

# Medical Classification Of Potential BW Agents 1

## BACTERIA

Table 1 shows those diseases whose causative organisms are considered as potential BW agents. Its contents should not be construed as a sanctioned threat list.

Class	Agent	Disease
Bacterial	<i>Bacillus anthracis</i> <i>Brucella species</i> <i>Vibrio cholerae</i> <i>Escherichia coli</i> <i>Rickettsia typhi</i> <i>Burkholderia mallei</i> <i>Burkholderia pseudomallei</i> <i>Yersinia pestis</i> <i>Coxiella burnetii</i> <i>Rickettsia rickettsii</i> <i>Salmonella species</i> <i>Orientia tsutsugamushi</i> <i>Shigella dysenteriae</i> <i>Francisella tularensis</i> <i>Salmonella typhi</i>	Anthrax Brucellosis Cholera E. Coli Epidemic typhus Glanders Meliodosis Plague Q fever Rocky Mountain spotted fever Salmonellosis Scrub typhus Shigellosis Tularaemia Typhoid fever
Viral	Junin virus Machupo virus Chikungunya virus Crimean-Congo haemorrhagic fever virus Ebola virus Eastern equine encephalomyelitis virus European tick borne encephalitis virus Influenza viruses Hantaviruses  Lassa virus Marburg virus Monkeypox virus Omsk haemorrhagic fever virus Rift Valley fever virus Flaviviruses  Variola virus Venezuelan equine encephalitis virus Western equine encephalitis virus Yellow fever virus	Argentine haemorrhagic fever Bolivian haemorrhagic fever Chikungunya fever Crimean-Congo haemorrhagic fever Ebola Eastern equine encephalitis European tick borne encephalitis Influenza Haemorrhagic fever with renal syndrome Lassa Marburg Monkeypox Omsk haemorrhagic fever Rift Valley fever Russian Spring-Summer encephalitis group Smallpox Venezuelan equine encephalitis Western equine encephalitis Yellow fever
Toxins	Aflatoxins Botulinum toxins <i>Clostridium perfringens</i> toxins Palytoxin Ricans Saxitoxins Staphylococcal enterotoxins Tetradotoxin Trichothecene mycotoxins	Aflatoxin poisoning Botulism Clostridium Perfringens toxin poisoning Palytoxin poisoning Ricin poisoning Saxitoxin poisoning Staphylococcal enterotoxin poisoning Tetradotoxin poisoning Mycotoxin poisoning

Table 1. Potential Biological Agent.

## CLINICAL DATA SHEETS FOR SELECTED BW AGENTS

### Introduction

The following information provides clinical information to assist in the recognition, diagnosis and management of selected diseases, well recognised for their potential as biological weapons. It is not intended to be comprehensive, nor should it be interpreted as a sanctioned "threat list."

Likely agents are:

### Bacteria.

- Anthrax.
- Brucellosis.
- Cholera.
- Glanders.
- Meliodosis.
- Plague.
- Q-Fever.
- Tularaemia.

### Viruses.

- Crimean-Congo Haemorrhagic Fever.
- Influenza.
- Rift Valley Fever.
- Smallpox.
- Venezuelan Equine Encephalitis.

### Toxins.

- Botulinum Toxin.
- *Clostridium perfringens* Toxins.
- Ricin.
- Saxitoxin.
- Staphylococcal Enterotoxin B.
- Tricothecene Mycotoxins.

Many products referenced in this annex are currently considered investigational new drugs (IND). This indicates that the product (drug, vaccine, antitoxin, etc) has been shown to be safe and effective in animal studies and has been approved for limited use as an investigational product in humans. In general, IND products must be obtained through official channels from the government of the producing nation and administered under a research protocol approved by a recognised institutional review board.

Viruses and Toxins are considered in Medical Classification of Potential BW Agents 2 and 3 respectively.

## Anthrax



Fig 1. Scanning electronmicrograph *Bacillus anthracis*.

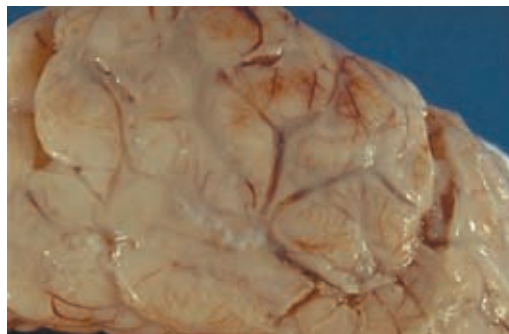


Fig 2. *Anthrax meningitis*.

### Clinical Syndrome

**Characteristics.** Anthrax is a zoonotic disease caused by *Bacillus anthracis*. The organism sporulates readily in the environment and the spore is the infectious form. Under natural conditions, humans become infected by contact with infected animals or contaminated animal products. Human anthrax is usually manifested by cutaneous lesions. A BW attack with anthrax spores delivered by aerosol would primarily cause inhalation anthrax, a rare form of the naturally occurring disease. Consumption

of contaminated material leads to gastrointestinal anthrax. Many of the effects of anthrax are mediated through its toxin, which consists of 3 components: the Protective Antigen (PA), Lethal Factor (LF) and Edema factor (EF).

**Clinical Features.** The inhalation form begins after an incubation period normally 1-6 days but may be up to 60 days, believed to be dependant on dose and susceptibility factors. Onset is gradual and non-specific, with fever, malaise, fatigue, nausea, vomiting and abdominal pain sometimes in association with a non-productive cough and mild chest discomfort. In some cases, there may be a short period of improvement. The initial symptoms are followed in 2-3 days by the abrupt development of severe respiratory distress with dyspnoea, diaphoresis, stridor, and cyanosis. Physical findings may include evidence of pleural effusions, oedema of the chest wall, and meningitis. Chest X-ray commonly reveals a dramatically widened mediastinum, often with pleural effusions. Shock and death usually follow within 24-36 hours of respiratory distress onset.

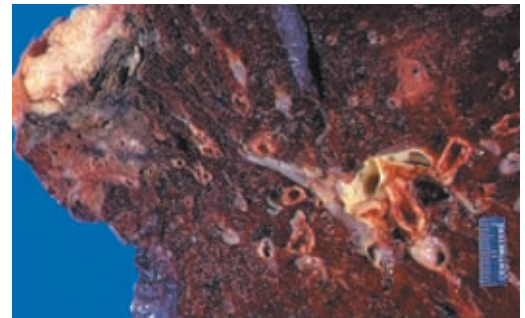


Fig 3. *Anthrax pneumonia*.



Fig 4. *Respiratory anthrax showing widened mediastinum.*

### Diagnosis

**Routine Laboratory Findings.** Laboratory evaluation may reveal a neutrophilic leucocytosis. Pleural and cerebrospinal fluids are usually haemorrhagic.

**Differential Diagnosis.** An epidemic of inhalation anthrax in its early stage with non-specific symptoms could be confused with a wide variety of viral, bacterial, and fungal infections. The onset resembles influenza with frequent non-productive cough and

occasional sore throat but coryza is notably absent. Progression over 2-3 days with the sudden development of severe respiratory distress followed by shock and death in 24-36 hours in essentially all untreated cases eliminates diagnoses other than inhalation anthrax. The presence of a widened mediastinum on chest X-ray, in particular, should alert one to the diagnosis. Other suggestive findings include chest-wall oedema, haemorrhagic pleural effusions, and haemorrhagic meningitis. Other diagnoses to consider include aerosol exposure to SEB; but in this case onset would be more rapid after exposure (if known), and no prodrome would be evident prior to onset of severe respiratory symptoms. Mediastinal widening on chest X-ray will also be absent. Patients with plague or tularaemia pneumonia will have more obvious pulmonary infiltrates and clinical signs of pneumonia.

**Specific Laboratory Diagnosis.** *Bacillus anthracis* will be readily detectable by blood culture with routine media. Smears and cultures of pleural fluid and abnormal cerebrospinal fluid may also be positive. The previous use of antibiotics may cause a false negative result on culture. Impression smears of mediastinal lymph nodes and spleen from fatal cases should be positive. Immunoassays to detect anthrax toxins in the blood are diagnostic. Nasal swabs may be of use. PCR is available.

**Therapy.** Almost all cases of inhalation anthrax in which treatment was begun after patients were symptomatic have been fatal, regardless of treatment. Historically, penicillin has been regarded as the treatment of choice, with 2 megaunits given intravenously every 2 hours. The current recommendations for prophylaxis and treatment suggest ciprofloxacin and other fluoroquinolones as the first choice and tetracyclines as the primary alternative. Penicillin is effective but the incidence of penicillin resistance in naturally occurring anthrax may be as high as 15%. Other drugs that could be used in hospitalised patients include gentamicin, other aminoglycosides, clindamycin and chloramphenicol. It is not difficult to induce resistance to penicillin, tetracyclines, erythromycin, and many other antibiotics through laboratory manipulation of organisms. All naturally occurring strains tested to date have been sensitive to chloramphenicol, gentamicin, and ciprofloxacin. On the basis of recent therapeutic

evidence combined antibiotic therapy may be beneficial. In the absence of information concerning antibiotic sensitivity, treatment should be instituted at the earliest signs of disease according to Table 2.

Supportive therapy for shock, fluid volume deficit, and adequacy of airway may all be needed. Drainage of effusions may be beneficial. Anti-toxin therapy has been suggested as a possible adjunct but currently no products are available. There is no human to human transmission and ROM is not required.

### Prophylaxis

**Vaccine.** Licensed vaccines consist of alum-precipitated preparation of purified *B. anthracis* protective antigen (PA) and have been shown to be effective in preventing or significantly reducing the incidence of inhalation anthrax. Limited human data suggest that after completion of the primary immunising course protection against both cutaneous and inhalation anthrax is afforded. Studies in rhesus monkeys indicate that good protection is afforded after two doses (10-16 days apart) for up to 2 years. It is likely that 2 doses in humans is protective as well, but there is too little information to draw firm conclusions. As with all vaccines, the degree of protection depends upon the challenge dose; vaccine-induced protection is undoubtedly overwhelmed by extremely high spore challenge. At least 3 doses of the vaccine are recommended for prophylaxis against inhalation anthrax. After the primary course annual boosters are given to maintain protection. Contraindications for use are sensitivity to vaccine components and/or history of clinical anthrax. Reactogenicity is mild to moderate. Some recipients will experience mild discomfort at the inoculation site for up to 72 hours (tenderness, erythema, oedema, pruritus), while a smaller proportion will experience more severe local reactions (potentially limiting use of the extremity for 1-2 days). Modest systemic reactions (myalgia, malaise, low-grade fever) are uncommon, and severe systemic reaction (anaphylaxis, which precludes additional vaccination) is rare. The vaccine should be stored at 2-8°C, refrigerator temperature not frozen.

