunately, there is no screening test for the detection of anthrax and nasal swabs should not be used for diagnosis. Nasal swabs and serology are epidemiological tools for characterising an outbreak and cannot be used to exclude anthrax. There is therefore no purpose in referring unexposed patients with influenza-like symptoms to the Communicable Diseases Centre (CDC) for "screening". If a person has been exposed to an anthrax attack, they will require antibiotics regardless of the results of such tests. The US army has stocks of anthrax vaccines but this is not currently available for the general population or health service personnel.

SMALLPOX[2]

Smallpox was eradicated in 1977, but there are serious concerns that it could be used as a biological weapon. There are two strains of this Orthopox virus, *Variola major*, which produces severe disease with a case fatality rate exceeding 30% and *Variola minor*, with a fatality rate of 1-2%. It is estimated that only one-fifth of the World's population is immune to smallpox due to discontinuation of vaccination and waning immunity in those previously vaccinated. The virus is highly infectious in aerosol form and its high transmissibility could lead to large numbers of secondary and tertiary cases.

Between seven and seventeen days after inhalation, the patient develops malaise, fever, rigors, vomiting, headache, backache and an erythematous rash. Severe abdominal pain and delirium may also occur. Vesicles often appear in the mouth and pharynx before being present on the skin. These vesicles may shed virus many days before the skin rash develops but it is believed that transmission does not occur during this period. The cutaneous rash progresses from macules to papules to vesicles to pustules and then healing scabs. Two less common variants of the rash are haemorrhagic smallpox and malignant smallpox, also called "flat-type". These conditions would be difficult to diagnose unless a confirmed case of smallpox had already occurred. Smallpox deaths usually occur during the second week of illness due to circulating immune complexes. Secondary bacterial infections and involvement of other organs are not common, although encephalitis sometimes occurs.

Smallpox is most likely to be confused with varicella (chicken pox). Although it also resembles vaccinia, cowpox and monkeypox, epidemiological features would likely distinguish these diseases. Smallpox is a biosafety level four organism and samples from suspected cases would have to be sent overseas for identification. Varicella is a common disease and it is therefore likely that prior to a confirmed epidemic, doctors would misdiagnose smallpox as this disease. Three features assist discrimination between smallpox and varicella: the distribution of the rash, the evolution of the lesions and the severity of the disease.

In smallpox, the density of the lesions on the face, the arms and the legs is greater than on the trunk. In contrast, in varicella, there are more lesions on the trunk than on the extremities. It is unusual in varicella to have large numbers of lesions on the palms and soles but this is common in smallpox. In smallpox, all of the lesions in one body site evolve together and will therefore be at the same stage of development. In varicella, adjacent lesions are frequently at different stages of development and macules, papules, pustules and vesicles may all be seen together. Varicella is usually a mild illness. The uncommon deaths which occur are usually due to varicella pneumonia or secondary bacterial infection. A patient dying of "varicella" who does not have apparent pneumonia or bacterial infection should be suspected of having smallpox. Family practitioners who see a patient with a varicella-like illness, with any of the features listed in Table 1, should inform CDC and refer the case for further assessment.

Table 1: Recommended criteria for referral to CDC for further assessment of suspicious cases of vesiculo-pustular rash resembling varicella/ smallpox

Recent contact of a fatal varicella case
Multiple lesions on the palms and soles
Many more lesions on face/arms/legs than on trunk
All lesions at the same stage of development

There is no treatment which has been clinically tested against smallpox. Contacts of a primary case or those who are known to have been exposed to an aerosol attack would need to be vaccinated. In an emergency, vaccine could be obtained from the Centers for Disease Control and Prevention in the USA, but as stocks are limited (5-7 million doses) pre-exposure vaccination of the general population is currently not feasible. Patients with smallpox are highly infectious and should be kept in strict respiratory isolation until all of the scabs separate. Unfortunately, most hospitals have a very limited number of negative pressure rooms and in the event of a terrorist release these could be quickly exhausted. Singapore is probably better prepared for controlling a large smallpox outbreak than most other developed countries. CDC was previously the quarantine and treatment centre for smallpox, at which time it was called the Middleton Hospital. The design of CDC with several wards which are physically distant would enable a substantial number of smallpox cases to be cared for separately from other patients.

