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

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Francisella tularensis **is one of the most infectious pathogenic bacteria known, requiring inoculation or inhalation of as few as 10 organisms to initiate human infection. Inhalational tularaemia following intentional release of a virulent strain of *F. tularensis* would have great impact and cause high morbidity and mortality. Another route of contamination in a deliberate release could be contamination of water.**

Seven clinical forms, according to route of inoculation (skin, mucous membranes, gastrointestinal tract, eyes, respiratory tract), dose of the inoculum and virulence of the organism (types A or B) are identified. The pneumonic form of the disease is the most likely form of the disease should this bacterium be used as a bioterrorism agent. Streptomycin and gentamicin are currently considered the treatment of choice for tularemia. Quinolone is an effective alternative drug. No isolation measures for patients with pneumonia are necessary. Streptomycin, gentamicin, doxycycline or ciprofloxacin are recommended for post-exposure prophylaxis.

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Introduction

Tularaemia (rabbit fever or deerfly fever) is a bacterial zoonosis caused by a small, non-motile, Gram negative coccobacillus, *Francisella tularensis*. This agent is one of the most infectious pathogenic bacteria known, requiring inoculation or inhalation of as few as 10 organisms to initiate human infection [1,2]. Tularaemia is distributed worldwide but occurs especially in the northern hemisphere, in Europe, North America, the Middle East, the former Soviet Union, China and Japan.

Tularaemia outbreaks have been commonly reported in some areas of Europe such as in Sweden, Finland, Spain and Kosovo[3-5]. In 2000, 270 cases in Sweden and 327 cases in Kosovo were reported [4,5]. During the last decade of the 20th century, 1368 cases were reported in the United States (US) (<200/year) [3]. In some endemic regions, outbreaks occur frequently, whereas adjacent parts of the same country may be completely free of the disease [4]. Usually, cases are reported during the summer, from June to September, when arthropod-borne transmission is more common.

F. tularensis may be found in contaminated water or soil, infected ticks or deerflies, wild animals (hares, rabbits, squirrels, muskrats, beavers, deer) and occasionally certain domestic animals (sheeps, cats or dogs) [3,6,7]. A variety of small animals are probably the natural reservoirs of infection. They acquire infection through bites by ticks, flies, and mosquitoes, or by contact with contaminated environments. Humans become infected by various modes, including arthropod bites (ticks, deerflies, mosquitoes), which represent a major route of contamination, handling infectious animal tissues or fluids, direct contact with or ingestion of contaminated water, food, or soil, and inhalation of infective aerosols (e.g. aerosolisation by using a lawn mower or a brush cutter) [1,8,9].

Tularaemia and bioterrorism

Inhalational tularaemia following intentional release of a virulent strain of *F. tularensis* would have the greatest adverse human consequence because of its very high infectivity after aerosolisation. Outbreaks of pneumonic tularaemia, particularly in low incidence areas, should prompt consideration of bioterrorism [1]. It has been estimated that an aerosol dispersal of 50 kg of virulent *F. tularensis* over a metropolitan area with 5 million inhabitants would result in 250 000 incapacitating casualties, including 19 000 deaths [10]. An outbreak of tularaemia reported in Soviet and German soldiers during the second world war may have been the result of intentional release [1]. *F. tularensis* has been studied, weaponised and stockpiled by several countries, including Japan and the US [1].

Another route of contamination in a deliberate release could be contamination of water [1]. Transmission from person to person has never been reported.

Microbiological characteristics

F. tularensis is a non-motile, obligatory aerobic, facultative intracellular Gram negative coccobacillus. Three subspecies are known: *F. tularensis* subsp *tularensis* (type A), *F. tularensis* subsp *holarctica* (type B) and *F. tularensis* subsp *mediasiatica* [11]. These subspecies are not serologically distinguishable. The subcutaneous injection of 10 to 1 million type A organisms is usually fatal to rabbits, whereas inoculation with 1 million type B organisms is not associated with death in these animals. In addition, by either the subcutaneous or aerosol route, infection with 50 type A organisms will induce moderately severe disease in humans, whereas inoculation with 12 000 type B organisms produces mild, self-limiting infection [12]. Type A is the most common type reported in North America whereas type B is more frequent in Eurasia [13]. Franscisellas do not produce toxins. *F. tularensis* has a thin lipopolysaccharide-containing envelope. It is also a hardy, non-spore-forming organism that can remain alive for weeks at low temperature in water or soil or decaying animal carcasses, and for years in frozen rabbit meat [9].