**Antibiotics.** Choice of antibiotics for prophylaxis is guided by the same principles as that for treatment; ie. it is relatively easy to produce a penicillin-resistant organism in

Category	Intravenous Therapy	Oral Therapy	Duration
Adults and Immunocompromised personnel	Ciprofloxacin 400 mg every 12 hours OR Doxycycline 100 mg every 12 hours AND one or two additional antimicrobials	Ciprofloxacin 500 mg every 12 hours OR Doxycycline 100 mg every 12 hours	IV treatment initially. Switch to oral antimicrobial therapy when clinically appropriate. Continue for 60 days (IV and po combined)

Table 2. Treatment of Inhalational Anthrax Patients.

the laboratory, and possible, albeit somewhat more difficult, to induce tetracycline resistance. Therefore, if there is information indicating that a biological weapon attack is imminent, prophylaxis with ciprofloxacin (500 mg po every 12 hours), or doxycycline (100 mg po every 12 hours) is recommended. Other fluoroquinolones and tetracyclines are suitable alternative chemoprophylactics. Should the attack be confirmed as anthrax, antibiotics should be continued for at least 4 weeks in all exposed personnel previously fully vaccinated. Individual nations may elect to vaccinate all potentially exposed non- or partially-immunised personnel who will then require antibiotics until the third dose of vaccine has been given. Upon discontinuation of antibiotics, patients should be closely observed; if clinical signs of anthrax occur, patients should be treated as indicated above. If vaccine is not available, contraindicated or contrary to national policy, antibiotics should be continued for at least 60 days and the patient must be closely observed upon discontinuation of therapy.

## Brucellosis

### Clinical Syndrome

*Characteristics.* Brucellosis is a systemic zoonotic disease caused by one of four species of bacteria: *Brucella melitensis*, *B. abortus*, *B. suis* and *B. canis*; virulence for humans decreases somewhat in the order given. These bacteria are small gram-negative, aerobic, non-motile coccobacilli that grow within monocytes and macrophages. They reside quiescently in tissue and bone marrow, and are extremely difficult to eradicate even with antibiotic therapy. Their natural reservoir is domestic animals, such as goats, sheep, and camels (*B. melitensis*), cattle (*B. abortus*) and pigs (*B. suis*). *B. canis* is primarily a pathogen of dogs, and only occasionally causes disease in humans. Humans are infected when they inhale contaminated aerosols, ingest raw (unpasteurized) infected milk or meat, or have abraded skin or conjunctival surfaces that come into contact with the bacteria. Laboratory infections are quite common, but there appears to be no human-to-human transmission; isolation of infected patients is, therefore, not required. *Brucella species* have long been considered potential candidates for use in BW. The organisms are readily lyophilised, perhaps enhancing their infectivity. Under selected environmental conditions (for example, darkness, cool temperatures, high CO<sub>2</sub>), persistence for up to 2 years has been documented. When used as a BW agent, *Brucella species* would be most likely to be delivered by the aerosol route; the resulting infection would be expected to mimic natural disease.

*Clinical Features.* Brucellosis presents after

an incubation period normally ranging from 3–4 weeks, but may be as short as 1 week or as long as several months. Clinical disease presents typically as an acute, non-specific febrile illness with chills, sweats, headache, fatigue, myalgias, arthralgias, and anorexia. Cough occurs in 15–25%, but the chest X-ray usually is normal. Complications include sacroiliitis, arthritis, vertebral osteomyelitis, epididymo-orchitis and rarely endocarditis. Physical findings include lymphadenopathy in 10–20% and splenomegaly in 20–30% of cases. Untreated disease can persist for months to years, often with relapses and remissions. Disability may be pronounced. Lethality may approach 6% following infection with *B. melitensis*, but the disease is rarely fatal (0.5% or less) after infection with other serotypes (and when, it is usually after endocarditis develops).

### Diagnosis

*Routine Laboratory Findings* - Noncontributory.

*Differential Diagnosis.* The initial symptoms of brucellosis are usually non-specific. The differential diagnosis is therefore very broad and includes bacterial, viral, and mycoplasma infections. The systemic symptoms of viral and mycoplasma illnesses, however, are usually present for only a few days, while they persist for prolonged periods in brucellosis. Brucellosis may be indistinguishable clinically from the typhoidal form of tularaemia or from enteric fever itself.

*Specific Laboratory Diagnosis.* Serology by agglutination or enzyme-linked immunosorbent assay may suggest the diagnosis. A definitive diagnosis of brucellosis is established by culture of blood or bone marrow, which may be positive in up to 70% and 90% of cases, respectively. PCR is available.

*Therapy.* The recommended treatment is doxycycline (200 mg/day) plus rifampicin (900 mg/day) for 6 weeks. Alternative effective treatment consists of doxycycline (200 mg/day) for 6 weeks plus streptomycin (1 gm/day) for 3 weeks. Trimethoprim-sulphamethoxazole given for 4–6 weeks is less effective. In 5–10% of cases, there may be relapse or treatment failure. Laboratory infections with brucellosis are quite common, but there is no human-to-human transmission and ROM is not required.

*Prophylaxis.* Killed and live attenuated human vaccines have been available in many countries but are of unproven efficacy. There is no information on the use of antibiotics for prophylaxis against human brucellosis, but 3 weeks prophylaxis with rifampicin and doxycycline should be effective.

## Cholera

### Clinical Syndrome

*Characteristics.* Cholera is a diarrhoeal

disease caused by *Vibrio cholerae*, a short, curved, gram-negative bacillus. Humans acquire the disease by consuming water or food contaminated with the organism. The organism multiplies in the small intestine and secretes an enterotoxin that causes secretory diarrhoea. When employed as a BW agent, *V. cholerae* will most likely be used to contaminate water supplies.

**Clinical Features.** Cholera may present as mild diarrhoea or as a fulminant disease characterised by profuse watery diarrhoea with fluid losses exceeding 5 to 10 litres or more per day. Without treatment, death may result from severe dehydration, hypovolaemia and shock. Vomiting is often present early in the illness and may complicate oral replacement of fluid losses. There is little or no fever or abdominal pain

### Diagnosis

**Routine Laboratory Findings.** On microscopic examination of stool samples there are few or no red cells or white cells. Serum electrolytes may demonstrate hypokalaemia or if inappropriate fluid replacement has been given, may show hypernatraemia or hyponatraemia. Acidosis and renal failure may accompany severe dehydration.

**Differential Diagnosis.** Watery diarrhoea can also be caused by food- and water-borne pathogens (enterotoxigenic *E coli*, rotavirus or other viruses, other *Vibrio* species), or food poisoning due to ingestion of preformed toxins such as those of *Clostridium perfringens*, *Bacillus cereus*, or *Staphylococcus aureus*.

**Specific Laboratory Diagnosis.** Vibrios can be identified in stool by darkfield or phase contrast microscopy, and *V. cholerae* can be grown on a variety of culture media. Bacteriologic diagnosis is not necessary before treating cholera or related watery diarrhoea. Laboratory tests examining for cholera toxin are available.

**Therapy.** Treatment of cholera depends primarily on replacement of fluid and electrolyte losses. This is best accomplished using oral rehydration therapy with the World Health Organization solution (3.5 g NaCl, 2.5 g NaHCO<sub>3</sub>, 1.5 g KCl and 20 g glucose per litre). Intravenous fluid replacement is occasionally needed when vomiting is severe, when the volume of stool output exceeds 7 litres/day, or when severe dehydration with shock has developed. Antibiotics will shorten the duration of diarrhoea and thereby reduce fluid losses. Ciprofloxacin is highly effective (500 mg every 12 hours). Tetracycline (250 mg every 6 hr for 3-5 days) or doxycycline (200 mg initially followed by 100 mg every 12 hr for 3-5 days) is generally adequate. Other effective drugs include ampicillin (250 mg every 6 hr for 5 days) and trimethoprim sulphamethoxazole (one tablet every 12 hrs for 3-5 days). There is no direct human-to-human transmission therefore ROM is not required.

**Prophylaxis.** Improved oral cholera vaccines are presently being tested. Vaccination with the currently available killed suspension of *V. cholerae* provides about 50% protection that lasts for no more than 6 months. The initial dose is 2 injections given at least 1 week apart with booster doses every 6 months. The live attenuated lyophilised CVD 103 HgR vaccine is a single dose vaccine providing protection from 7 days post-vaccination for 6 months. An alternate whole cell inactivated vaccine plus recombinant b subunit toxin is administered in 2 doses given at an interval of 1 - 6 weeks with protection beginning 7 days after the second dose and lasting for a year.

## Glanders

### Clinical Syndrome

**Characteristics.** Glanders is caused by *Burkholderia mallei*, a gram-negative bacillus. *B. mallei* is primarily noted for producing disease in horses, mules, and donkeys. The disease is not widespread however, and in the past man has seldom been infected, despite frequent and often close contact with infected animals. Human cases have occurred primarily among veterinarians, horse and donkey caretakers, abattoir workers, and laboratory personnel. There is considerable evidence that *B. mallei* was used by the Japanese in WWII. In a BW attack the primary threat would be an aerosol release.

**Clinical Features.** Infection occurs by the organism invading the nasal, oral, and conjunctival mucous membranes, by inhalation into the lungs, and by invading abraded or lacerated skin. Glanders may occur in an acute localised form, as an acute pulmonary infection, or as an acute fulminant, rapidly fatal, sepsis. The incubation period ranges from 10- 14 days, depending on the inhaled dose and agent virulence. The septicaemic form begins suddenly with fever, rigors, sweats, myalgias, pleuritic chest pain, granulomatous or necrotising lesions, generalised erythroderma, jaundice, photophobia, lacrimation, and diarrhoea. Physical examination may reveal fever, tachycardia, cervical adenopathy and mild hepatomegaly or splenomegaly. Chest radiographs may show miliary nodules (0.5-1.0 cm) and/or a bilateral bronchopneumonia, segmental, or lobar pneumonia, consolidation, and cavitating lung lesions.

### Diagnosis

**Routine Laboratory Findings.** Gram stain of lesion exudates reveals small gram negative, bipolar bacteria. These stain irregularly with methylene blue or Wright's Stain. Blood cultures are usually negative until the patient is moribund but *B. mallei* can be cultured from infected secretions. The organisms can be cultured and identified with standard bacteriological media. The addition of 1-5%

glucose, 5% glycerol, or meat infusion nutrient agar may accelerate growth. Primary isolation requires 48 hours at 37.5° C.

**Differential Diagnosis.** Glanders, melioidosis, and smallpox may present with diffuse pustular rashes; strict isolation and ROM is indicated until smallpox can be excluded. Contact precautions are indicated while caring for patients with skin involvement. Glanders, melioidosis, and smallpox may present as acute pulmonary disease with purulent sputum. Respiratory isolation pending exclusion of plague is prudent if sputum studies disclose gram-negative bacilli with bipolar “safety pin” appearance when using Wright’s or methylene blue stains.

**Specific Laboratory Diagnosis.** Agglutination tests are not positive for 7-10 days, and a high background titre in normal sera (1:320 to 1:640) makes interpretation difficult. Complement fixation tests are more specific and are considered positive if the titre is equal to, or exceeds 1:20. PCR is available.