PLAGUE[3]

The causative organism of plague is a Gram negative bacillus, *Yersinia pestis*. Plague is a rodent zoonosis which is usually spread to humans by the bite of a rat flea causing the bubonic form of the disease. Suppurative lymphadenitis develops and this may lead to septicaemia and secondary pneumonia. A small number of persons develop septicaemia without bubo formation, a condition known as primary septicaemic plague. Respiratory droplets from those with pneumonia are highly infectious, resulting in primary pneumonic plague in contacts. If plague were used as a biological weapon, it is likely it would be released in aerosol form causing the primary pneumonic form of the disease.

Symptoms of pneumonic plague develop one to six days after inhalational exposure. Patients develop breathlessness and cough productive of bloody or watery, occasionally purulent sputum. Many patients also suffer nausea, vomiting, diarrhoea and abdominal pain and this may suggest the diagnosis of plague. Buboes would generally be absent and if present, might suggest flea-borne disease. Septicaemia develops very rapidly with high fever, rigors, prostration and often meningism. Digital necrosis is a frequent complication (figure 1), but is a late feature of the disease. The chest X-ray reveals consolidation and laboratory tests may reveal multi-organ failure and disseminated intravascular coagulation. Clinically, this presentation is hard to distinguish from other forms of severe pneumonia with septicaemia and plague is unlikely to be suspected unless a terrorist warning has been given. However if several, previously healthy subjects presented

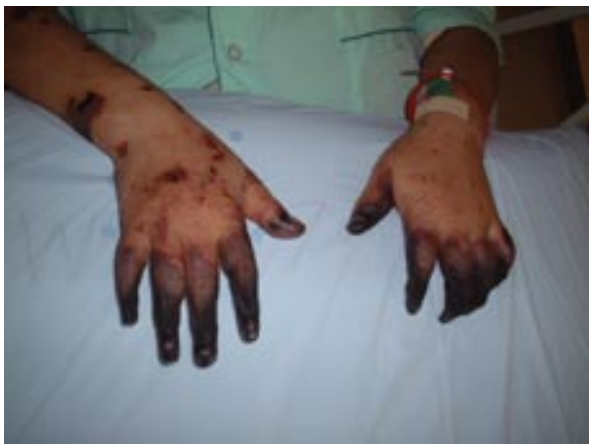

Figure 1: Necrosis of the digits following meningococcal septicaemia. This complication is also a frequent feature of plague and probably explains why this disease was called the Black Death.

simultaneously with severe life-threatening septicaemia, bioterrorism should be suspected. The presence of consolidation or infiltrates on chest X-ray would help distinguish plague from inhalational anthrax. Plague would be confirmed by culture of blood, sputum or lymph node aspirates. There is potential for *Y.pestis* to be misidentified and it is essential that any clinician who suspects plague should speak to the microbiologist directly.

Patients with plague need to be nursed in strict respiratory isolation until they have received at least forty-eight hours of antibiotics and are clinically improving. Recommended treatment is with streptomycin 1g intramuscularly bd or gentamicin 5mg/kg IV once daily. Alternative choices include doxycycline 100mg bd IV or ciprofloxacin 400mg bd IV or for treatment of meningitis, chloramphenicol 25mg/kg IV qds. The minimum treatment course should be ten days. Unless a patient receives appropriate treatment within eighteen hours of the onset of symptoms, survival is unlikely. All those who have been in face-to-face contact with a pneumonic plague patient or who have been exposed to an aerosol attack should receive oral doxycycline 100mg bd or ciprofloxacin 500mg bd for seven days. It is also recommended that contacts wear a surgical mask and follow respiratory droplet precautions until they have received forty-eight hours of antibiotics. Plague vaccine is ineffective in preventing primary pneumonic plague and is no longer available.