Clinical features

After an incubation period of 3 to 5 days (range 1-25 days), seven clinical forms, according to route of inoculation (skin, mucous membranes, gastrointestinal tract, eyes, respiratory tract), dose of the inoculum and virulence of the organism (types A or B) are identified [1,2] (TABLE I). The different presentations include

pneumonic, ulceroglandular, typhoidal, glandular, oculoglandular, oropharyngeal and septicaemic. After inoculation, *F. tularensis* is ingested by and multiplies within macrophages.
Usually, whatever the clinical form, the onset of tularaemia is abrupt with fever, chills, myalgias, arthralgias, headache, coryza, sore throat, and sometimes pulse-temperature dissociation, nausea, vomiting and diarrhoea.
Respiratory tularaemia usually results from the direct inhalation of contaminated aerosols (primary pneumonia or inhalational tularaemia) or follows secondary haematogenous spread from a distal site (secondary pneumonia) [6,14]. In the US, approximately 10 to 20% of patients with tularaemia present with pneumonia [8,12,14]. In Sweden, during the 2000 tularaemia outbreak, more than 5% of patients were reported to have pneumonia [4]. Inhalational tularaemia would appear to be more common in a disease endemic area than in an emergent area [4]. Inhalational exposure commonly presents as an acute flu-like illness without prominent signs of respiratory disease.
Features include fever, chills, headache, muscle aches, joint pain, non-productive cough, pharyngitis, and pleuritic chest pain. Signs from the respiratory system may, however, be minimal or absent. Chest radiography shows frequently peribronchial infiltrates, typically progressing to bronchopneumonia, pleural effusions and hilar lymphadenopathy. Interstitial pneumonia, cavitary lesions, bronchopleural fistulae and calcifications have been reported in some patients. A complete blood count is often normal. Progression to severe pneumonia with breathing difficulty, bloody sputum, respiratory failure, systemic forms and death may occur if appropriate treatment is not started.
The main differential diagnoses are diseases similar to other bioterrorism agents such as plague, pulmonary anthrax (even if the progression of tularaemia is slower than plague or anthrax) or Q fever.
The diagnosis of tularaemia due to a deliberate release would be suggested if large numbers of patients present with an atypical pneumonia.

Ulceroglandular tularaemia (75% to 85%) is the most common form reported in patients with tularaemia [4,5]. It arises from handling a contaminated carcass or following an arthropod bite. Typically a local papule appears at the site of inoculation associated with symptoms including fever and aches. The lesion may be pruritic and enlarges to form a pustule, which ruptures and develops into a painful, indolent ulcer, possibly covered by an eschar. Ulcers are usually single lesions of 0.4 to 3.0 cm in diameter. A localised vesiculopapular eruption may also occur. Lesions acquired from mammalian vectors are usually located on the upper extremities, whereas lesions acquired from arthropod vectors are usually located on the lower extremities. The lesion is associated with tender enlargement of one or more regional lymph nodes, which may become fluctuant and rupture releasing caseous material. Local disease often continues to progress despite appropriate antibiotic therapy. Neither severe diseases nor complications are usually noted with this form of the disease. Lymphadenopathy may persist for as long as 3 years.

Glandular tularaemia *(5% to 10%)* presents with lymphadenopathy and fever but without ulcer.

Oculoglandular tularaemia *(1% to 2%)* follows airborne exposure, autoinoculation or after cleaning infected animal carcasses**.** Ulceration of the cornea produces purulent conjunctivitis, chemosis, periorbital oedema, conjunctival nodules or ulceration, pain and is accompanied by tender preauricular or cervical lymphadenopathy [1,15].

Oropharyngeal tularaemia *(25%)* is acquired by drinking contaminated water or ingesting contaminated food, direct inoculation from the hands to the mouth and sometimes by inhaling contaminated droplets or aerosols. Affected persons may develop a stomatitis, but more commonly an exudative pharyngitis or tonsillitis ensues with or without painful mucosal ulceration. A retropharyngeal abscess or suppuration of regional lymph nodes may occur.

Typhoidal tularaemia is used to define a non-specific acute flu-like illness, often with diarrhoea and vomiting, headache, chills, rigors, myalgia and arthralgia, prostration and weight loss. There are no clinical signs indicating either site of inoculation or anatomic localisation of infection. Typhoidal tularaemia may follow ingestion or inhalation of *F. tularensis*. Pneumonia, mucocutaneous lesions and regional lymphadenopathy are usually absent.