**Therapy.** The recommended therapy will vary with the type and severity of the clinical presentation.

The following oral regimens have been suggested for localised disease: amoxicillin-clavulanate 60 mg/kg/day in 3 divided doses; tetracycline 40 mg/kg/day in 3 divided doses; or trimethoprim-sulphamethoxazole (TMP 4 mg/kg/day-sulpha 20 mg/kg/day) in 2 divided doses. The duration of treatment should be for 60 – 150 days.

If the patient has localised disease with signs of mild toxicity, then a combination of 2 of the oral regimens is recommended for a duration of 30 days, followed by monotherapy with either amoxicillin-clavulanate or trimethoprim-sulphamethoxazole for 60 – 150 days. If extrapulmonary suppurative disease is present, then therapy should continue for 6-12 months. Surgical drainage of abscesses may be required.

For severe disease, parental therapy with ceftazidime 120 mg/kg/day in 3 divided doses combined with trimethoprim-sulphamethoxazole (TMP 8 mg/kg/day – sulfa 40 mg/kg/day) in 4 divided doses for 2 weeks, followed by oral therapy for 6 months.

Other antibiotics that have been effective in experimental infection in hamsters include doxycycline, rifampicin and ciprofloxacin. The limited number of infections in humans has precluded therapeutic evaluation of most of the antibiotic agents; therefore, most antibiotic sensitivities are based on animal and *in vitro* studies. Various isolates have markedly different antibiotic sensitivities; therefore, each isolate should be tested for its own resistance pattern.

**Prophylaxis.** At this time there is no vaccine available for human use and pre-

exposure or post-exposure prophylaxis is available.

**Control.** There is no human-to-human transmission and ROM is not required.

## Melioidosis

### Clinical Syndrome

**Characteristics.** Melioidosis is an infectious disease of humans and animals caused by *Burkholderia pseudomallei*, a Gram-negative bacillus. It is especially prevalent in South East Asia but has been described from many countries around the world. The disease has a variable and inconstant clinical spectrum. A BW attack with this organism would most likely be by the aerosol route.

**Clinical Features.** Infection by inoculation results in a subcutaneous nodule with acute lymphangitis and regional lymphadenitis, generally with fever. Pneumonia may occur after inhalation or haematogenous dissemination of infection. It may vary in intensity from mild to fulminant, usually involves the upper lobes, and often results in cavitation. Pleural effusions are uncommon. An acute fulminant septicæmia may occur characterised by rapid appearance of hypotension and shock. A chronic suppurative form may involve virtually any organ in the body.

### Diagnosis

**Routine Laboratory Findings.** The white blood cell count may range from normal to 20,000 per mm<sup>3</sup>, and a mild anaemia may develop during the illness.

**Differential Diagnosis.** Melioidosis should be considered in the differential diagnosis of any febrile illness, especially if multiple pustular skin or subcutaneous lesions develop, if the illness presents with fulminant respiratory failure, or there is a chest X-ray pattern suggestive of tuberculosis but without acid-fast bacilli on smear.

**Specific Laboratory Diagnosis.** Microscopic examination of sputum or purulent exudates will reveal small, Gram-negative bacilli with bipolar staining using methylene blue or Wright’s stain. *B. pseudomallei* can be cultured on routine media and identified by standard bacteriologic procedures. A number of serological tests are useful in diagnosis when they show a fourfold titre rise in paired sera. PCR is available.

**Therapy.** Antibiotic therapy is difficult and prolonged courses are required to reduce the incidence of relapse. Treatment starts with a minimum of 2 weeks intravenous therapy using ceftazidime (1120 mg/kg/day in 3 divided doses) in combination with another antibiotic or doxycycline (200mg daily), followed by up to 6 months of oral therapy using

amoxicillin-clavulanic acid, trimethoprim-sulphamethoxazole or other drugs at the standard dose.

*Prophylaxis.* There are no means of immunisation. Vigorous cleansing of abrasions and lacerations may reduce the risk of disease after inoculation of organisms into the skins.

*Control.* There is no human-to-human transmission and ROM is not required.



Fig 5. Septicaemic plague.

## Plague

### Clinical Syndrome

*Characteristics.* Plague is a zoonotic disease caused by *Yersinia pestis*. Under natural conditions humans become infected as a result of contact with rodents, and their fleas. The transmission of the gram-negative coccobacillus is by the bite of the infected flea, *Xenopsylla cheopis*, the oriental rat flea, or *Pulex irritans*, the human flea. Under natural conditions, 3 syndromes are recognised: bubonic, primary septicaemic, or pneumonic. A proportion of cases of bubonic plague develop pneumonia, which spreads by droplets to cause primary pneumonic plague in susceptible contacts thereafter. In a BW scenario, the plague bacillus could be delivered via contaminated vectors (fleas) causing the bubonic type or, more likely, via aerosol causing the pneumonic type, which is highly contagious.



Fig 6. Pneumonic plague.

*Clinical Features.* In bubonic plague, the incubation period ranges from 2 to 10 days. The onset is acute and often fulminant with malaise, high fever, and one or more tender lymph nodes. Inguinal lymphadenitis (bubo) predominates, but cervical and axillary lymph nodes can also be involved. The involved nodes are tender, fluctuant, and necrotic. Bubonic plague may progress spontaneously to the septicaemic form with organisms spread to the central nervous system, lungs (producing pneumonic disease) and elsewhere. The mortality is 50% in untreated patients with the terminal event being circulatory collapse, haemorrhage, and peripheral thrombosis. In primary pneumonic plague, the incubation period is 2 to 3 days. The onset is acute and fulminant with malaise, high fever, chills, headache, myalgia, cough with production of a bloody sputum, and toxæmia. The pneumonia progresses rapidly, resulting in dyspnoea, stridor, and cyanosis. In untreated patients, the mortality is 100% with the terminal event being respiratory failure, circulatory collapse, and a bleeding diathesis.

*Presumptive.* Presumptive diagnosis can be made by identification of the Gram-negative coccobacillus with safety-pin bipolar staining organisms in Giemsa or Wayson's stained slides from a lymph node needle aspirate, sputum, or cerebrospinal fluid (CSF) samples. When available, immunofluorescent staining is very useful. Elevated levels of antibody to *Y. pestis* in a non-vaccinated patient may also be useful for retrospective confirmation.

*Definitive.* *Y. pestis* can be readily cultured from blood, sputum, and bubo aspirates. Most naturally occurring strains of *Y. pestis* produce an "FI" antigen in vivo which can be detected in serum samples by immunoassay. A fourfold rise of *Y. pestis* antibody levels in paired serum samples is also diagnostic.



Fig 7. Scanning electronmicrograph of *Yersinia pestis*.

*Differential.* Buboes may be confused with tularaemia adenitis. The systemic form of the disease with signs of shock and bleeding has to be differentiated from meningococcaemia, enteric Gram-negative sepsis, and rickettsiosis as well as viral haemorrhagic fevers. In pneumonic plague, tularaemia, anthrax, and staphylococcal enterotoxin B (SEB) agents need to be considered. Continued deterioration without stabilisation effectively rules out SEB. The presence of a widened mediastinum on chest X-ray should alert one to the diagnosis of anthrax.

*Therapy.* Strict isolation procedures for all cases are indicated, and ROM may be considered. Standard doses of gentamicin and other aminoglycosides, fluoroquinolones, tetracyclines, and chloramphenicol are highly effective if begun early. Significant reduction in morbidity and mortality is possible if antibiotics are given within the first 24 hours after symptoms of pneumonic plague develop. Ciprofloxacin 400mg iv every 12 hours or 500mg po every 12 hours or doxycycline 200mg daily for 10 days are currently recommended. Supportive management of life-threatening complications from the infection, such as shock, hyperpyrexia, convulsions, and disseminated intravascular coagulation (DIC), need to be initiated as they develop.

*Prophylaxis.* A killed whole-cell vaccine is licensed in Australia but is only effective against the bubonic form. Live-attenuated vaccines are available elsewhere but are highly reactogenic and without proven efficacy against aerosol challenge.

## Q Fever

### Clinical Syndrome

*Characteristics.* Q fever is a zoonotic disease caused by a rickettsia, *Coxiella burnetii*. The organism is very resistant and survives for long periods in the environment. The most common animal reservoirs are sheep, cattle and goats, and it is particularly concentrated in parturition fluids. Humans acquire the disease by inhalation of particles contaminated with the organisms. A BW attack would cause disease similar to that occurring naturally.

*Clinical Features.* Following an incubation period of 10-20 days, Q fever generally occurs as a self-limiting febrile illness lasting 2 days to 2 weeks. Pneumonia occurs frequently, usually manifested only by an abnormal chest X-ray. A non-productive cough and pleuritic chest pain occur in about 25% of patients with Q fever pneumonia. Complications include chronic fatigue, chronic hepatitis, endocarditis, aseptic meningitis, encephalitis, and osteomyelitis.

### Diagnosis

*Routine Laboratory Findings.* The white blood cell count is elevated in 30% of patients. Most patients with Q fever have a mild elevation of hepatic transaminase levels.

*Differential Diagnosis.* Q fever usually presents as an undifferentiated febrile illness, or a primary atypical pneumonia, which must be differentiated from pneumonia caused by mycoplasma, legionnaire's disease, psittacosis or *Chlamydia pneumoniae*. More rapidly progressive forms of pneumonia may resemble bacterial pneumonias including tularaemia or plague.

*Specific Laboratory Diagnosis.* Identification of organisms by staining sputum is not helpful. Isolation of the organism is difficult and impractical. The diagnosis can be confirmed serologically.

*Therapy.* Tetracycline (250 mg every 6 hours) or doxycycline (100 mg every 12 hours) for 5-7 days is the treatment of choice.

*Prophylaxis.* An Australian vaccine is available, but prior testing for immunity is required. Administration of this vaccine in immune individuals may cause severe cutaneous reaction including necrosis at the inoculation site. This is avoided by the use of a skin sensitivity test a few days prior to the vaccination. Subsequent vaccination of non-reactors with a single dose of a killed suspension of *C. burnetii* provides complete protection against naturally occurring Q fever but <90% protection against experimental aerosol exposure in human volunteers. Protection lasts for at least 5 years.

*Control.* There is no human-to-human transmission and ROM is not required.

## Tularaemia

### Clinical Syndrome

*Characteristics.* Tularaemia is a zoonotic disease caused by *Francisella tularensis*, a Gram-negative bacillus. Humans acquire the disease under natural conditions through inoculation of skin or mucous membranes with blood or tissue fluids of infected animals, or bites of infected deerflies, mosquitoes, or ticks. Less commonly, inhalation of contaminated dusts or ingestion of contaminated foods or water may produce clinical disease. A BW attack with *F. tularensis* delivered by aerosol would primarily cause septicaemic (typhoidal) or pneumonic symptoms of tularaemia, with a mortality of 30% untreated (higher than the 5 - 10% mortality of naturally acquired disease). Many exposed individuals would develop pneumonic tularaemia (primary or secondary), but clinical pneumonia may be absent or non-evident.



