Clinical guidelines on anthrax, botulism, plague and smallpox

The Physician’s Guide to Communicable Diseases in Singapore was published by the Ministry of the Environment and Tan Tock Seng Hospital in 1998 to provide a convenient and practical clinical reference material on communicable diseases in Singapore. The Guide will be revised soon. In view of the recent events, some of the additional diseases to be included in the revised edition are attached for your advance information.

Anthrax, botulism and smallpox are not legally notifiable in Singapore. However, their presence is of public health importance. All suspected and confirmed cases should be immediately notified to the Quarantine and Epidemiology Department, Ministry of the Environment, at telephone number 1800-731 9222 (Mon to Fri 8:30 am - 5.30 pm, Sat 8:30 am - 1 pm) or 1800-453 2222 (after working hours and public holidays).

Please note that all suspected and confirmed cases of anthrax, botulism, plague and smallpox should be referred and admitted to hospital immediately. Suspected or confirmed cases of anthrax and botulism may be admitted to any public acute hospital. Suspected or confirmed cases of plague and smallpox should be admitted to the Communicable Disease Centre at Tan Tock Seng Hospital. However, seriously ill cases should be sent to the nearest public acute hospital without delay.

ANTHRAX

Disease description

Anthrax is a zoonotic disease caused by the gram-positive spore-forming bacterium, *Bacillus anthracis*. The spores are the usual infective form. There are three forms of anthrax, of which the primary concern for intentional infection by the organism is through inhalation after aerosol dissemination of spores.

- **Cutaneous**

Most common form of naturally occurring anthrax. Humans generally contract the disease when handling contaminated hair, wool, hides, flesh, blood and excreta of infected animals. Usually manifests as a black, necrotic skin lesion.
- Gastrointestinal
  Rare, but highly fatal form that occurs after ingestion of contaminated meat.

- Inhalational
  Most lethal form (mortality > 80%) that occurs following inhalation of spores.

**Incubation period**
- Commonly 1 - 6 days (up to 30 days)

**Clinical features**
- Cutaneous: oedematous skin ulcer covered by black eschar. Satellite vesicles may be present (Fig. 1).
- Gastrointestinal: rapid onset abdominal pain with haemorrhagic ascites.
- Inhalational: fever, malaise, fatigue, cough, mild chest discomfort. May briefly improve after 2-4 days; however within 24 hrs after this brief improvement, respiratory distress and shock occurs. Usually progresses to death within 36 hours. Approximately half will develop hemorrhagic meningitis with concomitant headache, stiff neck and mental status changes. After significant symptoms have appeared, inhalational anthrax is almost always fatal, regardless of treatment.

**Investigations**
- CXR: widened mediastinum without infiltrates in a young or otherwise healthy patient with a typical presentation (Fig. 2).
- Gram stain and culture of blood, CSF (if meningitic), faeces (if GIT involved).

*Figure 1*
Cutaneous Anthrax, black necrotic skin lesion surrounded by marked oedema

*Source: Workshop on Management of Emerging Infectious Diseases organised by Singapore Army Force Medical Corps and United States Army Medical Research Institute of Infectious Diseases*
Management

Treatment should be initiated as soon as diagnosis is suspected; never delay by waiting for confirmation testing. Antibiotic administration at the earliest signs of disease is essential. Empirical treatment using ciprofloxacin or doxycycline; to review when sensitivity is known.

Adults:

(a) IV ciprofloxacin 400mg bd empirically
(b) IV doxycycline 100mg bd (if available)
(c) IV penicillin G 2 million U q 2 hrs - if penicillin-sensitive organism

Children:

(a) IV ciprofloxacin 20-30 mg/kg/day bd (not to exceed 1g/day)
(b) IV doxycycline 2.5 mg/kg bd for patients ≤ 45kg; adult dose if ≥ 45kg.

Chemoprophylaxis

• Prophylaxis should be provided to all persons who may have been directly exposed to the spores. It is critical to administer chemoprophylactic antibiotics as soon as possible after potential exposure. Contacts; ie family, friends, healthcare providers do not require prophylaxis unless they too had been exposed to the spores.

• Oral ciprofloxacin 500mg bd is the recommended first line medication in a situation with anthrax as the presumptive agent.