Tularaemia sepsis is potentially severe and fatal. Any form of tularaemia may be complicated by sepsis. Non-specific signs such as fever, abdominal pain, diarrhoea, and vomiting may be prominent early in the course of illness. Pulse-temperature dissociation occurs in less than 50% of cases. Then patients typically appear toxic and may progress to septic shock, disseminated intravascular coagulation, haemorrhage, acute respiratory distress syndrome, confusion, organ failure and coma.
Pericarditis can complicate both syndromes (2). Mild hepatitis is common. Occasionally, erythema nodosum, enteritis, appendicitis, peritonitis and meningitis have been reported [2,16-18].
Without antibiotics, the overall mortality for type A of tularaemia is 8% (range 5% to 15%); 4% for ulceroglandular and 30%-50% for typhoidal, septicaemic and pneumonic types. With appropriate treatment, mortality is reduced to 1%. Type B infections are rarely fatal [1,2].

Diagnosis

Clinical diagnostic suspicion remains crucial. Nevertheless, within an outbreak, the first case of tularaemia is not always readily diagnosed. Case definitions of suspected or confirmed cases and cases due to deliberate release are shown in Tables 2 and 3.

F. tularensis may be identified by direct examination of secretions, exudates, or biopsy specimens using direct fluorescent antibody or immunohistochemical stains.
Specimens of sputum, pharyngeal washings, fasting gastric aspirates, pleural fluid, exudates from cutaneous lesions, biopsies of lymph nodes and blood may be culture positive for *F. tularensis*. It is difficult to culture, and the handling of this bacterium poses a significant risk of infection to laboratory personnel. Nevertheless, a laboratory experienced in handling *F. tularensis* should perform antibiotic sensitivity.
Antigen detection assays, PCR, enzyme-linked immunosorbent assay (ELISA) may be used to identify *F. tularensis*. These two last methods have not been adequately evaluated for the diagnosis of pneumonic tularaemia. Nevertheless, a fourfold change in titre between acute and convalescent serum specimens, a single titre of at least 1/160 to tube agglutination or 1/128 for microagglutination is diagnostic for *F. tularensis* [1,19-21]. Serum antibody titres do not attain diagnostic level until 10-14 days after onset of illness. Serologic testing is useful only retrospectively but confirms the diagnosis. For definitive laboratory confirmation, culture and an increase in specific antibodies in paired sera are required. The raise in titres is commonly seen 10-14 days after the onset of the disease.

Treatment

Many guidelines have been published for treatments and prophylaxis of tularaemia [1,19-27] (TABLE 4). Streptomycin and gentamicin are currently considered the treatment of choice for tularaemia [24-26]. Treatment with aminoglycosides should be continued for 10 days [1,19-23]. Quinolone may be an effective alternative drug [24]. Despite the absence of large data in patients with tularaemia, ciprofloxacin principally or ofloxacin should be prescribed for 10 to 14 days [1,23]. If administered, during a short duration, tetracyclines and chloramphenicol are associated with relapses and should be given for at least 14 to 21 days [1,23]. In severe cases, combination of two antibiotics such as aminoglycosides and fluoroquinolones should be considered. Macrolides antibiotics in treating tularaemia is not recommended [1]. Usually, the beta-lactams are considered ineffective. No isolation measures for patients with pneumonia are necessary.

Streptomycin, gentamicin, doxycycline or ciprofloxacin are recommended for post-exposure prophylaxis and must be taken for at least 14 days.

An unlicensed live-attenuated vaccine is available, which does appear to offer protection against ulceroglandular and pneumonic tularaemia. In the absence of larger data, vaccination is not recommended for post-exposure prophylaxis [1,27].

In conclusion, *F. tularensis* is one of the most infectious pathogenic bacteria known. A biological attack with a virulent strain of aerosolised *F. tularensis* type A would have a great adverse human consequence. In humans, ulceroglandular tularaemia is the most common form of the disease and is usually a consequence of a bite from an arthropod vector that has previously fed on an infected animal. The pneumonic form of the disease occurs rarely but is the most likely form of the disease should this bacterium be used as a bioterrorism agent. The diagnosis of tularaemia due to a deliberate release would be mainly suggested in patients presenting with an atypical pneumonia.

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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