Fig 8. Tularaemia Lymphadenopathy.

### Clinical Features

A variety of clinical forms of tularaemia are seen, depending upon the route of inoculation and virulence of the strain. In humans, as few as 10-50 organisms will cause disease if inhaled or injected intradermally, whereas  $10^8$  organisms are required with oral challenge. Under natural conditions, ulceroglandular tularaemia generally occurs about 3 days after intradermal inoculation (range 2-10 days) and manifests as regional lymphadenopathy, fever, chills, headache, and malaise, with or without a cutaneous ulcer. In those 5-10% of cases with no visible ulcer, the syndrome may be called glandular tularaemia. Primary ulceroglandular disease confined to the throat is referred to as pharyngeal tularaemia. Oculoglandular tularaemia occurs after inoculation of the conjunctivae with a hand or fingers contaminated by tissue fluids from an infected animal. Gastrointestinal tularaemia occurs after drinking contaminated ground water, and is characterised by abdominal pain, nausea, vomiting, and diarrhoea.



Fig 9. Tularaemia Skin Lesion.

Bacteraemia is probably common after primary intradermal, respiratory, or gastrointestinal infection with *F. tularensis* and may result in septicaemic or "typhoidal" tularaemia. The typhoidal form also may occur as a primary condition in 5-15% of naturally-occurring cases; clinical features include fever, prostration, and weight loss, but without adenopathy. Diagnosis of primary typhoidal tularaemia is difficult, as signs and symptoms are non-

specific and there frequently is no suggestive exposure history. Pneumonic tularaemia is a severe atypical pneumonia that may be fulminant, and can be primary or secondary. Primary pneumonia may follow direct inhalation of infectious aerosols, or may result from aspiration of organisms in cases of pharyngeal tularaemia. Pneumonic tularaemia causes fever, headache, malaise, sub-sternal discomfort, and a non-productive cough; radiological evidence of pneumonia or mediastinal lymphadenopathy may or may not be present.

### Diagnosis

*Routine Laboratory Findings* - "None Specific."

*Differential Diagnosis.* The clinical presentation of tularaemia may be severe, yet non-specific. Differential diagnoses include other causes of persistent fever, such as typhoidal syndromes (for example, salmonella, rickettsiae, malaria) or pneumonic processes (for example, plague, mycoplasma, SEB). A clue to the diagnosis of tularaemia delivered as a BW agent might be a temporo-spatial cluster of patients presenting with similar systemic illnesses, a proportion of whom will have a non-productive pneumonia.

*Specific Laboratory Diagnosis.* Identification of organisms by staining ulcer fluids or sputum is generally not helpful. Routine culture is difficult, due to unusual growth requirements and/or overgrowth of commensal bacteria. Blood culture is occasionally positive. Rapid antigen detection tests have been developed. PCR is available. The diagnosis can be established retrospectively by serology.

*Therapy.* At least 14 days of treatment is required. Gentamicin and other aminoglycosides are effective at standard doses. Successful treatment has been reported with ciprofloxacin. Tetracyclines and chloramphenicol are also effective, but are associated with a significant relapse rate. Although the organism is sensitive to cephalosporins *in vitro* they do not work in clinical cases. Laboratory-related infections with this organism are very common, human-to-human spread is unusual and ROM is not required.

*Prophylaxis.* A live, attenuated tularaemia vaccine is available as an investigational new drug (IND) in the US. This vaccine has been administered to more than 5,000 persons without significant adverse reactions and is of proven effectiveness in preventing laboratory-acquired typhoidal tularaemia. Its effectiveness against the concentrated bacterial challenge expected in a BW attack is unproven. Current recommendations for prophylaxis against tularaemia suggest the use of ciprofloxacin (500mg every 12 hours).

## Medical Classification Of Potential BW Agents 2

### VIRUSES

#### Crimean-Congo Haemorrhagic Fever

##### Clinical Syndrome

*Characteristics.* Crimean-Congo Haemorrhagic Fever (CCHF) is a viral disease. The virus is transmitted by ticks, principally of the genus *Hyalomma*, with intermediate vertebrate hosts varying with the tick species. The disease was first recognised in the Crimea, but occurs over most of Africa, the Middle East, the Balkans, the former USSR, and eastern China. Little is known about variations in the virus' properties over the huge geographic area involved. Humans become infected through tick bites, crushing an infected tick, or at the slaughter of viraemic livestock. Domestic animals become infected but do not have significant disease. In naturally occurring epidemics, cases do not show narrow clustering and person-to-person spread is rare. However, nosocomial spread appears to occur. CCHF could be delivered by aerosol or vectors.

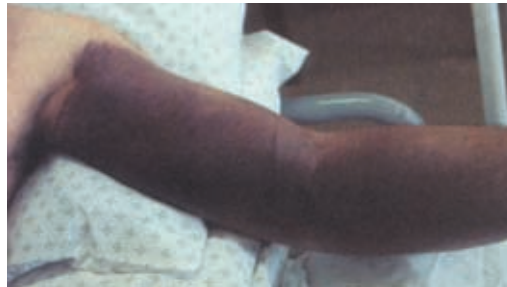


Fig 1. Congo Crimean haemorrhagic fever.

##### Clinical Features

Typical cases present with sudden onset of fever and chills 3-12 days after tick exposure. Flushing, conjunctival injection, and mild hypotension may be present. After 2-3 days, perhaps with a temporary remission of fever, the patient develops bleeding manifestations such as petechiae, ecchymoses, oozing from puncture sites, melaena, haematuria, and gastrointestinal (GI) haemorrhage. Crimean-Congo Haemorrhagic Fever may cause quite severe ecchymoses and extensive GI bleeding. There is severe headache, lumbar pain, nausea and vomiting, delirium, and prostration. Fatal cases are associated with extensive haemorrhage, coma, and shock. Other common physical findings are epigastric tenderness, modest hepatomegaly, and less frequently icterus.

Mortality among cases recognised as haemorrhagic fever is 15-30%. Convalescence in survivors is prolonged with asthenia, dizziness, and often hair loss. Milder clinical disease occurs in an unknown proportion of infections. There may be geographic variations, possibly related to viral strain differences.

##### Diagnosis

*Differential Diagnosis.* Thrombocytopenia and elevated aspartate aminotransferase (AST) may provide a clue to suggest CCHF in the febrile patient seen early in the course of infection. Other viral haemorrhagic fevers, meningococcaemia, rickettsial diseases, and similar conditions may resemble full-blown CCHF. Particular care should be taken in the case of massive GI bleeding not to confuse CCHF with surgical conditions.

*Routine Laboratory Findings.* Leukopenia, thrombocytopenia, and elevated AST are all seen early. Abnormal coagulation tests are common and usually indicate disseminated intravascular coagulation (DIC). Platelets  $\leq 20,000/\text{ml}$ , APT  $\geq 260$  sec, or AST  $\geq 200/\text{ml}$  carry a poor prognosis.

*Specific Laboratory Diagnosis.* Most fatal cases and half the others will have detectable antigen by rapid enzyme-linked immunosorbent assay (ELISA) testing of acute serum samples. IgM ELISA antibodies occur early in recovery. IgG ELISA and fluorescent antibodies also show rising titres. Virus isolation in suckling mice is usually successful from acute sera. PCR is available.

*Therapy.* Supportive therapy with replacement of clotting factors is indicated. Crimean-Congo Haemorrhagic Fever virus is sensitive to ribavirin *in vitro* and clinicians have been favourably impressed in uncontrolled trials. Patients should be treated with intravenous Ribavirin (30 mg/kg followed by 15 mg/kg every 6 hours for 4 days and 7.5 mg/kg every 8 hours for 6 days). Mild reversible anaemia may occur.

Because of several well-defined outbreaks within hospitals, protective measures for medical personnel are an issue. The weight of evidence points to large droplets or fomites as the mediators of transmission and so strict barrier nursing is indicated and probably sufficient for the care of naturally acquired disease. The virus is aerosol-infectious and additional precautions (for example, respirators) might be considered in a BW setting.

### Prophylaxis

Although there is little field experience and no definitive data on efficacy, the sensitivity of the virus to ribavirin and the severity of disease suggests that prophylaxis of high-risk exposures is indicated. Persons with percutaneous exposure to contaminated needles or instruments and those exposed directly to fresh blood from CCHF patients should receive 400 mg ribavirin po 3 times daily for one day and then continue with 400 mg po 3 times daily until 7 days after the last exposure. If more than 48 hours have elapsed after the first such exposure, 30 mg/kg should be given intravenous (IV) followed by 3 IV doses of 15 mg/kg at 8 hourly intervals; then continue with 400 mg po every 8 hours. If there is GI intolerance, the 400 mg oral dose can be substituted with 180 mg IV. Monitoring for anaemia is suggested.

In the case of a suspected BW attack, ribavirin could be considered for prophylaxis, but there is insufficient information to make a firm recommendation for dosing. Use of 400 mg 3 times daily may result in mild to modest anaemia in some recipients, and GI intolerance in a small proportion.

*Control.* There is no human-to-human transmission and ROM is not required, although barrier-nursing will help to prevent nosocomial spread.

## Influenza

### Clinical Syndrome

*Characteristics.* Influenza virus, an orthomyxovirus, is surrounded by an envelope, projecting from which are haemagglutinin (HA) and neuraminidase (N) spikes formed from viral glycoproteins. The HA molecule is the virus receptor. It is the major target for neutralising antibody and can display great antigenic variation between strains. The N spike is an enzyme that removes sialic acid; it is required during virion release from cells. Three types of influenza virus are recognised: A, B and C. Type A includes 3 current human subtypes (H1N1, H2N2 and H3N2) that have been infrequently associated with regional or widespread epidemics; type C has been associated with sporadic cases and minor localised outbreaks. Virus type is determined by the antigenic properties of the 2 relatively stable internal structural proteins, the nucleoprotein and the matrix protein. Influenza A subtypes are classified by the antigenic properties of the surface glycoproteins HA and N. Influenza viruses display great antigenic variation. Major antigenic change or antigenic shift may be associated with genetic re-assortment between strains, a process involving the interchange of genomic strands when more than one virion infects a cell. However, it is

possible that some antigenic shifts can be the result of the accumulation of several mutations within the HA gene. The population will be completely susceptible to the new antigenic shift variant, which facilitates its rapid spread. Antigenic drift is a consequence of mutation and selection in a partially immune population. Major pandemics (intercontinental epidemics) and panzootics of influenza viruses are associated with new antigenic shift variants, occurring every 10-30 years with intervening smaller scale epidemics. In 1918 a pandemic of influenza virus swept the world. In the space of 18 months it caused the deaths of 20-40 million people, far more than were killed in combat in the First World War. Between these major outbreaks, minor antigenic changes acquired by mutation can lead to variants that are less efficiently neutralised by the existing antibody in the population. These drift variants are associated with minor epidemics. Each new pandemic has a different virus, usually with a new HA and sometimes with a new N. Small intermittent peaks in disease occur between each major pandemic due to minor mutations to the HA. This change occurs in relation to neutralisation effects and is thus an evolutionary pressure. Birds are the natural reservoir for influenza isolates; all known haemagglutinin (H1 to 13) and neuraminidase (N1 to 9) types have been isolated from birds where influenza is an enteric virus which spreads through urine and faeces. Humans are the primary reservoir for human infections although likely sources of new human subtypes are reservoirs such as swine, birds and horses through genetic re-assortment. New subtypes of a virulent virus strain with new surface antigens cause pandemic influenza by spreading through an essentially non-immune population. When the sera of people alive during the period from 1900 to 1918 were analysed, it was found that many contained antibody to an influenza virus with the H3N8 combination suggesting this genotype, now found in an equine virus, once existed in a human influenza virus. Airborne spread predominates among crowded populations in enclosed spaces, such as aeroplanes; transmission may also occur by direct contact, since the influenza virus may persist for hours, particularly in the cold and in low humidity. True influenza virus infections are debilitating and can be fatal in the young, the old and the malnourished, in contrast to the mild illness commonly referred to as "flu" which is usually caused by common cold viruses.