• Alternatives are oral doxycycline 100mg bd or amoxicillin 500mg 8 hourly if strain is sensitive.

• For children, oral ciprofloxacin 10-15mg/kg/day bd, doxycycline 5mg/kg/day bd, amoxycillin 80mg/kg/day tds.

• Oral antibiotic prophylaxis should continue for at least 60 days.

Isolation precautions

• Standard precautions

• After an invasive procedure or autopsy is performed, the instruments and area used should be thoroughly disinfected with a sporidical agent such as 0.5% sodium hypochlorite.

• No quarantine is needed.

Case fatality

Exceeds 90% once symptoms of inhalational anthrax appear.
Death disposal

- Proper burial and cremation is needed to prevent further spread of the disease.
- Cremation is preferred. Embalming of bodies could be associated with special risks.

BOTULISM

Disease description

Botulinum toxins are a group of seven related neurotoxins (Types A-G) produced by the bacterium, Clostridium botulinum. Most cases of human botulism is caused by toxins types A, B, D or F. These toxins are the most potent neurotoxin known. The toxin can be formed in canned foods and subsequently ingested. The clinical syndrome produced by these toxins is known as botulism.

- Food-borne botulism
  Occurs when a person ingests pre-formed toxin.
- Infant botulism
  Occurs when susceptible infants consumed C. botulinum spores.
- Wound botulism
  Caused by the growth of C. botulinum bacteria in a wound.
  In addition, botulinum toxins can also be inhaled if intentionally released in the form of aerosol.

Incubation period

- Inhalational botulism: time to onset of paralytic symptoms after inhalation may actually be longer than for foodborne cases. Symptoms may appear 12 hr - 36 hours or longer after exposure.
- Food-borne botulism: symptoms appear 2 hr - 10 days (average 12 - 72 hours) after exposure.

Clinical features

- Cranial nerve palsies are prominent in the early stages of disease (Fig. 3). Symptoms include blurred vision due to mydriasis, diplopia, ptosis, and photophobia and dysarthria, dysphonia, and dysphagia. Flaccid skeletal muscle paralysis follows, in a symmetrical, descending, and progressive manner. Collapse of the upper airway may occur due to weakness of the oropharyngeal musculature. As the descending motor weakness involves the diaphragm and accessory muscles of respiration, respiratory failure may occur abruptly. Progression from onset of symptoms to respiratory failure has occurred in as little as 24 hours in cases of severe food-borne botulism.

Figure 3
Botulism: cranial nerve palsies and descending flaccid paralysis

Source: Workshop on Management of Emerging Infectious Diseases organised by Singapore Army Force Medical Corps and United States Army Medical Research Institute of Infectious Diseases
• The autonomic effects of botulism are manifested by typical anticholinergic signs and symptoms such as dry mouth, ileus, constipation, and urinary retention. Nausea and vomiting may occur as non-specific sequelae of an ileus. Dilated pupils (mydriasis) are seen in approximately 50 percent of cases. Sensory symptoms usually do not occur.

**Differential diagnosis**

Guillain-Barre syndrome, myasthenia gravis, stroke, organophosphate poisoning, magnesium intoxication, atropine poisoning.

**Laboratory investigations**

• Blood and faeces for culture.
• Serum can also be sent to identify toxins.

**Management**

• Supportive care, including prompt respiratory support. Intensive and prolonged nursing care may be required for recovery. This may take up to three months for the initial signs of improvement and up to a year for complete resolution of symptoms.
• Antitoxin: early administration is critical to neutralise circulating toxin in patients with symptoms that continue to progress. Antitoxin is less likely to be of benefit if given >72 hours after the onset of symptoms.

**Prophylaxis**

• A pentavalent toxoid of *C. botulinum* toxin types A,B,C,D and E is available as an investigational agent for pre-exposure prophylaxis. The currently recommended primary series is 0,2 and 12 weeks followed by a booster at 1 year.

• Human data are not available to support the recommendation of post-exposure prophylaxis with heptavalent antitoxin.

**Isolation precautions**

Secondary aerosols from affected patients pose no risk of botulism transmission.

Toxin is not absorbed through the skin. There is no risk to person-to-person transmission.

• Standard precautions for healthcare workers
• Decontamination of surfaces contaminated by the toxin can be achieved using soap and water or 0.5% hypochlorite solution.