BOTULISM[4]

Clostridium botulinum produces seven potent neurotoxins (designated types A-G). Although only types A, B, E and rarely type F have been found in cases of human botulism, studies on primates suggest all types are capable of causing human disease. The toxins prevent acetylcholine release from the presynaptic nerve terminal and block neuromuscular transmission. Botulism occurs in three situations: following ingestion of preformed toxin; during *C.botulinum* infection of the gastrointestinal tract (usually in infants); or when the bacteria infects a wound. In addition, three cases of botulism have occurred following inhalation and it is believed that terrorists would be most likely to exploit this route, by producing a botulinum toxin aerosol.

The incubation period for inhalational botulism is likely to depend on the dose of toxin inhaled and could be a few hours to several days. Initial symptoms and signs of botulism include blurred vision, diplopia, ptosis, dysarthria, dysphagia and ataxia with an alert mental status. A descending, symmetrical, progressive skeletal muscle paralysis then follows. Untreated, this can rapidly lead to death from respiratory failure or aspiration pneumonia. Botulism is very difficult to diagnose as it is easily mistaken for other conditions such as Guillain-Barre syndrome (especially Miller-Fisher variant), myasthenia gravis, poliomyelitis, tick paralysis, Lambert-Eaton syndrome, stroke, intoxication with alcohol or drugs and psychiatric illness. It is likely that many cases of food-borne botulism are unrecognised and in one outbreak in Canada, twenty-eight patients were incorrectly diagnosed. Features which help discriminate botulism from other flaccid paralyses are the absence of sensory abnormalities, the prominent cranial nerve palsies compared to the initial mild weakness of limb muscles and the symmetrical nature of the weakness. In food-borne botulism, toxin may be detected in stool, gastric aspirates, vomitus or suspected food, but these

samples will be negative following inhalational exposure. Blood and stool cultures may help exclude wound and gastrointestinal botulism. Serum should be sent for toxin identification, but it is uncertain whether this test would be positive following inhalational exposure.

Any case of suspected botulism should be immediately reported to the Ministry of Health. In a foodborne outbreak, this may help prevent further cases and following inhalational exposure, it may facilitate earlier diagnosis of other cases. An aerosol attack with botulinum toxin is likely to be recognised only after several cases have been diagnosed. The non-specific nature of the early symptoms could prove problematic as persons who believe they have been exposed may experience anxiety-induced subjective weakness. Those with a confirmed history of exposure would require close observation, preferably in hospital to enable treatment to be given at the first sign of symptoms.

Cases of suspected botulism should receive antitoxin without awaiting laboratory confirmation. Once the toxin has bound to its receptor, the antitoxin is ineffective and therefore early administration is essential. The licensed dose is a single 10ml vial, which provides between 5500 and 8500 IU of each of antitoxins A, B and E. If terrorist use of one of the other toxin types is suspected, the US army has an experimental heptavalent antitoxin containing types A-G. Supportive care of patients with botulism is essential. Adequacy of gag and cough reflexes, vital capacity, inspiratory force and oxygen saturation should all be monitored. In botulism, airway obstruction or aspiration is likely to occur before respiratory failure because of the predominant involvement of cranial nerves. Many patients will require intubation and may need to be ventilated for several months. Botulism cannot be spread from person-to-person and respiratory isolation is therefore not required.

A pentavalent toxoid (types ABCDE) has been used for more than thirty years to protect laboratory workers and troops from botulinum toxin. However, immunisation of the population is not feasible due to scarcity of the toxoid. It would not be effective as post-exposure prophylaxis as immunity takes several weeks to develop.

CONCLUSIONS

The threat of bioterrorism is probably now greater than it has ever been before. It is essential that physicians are aware of the diseases which could be caused by biological weapons and how to recognise them. Early diagnosis and appropriate public health intervention could save many lives and prevent serious disruption to society.

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