*Clinical Features.* The virus replicates in the ciliated epithelium inducing coughing. This factor, coupled with the short incubation period of 1 to 3 days produces an explosive outbreak of disease. In lethal

infections the virus penetrates beyond the basement membrane of the respiratory tract and is spread in a viraemia to secondary target organs like the liver and heart. The disease is contagious from just before the appearance of clinical symptoms for 3 to 5 days. The illness presents as an acute viral disease of the respiratory tract characterised by fever, headache, myalgia, prostration, coryza, sore throat, and cough. Cough is often severe and protracted but other manifestations are usually self-limited. The worst symptoms are usually over within 3 to 5 days, but full recovery takes up to 2 weeks. Confirmation of the disease requires laboratory investigation, but during an epidemic most cases are recognised on clinical grounds.

### Complications

*Pulmonary.* Primary viral influenza pneumonia occurs uncommonly, but is related to a poor outcome. Secondary bacterial pneumonia is much more common, and particularly affects the elderly and infirm. Whilst classical causes of bacterial pneumonia such as *Streptococcus pneumoniae* or *Haemophilus influenzae* are the commonest agents, *Staphylococcus aureus* can cause serious pneumonia with lung abscesses and is frequently fatal.

*Non-pulmonary.* Myositis, myocarditis and pericarditis occur occasionally. Severe exercise in patients with pericarditis or myocarditis can lead to sudden death. Other complications include encephalitis and rarely transverse myelitis and the Guillain-Barré syndrome.

### Diagnosis

*Routine Laboratory Findings.* There are no pathognomonic laboratory findings in influenza, although there may be a relative leucopaenia with an increase in the relative proportion of lymphocytes. In complicated influenza and with secondary infections, a variable white cell count with neutrophilia and other abnormalities associated with the disease may be seen.

*Differential Diagnosis.* A wide range of common respiratory viruses are often mistaken for influenza, especially the more severe cases. These cannot be confidently excluded by clinical examination. Many other diseases present with some or all of the symptoms of influenza, particularly fever, malaise and prostration. In many cases, further symptoms will appear, which are characteristic of other diseases, but some conditions may be difficult to detect without laboratory tests. Among the viruses used for BW, VEE and other encephalitic viruses may present a very similar picture to early influenza. Smallpox may resemble influenza for 2 or 3 days before the classical rash appears. Tularaemia, Q Fever and brucellosis all

resemble influenza; Anthrax has a similar picture in the early stages, but coryza is usually absent.

*Specific Laboratory Diagnosis.* During the early febrile stage of disease, laboratory confirmation is made by isolation of influenza viruses from pharyngeal or nasal secretions or washings in cell culture or embryonated eggs. Influenza can also be diagnosed by direct identification of viral antigens in nasopharyngeal cells and fluids by Fluorescent Antibody test or ELISA, or by amplification of viral RNA. Infection may also be confirmed by demonstration of a specific serologic response between acute and convalescent sera. The precedence of influenza virus replication can be confirmed by HA inhibition assays using sera or monoclonal antibodies specific for particular influenza types. Antigenic variants are defined by their HA and N, each variant being given a number. The causative virus should be identified by the WHO by submission of prototype strains to one of the four WHO Centres for Reference and Research on Influenza (Atlanta, London, Tokyo and Melbourne); throat secretion specimens, nasopharyngeal aspirates and paired blood samples may be sent to any WHO recognised national influenza centre.

*Therapy.* Amantadine has been used to treat severe influenza virus infections and prevents virus uncoating by blocking the M2 ion channel. Amantadine or rimantadine started within 48hrs of onset of influenza A illness and given for approximately 3 - 5 days reduces symptoms and virus titres in the respiratory secretions (dose 100mg bid for 2 - 5 days). During treatment with either drug, drug resistant viruses may emerge late in the course of treatment and may be transmitted to others; therefore, cohorting people on antiviral therapy should be considered, especially in closed populations. Patients should be watched for development of bacterial complications, and only then should antibiotics be administered. Treatment with neuraminidase inhibitors such as Zanamivir may reduce the severity and shorten illness if given early.

*Prophylaxis.* The appearance of symptoms may be suppressed with rimantidine and neuraminidase inhibitors. This may be useful for prophylaxis or treatment of early cases. None of these drugs has any effect on established cases.

*Vaccines.* Infection produces immunity to the specific infecting virus, but the duration and breadth of immunity depend on the degree of antigenic drift and the number of previous infections. Vaccines produce serologic responses specific for the included viruses and elicit booster responses to related strains with which the individual has had prior experience.

Immunisation with available inactivated

virus vaccines may provide 70-80% protection against infection in healthy young adults when the vaccine antigen closely matches the circulating strains of virus.

A single dose suffices for those with prior exposure to influenza A and B virus; 2 doses of vaccine 1 month apart are required for persons who have no previous immunisation history.

*Chemoprophylaxis.* Amantadine or rimantadine are effective in the chemoprophylaxis of influenza A, but not influenza B. Amantadine is associated with CNS side effects in 5-10% of recipients. The drug should be continued throughout the epidemic; it will not interfere with the response to influenza vaccine. Zanamivir is a more recent alternative, but it is expensive.

*Control.* ROM may be implemented in the event of an Influenza epidemic. It is also important to educate deployed personnel in basic personal hygiene such as hand washing and the danger of unprotected coughs and sneezes.

## Rift Valley Fever

### Clinical Syndrome

*Characteristics.* Rift Valley Fever (RVF) is a viral disease, which circulates in sub-Saharan Africa as a mosquito-borne agent. Epizootics occur when susceptible domestic animals are infected. Deaths and abortions among susceptible species such as cattle and sheep provide a diagnostic clue and a method of surveillance. Natural outbreaks are typically associated with very high density of vector populations that may occur during heavy and prolonged rains or in association with irrigation projects. During epidemics, the virus may be transmitted by many species of mosquitoes; the potential for introduction into areas with susceptible livestock and dense mosquito population is believed to be high. Humans become infected by the bite of mosquitoes or by exposure to virus-laden aerosols or droplets. The human disease appears to be similar whether acquired by aerosol or by mosquito bite. A BW attack, most likely to be delivered by aerosol, would be expected to elicit the rather specific spectrum of human clinical manifestations and to cause disease in sheep and cattle in the exposed area. If disease occurred in the absence of heavy vector populations or without domestic animals as amplifiers of mosquito infection, a BW attack would also be a likely cause. Domestic animals are probably susceptible to aerosol infection or could be covertly infected to initiate an epidemic that might propagate itself by the usual means.

*Clinical Features.* The incubation period is 2 to 5 days and is usually followed by an incapacitating febrile illness of similar duration. The typical physical findings are

fever, conjunctival injection, and sometimes abdominal tenderness. A few petechiae or epistaxis may occur. A small proportion of cases (approximately 1%) will progress to a viral haemorrhagic fever syndrome, often with associated hepatitis. These cases may manifest petechiae, mucosal bleeding, icterus, anuria, and shock; mortality in this group is roughly 50%. A similar proportion will develop clinically significant ocular changes; macular lesions associated with retinal vasculitis, haemorrhage, oedema, and infarction. Ocular manifestations begin after the patient enters convalescence from acute illness and about half of the patients will have permanent visual defects. A small number of infections will lead to a late encephalitis. After apparent recovery from a typical febrile illness, the patient develops fever, meningeal signs, obtundation, and focal defects. These patients may die or often have serious sequelae.



Fig 2. Rift Valley Fever.

### Diagnosis

*Differential Diagnosis.* The clinical syndrome in an individual is not pathognomonic, but the occurrence of an epidemic with febrile disease, haemorrhagic fever, eye lesions, and encephalitis in different patients would be characteristic of RVF.

*Routine Laboratory Findings.* In acute uncomplicated disease, there is often a transient leucopaenia, but liver and clotting function tests are normal. In haemorrhagic fever, abnormalities of hepatic and coagulation tests are proportional to severity of disease. DIC may be present. Patients with encephalitis have up to several hundred cells/mm in CSF, predominantly lymphocytes.

*Specific Laboratory Diagnosis.* Demonstration of viral antigen in blood by ELISA is rapid and successful in a high proportion of acute cases of uncomplicated disease or haemorrhagic fever. IgM antibodies appear with cessation of viraemia and are present when ocular or central nervous system (CNS) manifestations are noted. False positive reactions may occasionally be noted in patients with multiple sandfly fever infections. Encephalitis patients have IgM and IgG antibodies in CSF. A proportion of cases should be studied by classical means such as determination of neutralising antibodies and virus isolation. Wide-scale

surveillance is readily accomplished by simultaneous determination of IgG (infection or vaccination at an indeterminate time) and IgM (recent exposure) antibodies in human or domestic animal blood. PCR is available.

**Therapy.** The virus is sensitive to ribavirin *in vitro* and in rodent models. No studies have been performed in human or the more realistic monkey model to ascertain whether administration to an acutely ill patient would be of benefit. It would be reasonable to treat patients with early signs of haemorrhagic fever with intravenous ribavirin (30 mg/kg followed by 15 mg/kg every 6 hours for 4 days and 7.5 mg/kg every 8 hours for 6 days). This regimen is safe and effective in haemorrhagic fevers caused by some viruses, although a reversible anaemia may appear. Therapy may be stopped 2-3 days after improvement begins or antibody appears. Penetration of ribavirin into the CNS is slow and perhaps limited, but in the absence of any other specific therapy, the drug might be used in ocular and encephalitic cases. In haemorrhagic fever, supportive therapy may be indicated for hepatic and renal failure, as well as replacement of coagulation factors.