If contamination of foodstuffs suspected, boiling foods for 10 minutes will destroy toxins.

Quarantine is not necessary.

**Case fatality**

High mortality if no respiratory support.

**SMALLPOX**

**Disease description**

Smallpox is caused by the *Orthopoxvirus*, variola. This acute viral disease is unique to humans. Smallpox has a high case fatality rate and is highly contagious. There are at least 2 strain, variola major and the variola minor.

Variola major: the more severe form with case fatality rate up to 30-50% in susceptible populations.

Variola minor: milder from of the disease with more diminutive pox lesions; case fatality rate of 1-2% in susceptible populations.
Although this disease has been eradicated, there are concerns that the virus is being exploited as a biological weapon.

**Incubation period**

7 -19 days (average 12 days)

**Clinical features**

Acute onset of fever, malaise, rigors, vomiting, headache and backache. 15% of patients developed delirium. Erythematous rash may be seen in some patients.

Exanthem appears 2-3 days in the disease progression together with discrete rash on the face, hands and forearms *(Fig. 4)*.

Rash spread centrally to the trunk. Skin lesions quickly progress from macules to papules and eventually to pustular vesicles. Lesions are more abundant on the face and extremities. This centrifugal distribution is an important diagnostic feature.

In distinct contrast with chickenpox, lesions on various segments of the body remain generally synchronous in their stages of development.

- From 8-14 days after onset, the pustule scabs that leave depressed depigmented scar upon healing.
- Smallpox virus can be readily recovered from scabs throughout convalescence. Therefore, patients should be isolated and considered infectious until all scabs separate.
- Two rare forms of smallpox have been reported.
  a) Purpura variolosa or hemorrhagic type smallpox: 3% of persons with variola major would develop purpura variolosa. Dark, purplish, blotchy flushing of skin appears at the initial stage of the disease. Patients suffer from severe loss of blood into

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**Figure 4**
Smallpox: distribution of skin lesions

*Source: WHO*
skin and internal organs and die before the typical smallpox rash appears.

b) Flat type smallpox: occurs in 5% of people with variola major. Skin lesions of these patients develop more slowly, never raised above the surface of the skin.

**Key differential diagnosis**

Chickenpox, monkeypox, disseminated herpes zoster.

**Laboratory investigations**

Electron microscopy, PCR, viral isolation (culture of pharyngeal swab or lesions)

Guarnieri bodies on Giemsa or modified silver stain.

**Management**

- Supportive care.
- Antibiotics may be used for secondary bacterial infection.

Any confirmed case of smallpox is an international emergency with immediate report made to public health authorities.

**Prophylaxis**

Vaccination after exposure to a case of smallpox may prevent or ameliorate disease. However, supplies of smallpox vaccine are scarce worldwide.

**Isolation precautions**

Isolate patients preferably in negative pressure isolation room. Patients should be considered infectious until all scabs separate and should be quarantined during this period.

Droplet and airborne precaution for a minimum of 17 days following exposure for all persons in direct contact with the index case.

**Case fatality**

30-50%

**PLAGUE**

**Disease description**

Plague is caused by *Yersinia pestis*. It is primarily a disease of rodents and their fleas. It is a severe disease in humans with case fatality rates of 50-60% if left untreated. Plague has been responsible for widespread pandemics with high mortality in the pre-antibiotic era. It was known as the “Black Death” during the fourteenth century, causing an estimated 50 million deaths.

There are three main forms of plague in humans.

Bubonic plague: the result of an insect bite in which the plague bacillus, *Yersinia pestis* travels through the lymphatic system to the nearest lymph node where it forms a swelling. Commonly presents with acute and fulminant onset of non-specific symptoms including fever, malaise, headache, myalgias, nausea, vomiting and abdominal pain. After which the bubo develops. The bubonic form may progress to septicemic and/or pneumonic form.

Septicaemic form: bacteremia is common in patients with bubonic plague. About a quarter of bubonic plague patients progress to clinical septicae-
mia. This may produce thrombosis, necrosis, gangrene and DIVC.

