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BICHAT GUIDELINES* FOR THE CLINICAL MANAGEMENT OF GLANDERS AND MELIOIDOSIS AND BIOTERRORISM-RELATED GLANDERS AND MELIOIDOSIS

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Glanders and melioidosis are two infectious diseases that are caused by *Burkholderia mallei* and *Burkholderia pseudomallei* respectively. Infection may be acquired through direct skin contact with contaminated soil or water. Ingestion of such contaminated water or dust is another way of contamination. Glanders and melioidosis have both been studied for weaponisation in several countries in the past. They produce similar clinical syndromes. The symptoms depend upon the route of infection but one form of the disease may progress to another, or the disease might run a chronic relapsing course. Four clinical forms are generally described: localised infection, pulmonary infection, septicaemia and chronic suppurative infections of the skin.

All treatment recommendations should be adapted according to the susceptibility reports from any isolates obtained. Post-exposure prophylaxis with trimethoprim-sulfamethoxazole is recommended in case of a biological attack. There is no vaccine available for humans.

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Introduction

Glanders and melioidosis are two infectious diseases that are caused by *Burkholderia mallei* and *Burkholderia pseudomallei* respectively. They produce similar symptoms [1-7].

Glanders is primarily a disease affecting horses, but it also affects donkeys and mules and can be naturally contracted by goats, dogs and cats. It is generally rare, but believed to be endemic in Africa, Asia, the Middle East, Central and South America. The reason for the low transmission rate of glanders to man from infected animal is unknown. Human disease is rare and has been reported among laboratory workers and patients in direct and prolonged contact with infected animals (veterinarians, horse caretakers, abattoir workers). No epidemics of human disease have been reported to date.

Melioidosis is endemic in South East Asia and northeast Australia; while cases have been reported in Africa, South Pacific, India, the Middle East, Central and South America, where the causative organism is widely distributed in the soil and water [3]. Infection may be acquired through direct skin contact with contaminated soil or water (abraded or lacerated skin). Ingestion of such contaminated water or dust is another route of transmission. The bacteria enter the body through the skin and through mucosal surfaces of the eyes and nose.

Glanders, melioidosis and bioterrorism

Glanders and melioidosis have both been studied for weaponisation in several countries in the past. Glanders was reported to have been used during both the first and second world wars [1-5]. During the first world war, it was used to infect large numbers of Russian horses and mules on the Eastern Front, affecting troop movements. During the second world war, the Japanese deliberately infected animals and humans at the Pinfang Institute in China. *B. pseudomallei* was studied, but has never been used for biological warfare.

Several human cases of infection through aerosolisation have been reported in laboratories. Attack rates caused by laboratory aerosol were as high as 46%, with severe human cases. Very few organisms are required to cause disease by aerosolisation, possibly the main route of contamination for humans after a deliberate release of *Burkholderia species*. Very few cases of human-to-human transmission of glanders are documented (2 suspected cases of sexual transmission and several cases in family members caring for patients), which makes it unlikely that a single deliberate release would cause a continuing epidemic [6,7].

Despite being extremely rare diseases in the Western world, it is useful to describe both these agents as they have potential as biological weapons in view of their efficient aerosol dispersal ability and their history of use,

Microbiological characteristics

B. mallei and *B. pseudomallei* (also called Whitmore's bacillus) are small, Gram-negative, strictly aerobic bacteria with a safety-pin bipolar appearance using methylene blue or Wright's stain. *B. pseudomallei* is motile due to a polar flagella, *B. mallei* is non-motile.

These bacteria are straight or slightly curved, catalase- and usually oxydase-positive. They grow at temperatures between 4-43°C. Cultures have a pervasive tell tale earthy/grape odour that can be detected when the incubator is opened. Colonies are a mix of wrinkled and smooth morphologies. *Burkolderia sps* is an oxidiser, not a fermenter, and shows pink colonies on MacConkey plates.

Clinical features

Glanders and melioidosis produce similar clinical syndromes (TABLE I). The symptoms depend upon the route of infection but one form of the disease may progress to another, or the disease might run a chronic relapsing course. Four clinical forms are generally described: localised infection, pulmonary infection, septicaemia and chronic suppurative infections of the skin [1-7].

Incubation periods vary from 1 to 14 days, depending on the clinical form of the disease.

Pulmonary form

This form develops usually after inhalation or through haematogenous spread of the bacteria. The incubation period is

10-14 days. This could be the major form of the disease in a bioterrorist attack. When bacteria are aerosolised, they enter the respiratory tract and pulmonary infection may develop, manifested by pneumonia, pulmonary abscesses and pleural effusion. Onset of symptoms is usually abrupt. Patients present with non-specific symptoms such as cough and pleuritic chest pain, fever, rigors, sweats. Ulcerative lesions and nodules of the nasal cavity may be present, where in some cases, the septum may perforate. Chest radiography may show a bilateral bronchopneumonia, miliary nodules (0.5-1 cm), small multiple lung abscesses involving upper lungs, segmental or lobar infiltrates and cavitating lesions, which are often mistaken for tuberculosis. In cases of inhalational melioidosis, cutaneous abscesses may also develop and take months to appear. Without specific treatment, the disease progresses and results in bacteraemia and septicaemia. Patients with cystic fibrosis are prone to developing the pulmonary form of the disease.