**Prophylaxis.** Avoidance of mosquitoes and contact with fresh blood from dead domestic animals and respiratory protection from small particle aerosols are the mainstays of prevention. An effective inactivated vaccine is available as an IND vaccine in the US. The 3-dose schedule (0, 7 and 28 days; s/c) produces protective antibodies within 10-14 days and requires annual boosters. Chemoprophylaxis with ribavirin and alpha-interferon is currently under investigation.

## Smallpox

### Clinical Syndrome

**Characteristics.** Smallpox virus, an orthopoxvirus specific to humans, was an important cause of morbidity and mortality in the developing world until recent times. Eradication of the natural disease was completed in 1977 and the last human cases (laboratory infections) occurred in 1983; the world was declared free of smallpox virus in 1979. The virus officially exists today in only 2 laboratory repositories in the US and Russia. Appearance of human cases outside these laboratories would signal use of the virus as a biological weapon. Under natural conditions, the virus is transmitted by direct (face-to-face) contact with an infected case, by fomites, and by aerosols. Smallpox virus is highly stable and retains infectivity for long periods outside of the host. A related zoonotic virus, monkeypox, clinically resembles smallpox and causes sporadic human disease in West and Central Africa.

**Clinical Features.** The incubation period is typically 12 days (range, 7-19 days). The illness begins with a prodrome lasting 2-3 days, with generalised malaise, fever, rigors, headache, and backache. This is followed by

defervescence and the appearance of a typical skin eruption characterised by progression over 7-10 days of lesions through successive stages, from macules to papules to vesicles to pustules. The latter finally form crusts and, upon healing, leave depressed depigmented scars. The disease is infectious from the appearance of the fever until the last scab has healed. The distribution of lesions is centrifugal (more numerous on face and extremities than on the trunk). Lesions are in the same stage of development at any point in time. Fever may reappear around the 7th day after onset of rash. The case fatality rate is approximately 35% in unvaccinated individuals. A subset of patients develop a haemorrhagic diathesis with disseminated intravascular coagulopathy and have a poor prognosis. Other complications include arthritis, pneumonia, bacterial superinfection of skin lesions, osteomyelitis and keratitis. Permanent joint deformities and blindness may follow recovery. Vaccine immunity may prevent or modify illness. Fully immune individuals exposed to the virus by the respiratory route may develop fever, sore throat, and conjunctivitis ("contact fever") lasting several days. These individuals may be seriously ill but have a low mortality. However, even mild cases excrete fully virulent virus, which can lead to secondary spread of full-blown smallpox in susceptible individuals.

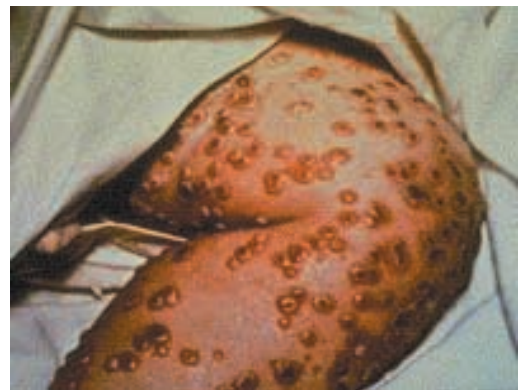


Fig 3. Smallpox Rash.

### Diagnosis

**Routine Laboratory Findings.** Leucopaenia is frequently present in severe cases of smallpox. The differential count shows granulocytopenia and a relative increase in lymphocytes. In the early haemorrhagic form, with onset of bleeding before the eruption, severe thrombocytopenia, global reduction in clotting factors, and circulating antithrombin are present, as well as a marked increase in immature lymphoid cells in the peripheral blood, sometimes mistaken for acute leukaemia.

**Differential Diagnosis.** The eruption of chickenpox (varicella) is typically centripetal in distribution (worse on trunk than face and extremities) and

characterised by crops of lesions in different stages of development. Chickenpox papules are soft and superficial, compared to the firm, spotty, and deep papules of smallpox. Chickenpox crusts fall off rapidly and usually leave no scar. Monkeypox cannot be easily distinguished from smallpox clinically, although generalised lymphadenopathy is a more common feature of the disease and mortality is lower at 15%. Other diseases that are sometimes confused with smallpox include typhus, secondary syphilis, malignant measles, erythema multiforme with bullae and allergic contact dermatitis. The haemorrhagic form of smallpox can be confused with any other viral or bacterial disease presenting in this way. Smallpox in vaccinated individuals may give a confusing picture that is difficult to diagnose.

**Specific Laboratory Diagnosis.** Skin samples (scrapings from papules, vesicular fluid, pus, or scabs) may provide a rapid identification of smallpox by direct electron microscopy, agar gel immunoprecipitation, or immunofluorescence. Virus may be recovered from these samples or blood by inoculation of eggs or cell cultures, but culture techniques requires several days. Serological tests may be useful for confirmation, or early presumptive diagnosis. PCR is available.

**Therapy.** There is no specific treatment available. The antiviral drug cidofovir is active *in vitro* and may be of value *in vivo*.

### Prophylaxis

**Vaccines.** Vaccinia virus is a live poxvirus vaccine that induces strong cross-protection against smallpox and monkeypox for 3 years or more. The vaccine is administered by dermal scarification; appearance of a vesicle or pustule within several days is indication of a "take". Contraindications to vaccination are pregnancy, clinical immunosuppression, eczema, or leukaemia/lymphoma. Complications are infrequent, but include:

- Progressive vaccinia in immunosuppressed individuals (case-fatality >75%).
- Eczema vaccinatum in persons with eczema or a history of eczema, or in contacts with eczema (case-fatality 10-15%).
- Postvaccinal encephalitis, almost exclusively seen after primary vaccination, occurring at an incidence of about 1/500,000, with a case-fatality rate of 25%.
- Generalised vaccinia, seen in immunocompetent individuals and having a good prognosis.
- Autoinoculation with a secondary lesion.
- Myocarditis

Vaccination or revaccination should be performed as early as possible after (and

within 4 days of) exposure, with careful surveillance for signs of illness.

Complications of vaccination have been treated with vaccinia immune globulin but the evidence for efficacy is limited.

**Antiviral Drug.** The antiviral drug, n-methylisatin b-thiosemicarbazone (Marboran, Methisazone) was used in the smallpox eradication campaign but there was no evidence that it was efficacious. Cidofovir and related drugs are currently being evaluated.

**Control.** Patients with smallpox should be treated by personnel vaccinated within the previous year and using universal precautions. Objects in contact with the patient, including bed linens, clothing, ambulance, etc require disinfection by fire, steam, or sodium hypochlorite solution. Due to the contagious nature of this disease suspicion or confirmation of exposure will lead to the consideration of the implementation of ROM and widespread vaccination.

## Venezuelan Equine Encephalitis

### Clinical Syndrome

**Characteristics.** Eight serologically distinct viruses belonging to the Venezuelan Equine Encephalitis (VEE) complex have been associated with human disease; the most important of these pathogens are designated subtype 1 variants S, B and C. These agents also cause severe disease in horses, mules, and donkeys (Equidae). Natural infections are acquired by the bites of a wide variety of mosquitoes; Equidae serve as the viraemic hosts and source of mosquito infection. In natural human epidemics, severe and often fatal encephalitis in Equidae always precedes that in humans. A BW attack with virus disseminated as an aerosol would cause human disease as a primary event. If Equidae were present, disease in these animals would occur simultaneously with human disease. Secondary spread by person-to-person contact occurs at a negligible rate. However, a BW attack in a region populated by Equidae and appropriate mosquito vectors could initiate an epizootic epidemic.

**Clinical Features.** In natural infection, incubation period is 1-5 days, and the onset of illness is extremely sudden, with generalised malaise, spiking fever, rigors, severe headache, photophobia, myalgia in the legs and lumbosacral area. Nausea, vomiting, cough, sore throat, and diarrhoea may follow. This acute phase lasts 24-72 hours. A prolonged period of aesthenia and lethargy may follow, with full health and activity regained only after 1-2 weeks. Approximately 4% of patients during natural epidemics develop signs of central nervous system infection, with meningismus, convulsions, coma, and paralysis. These neurological cases are seen almost exclusively

in children. The overall case-fatality rate is <1%, but in children with encephalitis, it may reach 20%. Permanent neurological sequelae are reported in survivors. The infectious dose by aerosol is very low and almost 100% of infected individuals are affected. The disease is similar to natural infection but intractable headache may persist for 2 months and full recovery may take 6 months or more. A VEE infection during pregnancy may cause encephalitis in the foetus, placental damage, abortion, or severe congenital neuroanatomical anomalies.

### Diagnosis

*Routine Laboratory Findings.* The white blood cell count shows a striking leucopaenia and lymphopaenia. In cases with encephalitis, the cerebrospinal fluid may be under increased pressure and contain up to 1000 white cells/mm<sup>3</sup> (predominantly mononuclear cells) and mildly elevated protein concentration.

*Differential Diagnosis.* An outbreak of VEE may be difficult to distinguish from influenza and other viral encephalitides on clinical grounds. Clues to the diagnosis are the appearance of a small proportion of neurological cases or disease in Equidae, but these might be absent in a BW attack.

*Specific Laboratory Diagnosis.* Viraemia during the acute phase of illness is generally high enough to allow detection by antigen-capture enzyme immunoassay. Virus isolation may be made from serum, and in some cases throat swab specimens, by inoculation of cell cultures. A variety of serological tests are applicable, including the IgM ELISA, indirect fluorescent assay (FA), haemagglutination inhibition, complement-fixation, and neutralisation. For persons without prior exposure to VEE complex viruses in tropical areas, a presumptive diagnosis may be made by finding antibodies in a single serum sample taken 5-7 days after onset of illness. PCR is available.

*Therapy.* There is no specific therapy. Patients with uncomplicated VEE infection

may be treated with analgesics to relieve headache and myalgia. Patients who develop encephalitis may require anticonvulsant and intensive supportive care to maintain fluid and electrolyte balance, adequate ventilation, and to avoid complicating secondary bacterial infections.

*Control.* Vector control for 5 days is required to prevent onward transmission from infective patients. This could include general measures to prevent infected individuals being bitten by mosquitoes.

### Prophylaxis

*Vaccine.* An experimental vaccine designated TC-83 is a live, attenuated cell-culture-propagated vaccine which has been used in several thousand people to prevent laboratory infections. The vaccine is given as a single 0.5 ml subcutaneous dose. Febrile reactions occur in up to 18% of persons vaccinated, and may be moderate to severe in 5%, with fever, myalgia, headache, and prostration. Approximately 10% of vaccinees fail to develop detectable neutralising antibodies, but it is unknown whether they are susceptible to clinical infection if challenged. Non-responders may be re-vaccinated with TC-83. Contraindications for use include an intercurrent viral infection or pregnancy. TC-83 is a licensed vaccine for Equidae.