Penumonic plague: an infection of the lung due to either inhalation (primary pneumonic plague) of the organism or spread to the lung from septicaemia. Primary pneumonic plague has an acute and fulminating onset of non-specific symptoms followed within 24 hours by a cough with bloody sputum. The pneumonia progresses rapidly resulting in dyspnea, stridor and cyanosis. Without treatment, the disease terminates with respiratory failure and circulatory collapse. Pneumonic plague is highly contagious.

**Incubation period:**
- Bubonic form: 2-10 days.
- Primary pneumonic form: 1-6 days (average 2-4 days)

**Laboratory investigations**
- Sputum for gram stain and culture.
- Lymph node aspiration, blood, or cerebrospinal fluid samples for culture.

**Medical management:**
Empirical treatment should begin when pneumonic plague is clinically suspected as the disease is almost always fatal if treatment is not initiated within 24 hours of the onset of symptoms.

(a) gentamicin 5mg/kg IM or IV once a day
(b) streptomycin 30mg/kg IM once a day
(c) doxycycline 200mg followed by 100mg bid.
(d) Chloramphenicol 25mg/kg IV loading dose followed by 15mg/kg IV qid is required for the treatment of plague meningitis.

Total duration of treatment is 10-14 days

**Chemoprophylaxis**
Face-to-face contact (within 2 meters) of patients with pneumonic plague or persons possibly exposed to a plague aerosol should be given antibiotic prophylaxis.

(a) doxycycline 100mg bid orally
(b) ciprofloxacin 500mg bid orally
(c) tetracycline 250mg qid orally
(d) chloramphenicol 25mg/kg qid orally.

- Give chemoprophylaxis for 7 days or the duration of risk of exposure plus 7 days.
- Contact of bubonic plague patients need only be observed for symptoms for a week. If symptoms occur, start antibiotics treatment.
- No vaccine is currently available for prophylaxis against pneumonic plague.

**Isolation:**
Suspected pneumonic plague cases require strict isolation with droplet precautions for at least 48 hours of antibiotic therapy; and in confirmed cases, until sputum cultures are negative.

**Case fatality:**
- Untreated bubonic plague: approximately 60%.
- Untreated pneumonic plague: nearly 100%. Survival is unlikely if treatment is delayed beyond 18 hours of infection.
Seroprevalence of adenovirus types 3 and 7 infection in Singapore

Adenoviruses are common pathogens that are often associated with respiratory and gastrointestinal illness and/or conjunctivitis in young children. Adenoviruses 3 and 7 cause both acute keratoconjunctivitis and respiratory tract infections. Adenovirus 7 is known to give rise to severe pneumonia in children with underlying heart or lung disease. It is also commonly associated with meningitis and encephalitis.

Adenoviruses 3 and 7 have been isolated sporadically from clinical specimens since the 1980s by the Department of Pathology, Singapore General Hospital.

To determine the immune status of the population against adenovirus infection in Singapore, sera collected from 545 children and adults from one year to above 50 years of age during the 1992 national serological survey on vaccine-preventable diseases were tested for neutralizing antibodies against adenovirus type 3 and type 7 using the HEp-2 cells at the National Institute of Public Health, Tokyo, Japan. An antibody titre of ≥1:4 was considered positive.

The age-specific prevalence of antibodies to adenovirus types 3 and 7 is shown in Fig. 5.

The survey showed that the seroprevalence of adenovirus type 3 was significantly higher than that of adenovirus type 7 in all age groups. Virtually all the 97 children below 2 years of age were negative for antibody to adenovirus 7. The results confirmed the low level of exposure of the population to adenovirus type 7 over the last 3 decades. The majority of the reinfection are mild or subclinical.

Figure 5
Prevalence of neutralizing antibody to adenovirus types 3 and 7 by age in Singapore

(Based on a research project jointly conducted by the Quarantine & Epidemiology Department, Ministry of the Environment, and the Infectious Disease Surveillance Center, National Institute of Infectious Diseases, Tokyo, Japan. The results of the study have been published in the Japanese Journal of Infectious Diseases, Vol 54, 2001, pg 128-129).
## Cases of specified notifiable diseases, Republic of Singapore, September 2001

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The data in this Bulletin are provisional, based on reports to the Quarantine & Epidemiology Department, Ministry of the Environment, and the Department of Clinical Epidemiology, Tan Tock Seng Hospital. Any comments or questions should be addressed to:

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