Summary of clinical and biological description of tularaemia

Clinical features
• Incubation period: **3 to 5** days **Tularaemia pneumonia** (primary and secondary pneumonia) • inhalational exposure presents as an acute flu-like illness • progression to severe pneumonia with bloody sputum, respiratory failure and death, if appropriate treatment is not started • chest radiography: peribronchial infiltrates, bronchopneumonia, pleural effusions and hilar lymphadenopathy **Ulceroglandular tularaemia,** most common form (75% to 85%) • local papule at the site of inoculation associated with fever and aches • papule pruritic→ enlarges to pustule → ruptures to painful, indolent ulcer, which may be covered by an eschar • tender enlargement of ≥ 1 regional lymph nodes, which may become fluctuant and rupture releasing caseous material **Glandular tularaemia** • lymphadenopathy and fever • No ulcer **Oculoglandular tularaemia** • purulent conjunctivitis, chemosis, conjunctival nodules or ulceration, periorbital oedema • tender preauricular or cervical lymphadenopathy **Oropharyngeal tularaemia** • stomatitis, exudative pharyngitis or tonsillitis ± painful mucosal ulceration • retropharyngeal abscess or suppuration of regional lymph nodes **Typhoidal tularaemia** • acute flu-like illness • diarrhoea, vomiting, headache, chills, rigors, myalgia, arthralgia, weight loss, prostration • No indication of inoculation site • No anatomic localisation of infection **Tularaemia sepsis** • non-specific signs confusion • septic shock, disseminated intravascular coagulation and haemorrhage, Acute Respiratory Distress Syndrome, organ failure and coma
Diagnosis
Confirmatory tests for identification of *F. tularensis* [28,29] • isolation of *F. tularensis* from a clinical specimen • demonstration of a specific antibody response in serially obtained sera **For probable case** • a single high titre • detection of *F. tularensis* in a clinical specimen by fluorescent assay
Treatment
• private room placement for patients with pneumonia is NOT necessary • treatment of choice: Streptomycin and gentamicin (10 days) • Quinolones effective alternative (10 to 14 days) • Tetracyclines and chloramphenicol are associated with high relapse rate, therapy at least 14 to 21 days • Combination of two (aminoglycosides and fluoroquinolones) in severe cases
Post-exposure prophylaxis
• Streptomycin, gentamicin, doxycycline or ciprofloxacin (14 days) • Vaccination is NOT recommended for post-exposure prophylaxis

TABLE 2

Case definitions of tularaemia

Possible case
• NA
Probable case
• a severe, unexplained febrile illness or febrile death in a previously healthy person • severe unexplained respiratory illness in otherwise healthy people • severe unexplained sepsis or respiratory failure not due to a predisposing illness • severe sepsis with unknown Gram-negative coccobacillary species that fails to grow on standard blood agar, identified in the blood or cerebrospinal fluid • a clinically compatible case that fulfils the laboratory criteria for a probable case or has an epidemiological link
Confirmed case
• a clinically compatible case with positive confirmatory laboratory tests

Source: [28,29]

TABLE 3

Definition of a deliberate release with *F. tularensis*

Suspected deliberate release
• Two or more **suspected** cases of tularaemia that are linked in time and place, especially ***geographically related groups*** of illness following a wind direction pattern
Deliberate release
• Single confirmed case of indigenously acquired tularaemia NOT explained by occupational exposure

TABLE 4

Recommendations for treatment and post-exposure prophylaxis of tularaemia

		Treatment of suspected or confirmed clinical cases (10-21 days)	Post-exposure prophylaxis (14 days)
Adults **Pregnant women**	**First line treatment (10 days)**	- Gentamicin: 5 mg/kg IV in 1 or 2 doses daily **or** - Streptomycin: 1 g IM twice daily	
It is recommended, when possible, to stop breastfeeding.	**Second line treatment; first line prophylaxis (14 days)**	- Ciprofloxacin: 400 mg IV bid followed by 500 mg per os bid **or** - Ofloxacin: 400 mg IV bid followed by 400 mg per os bid **or** - Levofloxacin: 500 mg IV once a day, followed by 500 mg per os once a day	- Ciprofloxacin: 500 mg per os bid **or** - Ofloxacin: 400 mg per os bid **or** - Levofloxacin: 500 mg per os once a day
	Third line treatment; second line prophylaxis (21 days)	- Doxycycline: 100 mg IV bid followed by 100 mg bid per os	- Doxycycline: 100 mg bid per os
Children	**First line treatment (10 days)**	- Gentamicin: 2.5 mg/kg IV 3 times daily **or** - Streptomycin: 15 mg/kg IM twice daily (max; 2g)	
	Second line treatment; first line prophylaxis (14 days)	- Ciprofloxacin: 10-15 mg/kg IV bid followed by 10-15 mg/kg per os bid	- Ciprofloxacin: 10-15 mg/kg per os bid
	Third line treatment; second line prophylaxis (21 days)	- Doxycycline: . >8 years and > 45 kg: adult dose . >8 years and < 45 kg or < 8 years: 2.2 mg/kg IV bid followed by 2.2 mg/kg per os bid (max 200 mg/d)	- Doxycycline: . >8 years and > 45 kg: adult dose . >8 years and < 45 kg or < 8 years: 2.2 mg/kg per os bid (max 200 mg/d)

Source: [23]