A second investigational product that has been tested in humans is the C-84 vaccine, prepared by formalin-inactivation of the TC-83 strain. The vaccine is presently not recommended for primary immunisation, on the basis of animal studies indicating that it may not protect against aerosol infection. However, it may be useful for aerosol protection for persons not responding to TC-83 (0.5 ml subcutaneously at 2 to 4 week intervals for up to 3 inoculations or until an antibody response is measured).

*Antiviral Drugs.* There is no known effective antiviral drug. Many strains are relatively resistant to interferon although modified interferons and interferon inducers may be of benefit in the future.

## Medical Classification Of Potential BW Agents 3

### TOXINS

#### Botulinum Toxins

##### Clinical Syndrome

*Characteristics.* Botulism is caused by intoxication with any of the seven distinct neurotoxins produced by the bacillus *Clostridium botulinum*. The toxins are proteins with molecular weights of approximately 150,000, which bind to the presynaptic membrane of neurons at peripheral cholinergic synapses to prevent release of acetylcholine and block neurotransmission. The blockade is most evident clinically in the cholinergic autonomic nervous system and at the neuromuscular junction. A BW attack with botulinum toxin delivered by aerosol would be expected to cause symptoms similar in most respects to those observed with food-borne botulism.

*Clinical Features.* Symptoms of inhalation botulism may begin as early as 24-36 hours following exposure or as late as several days. Initial signs and symptoms include ptosis, generalised weakness, lassitude, and dizziness. Diminished salivation with extreme dryness of the mouth and throat may cause complaints of a sore throat. Urinary retention or ileus may also occur. Motor symptoms are usually present early in the disease; cranial nerves are affected first with blurred vision, diplopia, ptosis and photophobia. Bulbar nerve dysfunction causes dysarthria, dysphonia and dysphagia. This is followed by a symmetrical, descending, progressive weakness of the extremities along with weakness of the respiratory muscles. Development of respiratory failure may be abrupt. On physical examination, the patient is alert, oriented and afebrile. Postural hypotension may be present. Ocular findings may include ptosis, extracellular muscle paralysis and fixed and dilated pupils. Mucous membranes of the mouth may be dry and crusted. Neurological examination shows flaccid muscle weakness of the palate, tongue, larynx, respiratory muscles and extremities. Deep tendon reflexes vary from intact to absent. No pathologic reflexes are present and the sensory examination generally is normal (although reports suggest that obtundation or sensory involvement may sometimes occur).

##### Diagnosis

*Routine Findings.* Routine laboratory

findings are of no value in diagnosis. The cerebrospinal fluid is normal.

*Differential Diagnosis.* The occurrence of an epidemic with large numbers of afebrile patients with progressive ocular, pharyngeal, respiratory and muscular weakness and paralysis hints strongly at the diagnosis. Single cases may be confused with various neuromuscular disorders such as atypical Guillain-Barré syndrome, myasthenia gravis, or tick paralysis. The edrophonium (tensilon) test may be transiently positive in botulism. Other considerations include enteroviral infections; but in these patients, fever is present, paralysis is often asymmetrical and the cerebrospinal fluid is abnormal. It may be necessary to distinguish nerve-agent and atropine poisoning from botulinum intoxication. Briefly, organophosphate nerve agent poisoning results in miotic pupils and copious secretions. In atropine poisoning, the pupils are dilated and mucous membranes are dry, but central nervous system excitation with hallucinations and delirium is present.

*Specific Laboratory Findings.* Detection of toxin in serum or gastric contents from cases of food-borne botulism is often feasible by mouse inoculation. Toxin has also been detected in serum following inhalation exposure in experimental animals. Serum should be obtained from representative cases for such attempts. Survivors will probably not develop an antibody response due to the small amount of toxin necessary to cause death.

##### Therapy

Respiratory failure secondary to paralysis of respiratory muscles is the most serious complication and, generally, the cause of death. Reported cases of botulism prior to 1995 had a mortality of 60%. With tracheostomy and ventilatory assistance, fatalities should be <5%. Intensive and prolonged nursing care may be required for recovery (which may take several weeks or even months).

In isolated cases of food-borne botulism, circulating toxin is usually present, perhaps due to continued absorption through the gut wall. Equine antitoxin has been used in these circumstances and is probably helpful. After aerosol exposure, antitoxin can be effective, sometimes even after onset of signs of intoxication. Administration of antitoxin is

reasonable if disease has not progressed to a stable state.

There is no prospect for additional human antitoxin to be produced. A number of commercial and investigational products have been produced. Many of the commercial antitoxins only include a limited range of serogroups. Use of non-human antiserum is associated with a significant risk of adverse effects, although this is reduced in some modern preparations.

### Prophylaxis

A pentavalent toxoid of *Clostridium botulinum* types A, B, C, D, and E is available under IND status in the US. This product has been administered to several thousand volunteers and occupationally at-risk workers and induces serum antitoxin levels that correspond to protective levels in experimental animal systems. The currently recommended schedule (0, 2, and 12 weeks, then a 1 year booster) induces solidly protective antitoxin levels in greater than 90 percent of those vaccinated after 1 year. Transient antitoxin levels are induced after 3 injections. Contraindications include sensitivity to alum, formaldehyde, and thiomersal, or hypersensitivity to a previous dose. Reactogenicity is mild, with 2-4% of cases reporting erythema, oedema, or induration, which peaks at 24-48 hours then dissipates. The frequency of local reactions increases with each subsequent inoculation; after the second and third doses, 7-10% will have local reactions, with higher incidence (up to 20% or so) after boosters. Severe local reactions are rare, consisting of more extensive oedema or induration. Systemic reactions are reported in up to 3%, consisting of fever, malaise, headache, and myalgia. Incapacitating reactions (local or systemic) are uncommon. The vaccine should be stored at 2-8°C refrigerator temperature not frozen.

Three or more vaccine doses (0, 2, and 12 weeks, then 1 year, if possible, by deep subcutaneous injection) are recommended only to selected individuals or groups judged at high risk for exposure to botulinum toxin aerosols. There is no indication at present for use of antitoxin as a prophylactic modality except under extremely specialised circumstances (for example, known impending exposure of small numbers of individuals).

## Clostridium Perfringens Toxins

### Clinical Syndrome

*Characteristics.* *Clostridium perfringens* is a common anaerobic bacterium associated with 3 distinct syndromes; gas gangrene or clostridial myonecrosis; enteritis necroticans (pig-bel); and clostridium food poisoning. Each of these syndromes has very specific requirements for delivering inocula of *C.*

*perfringens* to specific sites to induce disease, and it is difficult to imagine a general scenario in which the spores or vegetative organisms could be used as a BW agent. There are, however, at least 12 protein toxins elaborated, and one or more of these could be produced, concentrated, and used as a weapon. Waterborne disease is conceivable, but unlikely. The alpha toxin would be lethal by aerosol. This is a well-characterised, highly toxic phospholipase C. Other toxins from the organism might be co-weaponized and enhance effectiveness. For example, the epsilon toxin is neurotoxic in laboratory animals.

*Clinical Features.* The clinical picture of aerosolised *C. perfringens* alpha toxin would be expected to be that of a serious acute pulmonary insult. Absorbed alpha toxin could produce vascular leak, haemolysis, thrombocytopenia, and liver damage. Other toxins admixed could modify the illness. There is insufficient information available to speculate on a clinical syndrome produced by other *C. perfringens* toxins.

### Diagnosis

*Routine Findings.* Clinical laboratory findings might include anaemia (due to intravascular haemolysis), thrombocytopenia, elevated serum transaminases, and hypoxia.

*Differential Diagnosis.* Pulmonary findings might lead to confusion with staphylococcal enterotoxin B (SEB) initially. Liver damage, haemolytic anaemia, and thrombocytopenia are not associated with SEB and the pulmonary findings should be reversible in SEB.

*Specific Laboratory Diagnosis.* Acute serum and tissue samples should be collected and rapidly transported to a reference laboratory. Specific immunoassays are available; however, their utility in diagnosis of human disease is unproven. The enterotoxin can be detected in faecal samples from human food poisoning cases, and bacteria are readily cultured from clinical samples.

*Therapy.* No specific treatment is available for *C. perfringens* intoxication. The organism itself is sensitive to penicillin, and consequently, this is the current drug of choice. Recent data indicate that clindamycin or rifampicin may suppress toxin production and provide superior results in animal models.

*Prophylaxis.* There is no available prophylaxis against most *C. perfringens* toxins. Veterinary toxoids are in wide use.

## Ricin

### Clinical Syndrome

*Characteristics.* Ricin is a glycoprotein toxin (66,000 daltons) from the seed of the castor oil plant. It blocks protein synthesis by altering the rRNA, thus killing the cell.

Ricin's significance as a potential BW agent relates to its availability world wide, its ease of production, and extreme pulmonary toxicity when inhaled.

**Clinical Features.** Overall, the clinical picture depends on the route of exposure. All reported serious or fatal cases of castor ingestion have taken approximately the same course: rapid onset of nausea, vomiting, abdominal cramps and severe diarrhoea with vascular collapse; death has occurred on the third day or later. Following inhalation, one might expect non-specific symptoms of weakness, fever, cough, and hypothermia followed by hypotension and cardiovascular collapse. In monkeys, inhalation toxicity is characterised by a dose dependent preclinical period of 24-36 hours followed by anorexia and progressive decrease in physical activity. Death occurs 36-48 hours post challenge. In mice, histopathological change is characterised by necrotising, suppurative airways lesions: rhinitis, laryngitis, tracheitis, bronchitis, bronchiolitis, and interstitial pneumonia with perivascular and alveolar oedema. Histopathologic change in the airways is seen as early as 3 hours post challenge. The exact cause of death is unknown and probably varies with route of intoxication. High doses by inhalation appear to produce severe enough pulmonary damage to cause death.

### Diagnosis

**Routine Laboratory Findings.** Laboratory findings are generally non-specific. Neutrophilic leucocytosis beginning between 12-18 hours was reported in a case of human lethal intramuscular intoxication that was purposely inflicted. Leucocytosis, beginning 12-18 hours after challenge, also occurs following aerosol exposure of laboratory animals.

**Differential Diagnosis.** In oral intoxication, fever, gastrointestinal involvement, and vascular collapse are prominent, the latter differentiating it from infection with enteric pathogens. With regard to inhalation exposure, non-specific findings of weakness, fever, vomiting, cough, hypothermia, and hypotension in large numbers of patients might suggest several respiratory pathogens. The temporal onset of botulinum intoxication would be similar, but includes ptosis and general muscular paralysis with minimal pulmonary effects. SEB intoxication is likely to have a more rapid onset after exposure and a lower mortality rate but could be difficult to distinguish. Nerve agent intoxication is characterised by acute onset of cholinergic crisis with dyspnoea and profuse secretions.

**Specific Laboratory Diagnosis.** Based on animal studies, ELISA (for blood) or immunohistochemical techniques (for direct analysis of tissues) may be useful in confirming ricin intoxication. Post-mortem

pathologic change is route specific: inhalation results in airways lesions; ingestion causes gastrointestinal haemorrhage with necrosis of liver, spleen, and kidneys; and intramuscular intoxication causes severe local muscle and regional lymph node necrosis with moderate involvement of visceral organs. Ricin is extremely immunogenic; sera should be obtained from survivors for measurement of antibody response.