Septicaemia

Overwhelming infection may occur after exposure to the bacteria via any route of infection (inhalation, skin, ingestion etc). After an incubation period of 1 to 5 days, generalised symptoms include fever, myalgias, headache and diarrhoea. Flushing, cyanosis and a disseminated pustular eruption with regional lymphadenopathy, cellulitis or lymphangitis can be seen together with photophobia, lacrimation, cervical adenopathy, mild hepatomegaly and/or splenomegaly, tachycardia, generalised erythroderma, jaundice and generalised papular or pustular lesions. Then a multi-organ failure may occur. Septicaemia is fatal within 7 to 10 days (24-48 hours after the onset of the generalised symptoms). Despite antibiotic treatment, the mortality rate is still near 50% (>90% without antibiotics, 24-48 hours after onset). Immunosuppressed patients (diabetics, chronic renal patients and patients on steroids) are especially susceptible to melioidosis.

Localised infections

Bacteria usually enter the skin through a cut or abrasion. Then a localised infection with nodules and ulceration develops within 1 to 5 days at the site where the bacteria entered the body. The nodules are grey or white and firm, surrounded by a haemorrhagic zone, and may caseate or become calcified. Swollen lymph nodes may also develop. Infections involving the mucous membranes in the eyes, nose and respiratory tract will cause increased mucus production from the affected sites. Parotid abscesses are common in children with melioidosis. Besides skin abscesses, other well-described forms include osteomyelitis, septic arthritis, brain abscess or visceral abscesses.

Cases of severe urticaria have been reported during primary melioidosis.

Chronic infections

The chronic form of illness involves multiple abscesses within the skin, the muscles of the arms and legs or in the spleen and liver. Melioidosis, in addition to this chronic form, can become reactive many years after a primary infection.

Diagnosis

Case definitions for glanders and melioidosis are reported in Tables 2 and 3.

The disease is diagnosed in the laboratory by isolating *B. mallei* from sputum, blood, urine, pus or swabs of skin lesions (Gram negative coccobacillus and bipolar-staining with methylene blue or Wright stains, and culture). Blood culture usually remains negative. Agglutination tests and complement fixation tests are available.

Treatment

All treatment recommendations should be adapted according to the susceptibility reports from any isolates obtained.

Because human cases of glanders are rare, there is limited information about antibiotic treatment of the organism in humans [8-11]. Sulfadiazine has been found to be effective in animal experiments and in humans. *B mallei* is usually sensitive to tetracyclines, ciprofloxacin, streptomycin, gentamicin, imipenem, ceftazidime, and the sulfonamides [2]. Resistance to chloramphenicol has been reported. For localised disease, a 60 to 150 day course of oral amoxicillin + clavulanate, tetracycline, or trimethoprim-sulfamethoxazole may be used.

Severe melioidosis should be treated initially with IV antibiotics (ceftazidime, imipenem or meropenem), while a 20 week schedule should be completed with oral antibiotics such as doxycyline + co-trimoxazole or amoxicillin + clavulanate or, ciprofloxacin

For pulmonary disease, the treatment (imipenem or meropenem or ceftazidime + doxycycline) should be prolonged to 6-12 months (TABLE 4). For the septicaemic form, the duration of treatment is 2 weeks IV followed by oral therapy for 6 months [2,12].

Post-exposure prophylaxis with trimethoprim-sulfamethoxazole (co-trimoxazole) is recommended in case of a biological attack, although this is based on experimental data: but the utility of post exposure prophylaxis in humans is still discussed.

There is no vaccine available for humans (glanders or melioidosis).

In countries where glanders is endemic in animals, prevention of the disease in humans involves identification and elimination of the infection in the animal population. Within the healthcare setting, transmission can be prevented by using common blood and body fluid precautions, while healthcare staff known to be immunocompromised should not have direct contact with glanders or melioidosis cases.

Conclusion

In conclusion, glanders was used during the first and second world wars with apparent success in animals. Due to this and the characteristics of the causative agent, we have to consider *B mallei* and *B pseudomallei* as possible biological weapons, although human infections expected from such an act, would be limited to those due to the primary dispersion

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* **BICHAT**, the European Commission's Task Force on Biological and Chemical Agent Threats, has developed this set of guidelines that may be the basis of national authorities' guidance, and may also be used directly by clinicians, general practitioners and specialists when confronted with patients infected by agents that may be due to deliberate release of biological agents. Ref. Bossi P, Van Loock F, Tegnell A, Gouvras G. Bichat clinical guidelines for bioterrorist agents. *Euro Surveill.* 2004; 9(12)