**Therapy.** Management is supportive and should include maintenance of intravascular volume. Standard management for poison ingestion should be employed if intoxication is by the oral route. There is presently no antitoxin available for treatment.

**Prophylaxis.** There is currently no prophylaxis approved for human use. Active immunisation and passive antibody prophylaxis are under study, as both are effective in protecting animals from death following exposure by intravenous or respiratory routes. Ricin is not dermally active, therefore, respiratory protection is the most critical means of prevention.

## Saxitoxin

### Clinical Syndrome

**Characteristics.** Saxitoxin is the parent compound of a family of chemically related neurotoxins. In nature they are predominantly produced by marine dinoflagellates, although they have also been identified in association with such diverse organisms as blue-green algae, crabs, and the blue-ringed octopus. Human intoxications are principally due to ingestion of bivalve molluscs that have accumulated dinoflagellates during filter feeding. The resulting intoxication, known as paralytic shellfish poisoning (PSP), is known throughout the world as a severe, life-threatening illness requiring immediate medical intervention.

Saxitoxin and its derivatives are water-soluble compounds that bind to the voltage-sensitive sodium channel, blocking propagation of nerve-muscle action potentials. Consistent with this mechanism of action, victims typically present with neurological symptoms and in severe cases, death results from respiratory paralysis.

The natural route of exposure to these toxins is oral. In a BW scenario, the most likely route of delivery is by inhalation or toxic projectile. In addition, saxitoxin could be used in a confined area to contaminate water supplies.

**Clinical Features.** After oral exposure, absorption of toxins from the gastrointestinal tract is rapid. Onset of symptoms typically begins 10-60 minutes after exposure, but may be delayed several hours depending upon the dose and individual idiosyncrasy. Initial symptoms are numbness or tingling of

the lips, tongue and fingertips, followed by numbness of the neck and extremities and general loss of muscular coordination. Nausea and vomiting may be present, but typically occur in a minority of cases. Other symptoms may include a feeling of light-headedness, or floating, dizziness, weakness, aphasia, incoherence, visual disturbances, memory loss and headache. Cranial nerves are often involved, especially those responsible for ocular movements, speech, and swallowing. Induced reflexes are normal and the patient remains conscious. Respiratory distress and flaccid muscular paralysis are the terminal stages and can occur 2-12 hours after intoxication. Death results from respiratory paralysis. Clearance of the toxin is rapid and survivors for 12-24 hours will usually recover. Complete recovery may require 7-14 days. There are no known cases of inhalation exposure to saxitoxin in the medical literature, but data from animal experiments suggest the entire syndrome is compressed and death may occur in minutes.

### Diagnosis

*Routine Laboratory Findings.* Routine laboratory evaluation is not particularly helpful. Cardiac conduction defects may develop. Elevation of serum creatinine kinase levels in some patients has been reported.

*Differential Diagnosis.* Exposure to tetrodotoxin or the ciguatera toxins can manifest very similar signs and symptoms. Ciguatoxins (by oral exposure) typically demonstrate a much greater degree of gastrointestinal involvement, and can also be differentiated by a history of eating finfish rather than shellfish. Tetrodotoxin intoxication is nearly identical to that caused by the saxitoxins except that hypotension typically plays a greater role in severe intoxication. Differential diagnosis may require toxin detection. Gas chromatographic analysis of food or stomach contents can rule out pesticide exposure.

*Specific Laboratory Tests.* Diagnosis is confirmed by detection of toxin in the food, water, stomach contents or environmental samples. Saxitoxin, neosaxitoxin, and several other derivatives can be detected by ELISA or by mouse bioassay. Specific toxins can be differentiated by high pressure liquid chromatography (HPLC). The Association of Official Analytical Chemists has adopted an official method for mouse bioassay for the analysis of seafood.

*Therapy.* Management is supportive and standard management of poison ingestion should be employed if intoxication is by the oral route. Toxins are rapidly cleared and excreted in the urine, so diuresis may increase elimination. Charcoal haemoperfusion has been advocated, but remains unproven in its utility. Intubation and

mechanical respiratory support may be required in severe intoxication. Timely resuscitation would be imperative, albeit very difficult, after inhalation exposure on the battlefield. Specific antitoxin therapy has been successful in animal models, but is untested in humans.

*Prophylaxis.* No vaccine against saxitoxin exposure has been developed for human use.

## Staphylococcal Enterotoxin B

### Clinical Syndrome

*Characteristics.* Staphylococcal Enterotoxin B (SEB) is one of several exotoxins produced by *Staphylococcus aureus*, causing food poisoning when ingested. A BW attack with aerosol delivery of SEB to the respiratory tract produces a distinct syndrome causing significant morbidity and potential mortality.

*Clinical Features.* The disease begins 1-6 hours after ingestion with the sudden onset of fever, chills, headache, myalgia, and non-productive cough. In more severe cases, dyspnoea and retrosternal chest pain may also be present. Fever, which may reach 40°C, has lasted 2-5 days, but cough may persist 1-4 weeks. In many patients nausea, vomiting, and diarrhoea will also occur. Physical findings are often unremarkable. Conjunctival injection may be present, and in the most severe cases, signs of pulmonary oedema would be expected. The chest X-ray is generally normal, but in severe cases, there will be increased interstitial markings, atelectasis, and possibly overt pulmonary oedema. In moderately severe laboratory exposures, lost duty time has been <2 weeks, but, based upon animal data, it is anticipated that severe exposures will result in fatalities.

### Diagnosis

*Routine Laboratory Findings.* Laboratory findings are non-contributory except for a neutrophilic leukocytosis and elevated erythrocyte sedimentation rate.

### Differential Diagnosis

In food-borne SEB intoxication, fever and respiratory involvement are not seen, and gastrointestinal symptoms are prominent. The non-specific findings of fever, non-productive cough, myalgia, and headache occurring in large numbers of patients in an epidemic setting would suggest any of several infectious respiratory pathogens, particularly influenza, adenovirus, or mycoplasma. In a BW attack with SEB, cases would probably have their onset within a single day, while naturally occurring outbreaks would present over a more extended period.

Rapid progression of respiratory signs and symptoms to a stable state distinguishes SEB intoxication from other BW agents with respiratory symptoms (for example, inhalational anthrax, tularaemia, plague).

*Specific Laboratory Diagnosis.* Toxin is cleared from the serum rapidly and is difficult to detect by the time of symptom onset. Nevertheless, specific laboratory tests are available to detect SEB, and serum should be collected as early as possible after exposure. In situations where many individuals are symptomatic sera should be obtained from those not yet showing evidence of clinical disease. Most patients develop a significant antibody response, but this may require 2-4 weeks.

*Therapy.* Treatment is limited to supportive care. No specific antitoxin for human use is available.

*Prophylaxis.* There is currently no prophylaxis for SEB intoxication.

## Trichothecene Mycotoxins

### Clinical Syndrome

*Characteristics.* The trichothecene mycotoxins are a diverse group of more than 40 compounds produced by fungi. They are potent inhibitors of protein synthesis, impair DNA synthesis, alter cell membrane structure and function, and inhibit mitochondrial respiration. Secondary metabolites of fungi, such as T-2 toxin and others, produce toxic reactions called mycotoxicoses upon inhalation or consumption of contaminated food products by humans or animals. Naturally occurring trichothecenes have been identified in agricultural products and have been implicated in animal disease.

There are no well-documented cases of clinical exposure of humans to trichothecenes. However, strong circumstantial evidence has associated these toxins with alimentary toxic aleucia (ATA), the fatal epidemic seen in Russia during World War II and with alleged BW incidents ('yellow rain') in Cambodia, Laos and Afghanistan.

### Clinical Features

Consumption of these mycotoxins results in weight loss, vomiting, skin inflammation, mucosal membrane irritation, bloody diarrhoea, diffuse haemorrhage, and possibly death. The onset of illness following acute exposure to T-2 (IV or inhalation) occurs in hours, resulting in the rapid onset of circulatory shock characterised by reduced cardiac output, arterial hypotension, lactic acidosis and death within 12 hours.

The clinical signs and symptoms of ATA were haemorrhage, leucopaenia, ulcerative pharyngitis, and depletion of bone marrow. The purported use of T-2 as a BW agent resulted in an acute exposure via inhalation and/or dermal routes, as well as oral exposure upon consumption of contaminated food products and water. Alleged victims reported painful skin lesions, light-headedness, dyspnoea, and a rapid onset of haemorrhage, incapacitation and death.

Survivors developed a radiation-like sickness including fever, nausea, vomiting, diarrhoea, leucopaenia, bleeding and sepsis.

### Diagnosis

*Routine Laboratory Findings.* Haematological alterations in the rodent model (parenteral routes) include marked but transient leucocytosis, characterised by rapid lymphocytosis and a mild neutrophilia. This is followed by a leucopaenia that returns to normal values 4-7 days post-exposure. There is a reduced haematocrit with the presence of nucleated erythrocytes. Serum proteins and enzymes are not significantly altered after this acute exposure.

*Differential Diagnosis.* Other diagnoses to consider include radiation toxicity and plant or chemical toxicity.

*Specific Laboratory Diagnosis.* Specific diagnostic modalities are limited to reference laboratories. Gas-liquid chromatography (GC) and high pressure liquid chromatography (HPLC) have been used for detecting T-2 and related trichothecene mycotoxins in plasma and urine. Polyclonal and monoclonal antibodies to trichothecenes are also available for detection in liquid or solid samples after solvent extraction. Because of their long "half-life" the toxin metabolites can be detected as late as 28 days after exposure. Between 50-75% of the parent toxin and metabolites are eliminated in urine and faeces within 24 hours. Urine should be the biological fluid chosen for diagnostic purposes. A one-time urine sample with 0.10cc concentrated hydrochloric acid (HCl) added per 100cc of urine, to kill unwanted bacteria, should be submitted for analysis if the exposure was recent. Trichothecene mycotoxins can be detected in the urine out to approximately 14 days after exposure but if several days have elapsed since exposure, a 24 hour urine collection with HCl added should be submitted instead of a one time collection. The urine needs to be kept refrigerated.

*Therapy.* General supportive measures are used to alleviate acute T-2 toxicoses. Prompt (within 5-60 min of exposure) soap and water wash significantly reduces the development of the localised destructive, cutaneous effects of the toxin. After ingestion management should include standard therapy for poison ingestion. Some benefit may be derived from giving activated charcoal or superactivated charcoal (1-7g/kg po) as late as 5 hours after exposure to T-2 toxins. In animal studies, dexamethasone (1-10 mg/kg, IV) administered as late as 3 hours after exposure to T-2 toxin improved survival and reduced the incidence of massive bloody diarrhoea. No antitoxin is presently available for human use.

*Prophylaxis.* There is no proven prophylaxis.