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Editorial note: *These clinical guidelines were reviewed by the Task Force and by two experts designated by each Member State of the European Union. This review was completed at the end of February 2003. The revised guidelines were submitted to the Health Security Committee which approved them in April 2003 and agreed their publication in a widely disseminated journal so as to allow access to as large an audience as possible. The editorial process of Eurosurveillance also introduced modifications that improved the contents of these guidelines.*

TABLE 1

Glanders and melioidosis: summary

Clinical features
Glanders and melioidosis produce similar clinical syndromes
Pulmonary form: pneumonia, pulmonary abscesses, pleural effusion Chest radiograph: bronchopneumonia, military nodules, infiltrates, cavitating lesions
Septicaemia: headache, photophobia, myalgias, flushing, cyanosis, jaundice, skin lesions (erythroderma, pustules, rash) lymphadenopathy, splenomegaly, hepatomegaly
Localised infection: skin-, brain-, visceral- abscesses, lymphadenitis, osteomyelitis, septic arthritis, parotid abscesses in children
Chronic infection: multiple abscesses (skin, soft tissues), viscera
Diagnosis
Isolation of the bacteria (*B. mallei, B. pseudomallei)* from: o sputum, urine, blood, pus, wound cultures o Serology testing
Treatment
o Imipenem or meropenem or ceftazidime initially IV until improved o Doxycycline + Co-trimoxazole, PO to complete 20 wks or o Amoxicillin + clavulanate, PO to complete 20 wks
Prophylaxis
No vaccine available for humans Post-exposure: trimethoprim-sulfamethoxazole (based on animal experiments only)

TABLE 2

Case definitions for glanders and melioidosis

Possible case
o **NA**
Probable case
o A severe, unexplained febrile illness or febrile death in a previously healthy person o Severe unexplained respiratory illness in otherwise healthy people o Severe unexplained sepsis or respiratory failure not due to a predisposing illness o Severe sepsis with unknown Gram-negative bacteria o A clinically compatible case with an epidemiological link to a confirmed case or with at least one positive supportive test for laboratory identification
Confirmed case
o A case that clinically fits the criteria for suspected glanders or melioidosis, and in addition, definitive positive results are obtained on one or more pathological specimens

NA: Not applicable
Source: [13,14]

TABLE 3

Case definitions for glanders or melioidosis due to deliberate release

Suspected deliberate release
o Two or more **suspected** cases of glanders/melioidosis that are linked in time and place, especially geographical related groups of illness following a wind direction pattern
Deliberate release
- Single confirmed case of indigenously acquired glanders/melioidosis o Without history of travel to an endemic area o Without occupational exposure - Two or more confirmed cases of glanders/melioidosis that are linked in time and place, especially geographical related groups of illness following a wind direction pattern

TABLE 4

Recommendations for treatment and post-exposure prophylaxis of glanders and melioidosis

		Treatment of suspected or confirmed clinical cases (2-3 weeks)	Post-exposure prophylaxis in case of suspected or confirmed exposure to the pathogen
Adults **Pregnant women**	**First line treatment**	- Imipenem: 50 mg/kg/day, up to 1g IV four times daily **Or** - Meropenem: 500 mg to 1g IV three times daily.	No recommendations can currently be given
It is recommended, when possible, to stop breastfeeding.	**Second line treatment**	- Ceftazidime: 2g IV, three time daily	
	Combination treatment with imipenem or meropenem or ceftazidime in severe cases	- Doxycycline: 100 mg IV bid **or** -Trimethoprim-sulfamethoxazole: TMP (6-8 mg/kg/day) + SMX (40 mg/kg/day) IV in one or two divided doses followed by TMP (6-8 mg/kg/day) + SMX (40 mg/kg/day) orally in one or two divided doses.	
Children	**First line treatment**	- Imipenem: **> 40 kg** (idem adult) 50 mg/kg/day, up to 1g IV four times daily **> 3 years**: 15 mg/kg four times daily IV **3 months-3 years**: 15-25 mg/kg four times daily IV. **Or** - Meropenem: **> 3 months**: 10-20 mg/kg IV 3 times daily. **> 40 kg**: idem adult.	No recommendations can currently be given
	Second line treatment	- Ceftazidime: **.> 2 months**: 100mg/kg/day IV in 3 divided doses. **.< 2 months**: 60mg/kg/day IV in 2 divided doses.	
	Combination treatment with imipenem or meropenem or ceftazidime in severe cases	- Doxycycline: . >8 years and > 45 kg: adult dose . >8 years and < 45 kg or < 8 years: 2.2 mg/kg IV bid . < 8 years: 2.2 mg/kg IV twice daily (max 200 mg/d) **or, for children < 8 years** -Trimethoprim-sulfamethoxazole: TMP (6-8 mg/kg/day) + SMX (30-40 mg/kg/day) IV in two divided doses followed by TMP (6-8 mg/kg/day) + SMX (30-40 mg/kg/day) orally in one or two divided doses.	

Source: [12]