

## Summary

- Tularemia: bacterial infection by *Francisella tularensis*
- Contact with infected animals (e.g. wild rabbits), contaminated dust and water
- Fever, skin lesions and lymphadenopathy
- Other presentations include ocular, septicaemic and pneumonic forms
- Diagnosis: clinical presentation, culture and/or antibodies

## General

Tularemia (syn. tularaemia) is an infectious disease caused by a small, pleomorphic, aerobic, non-motile and non-spore-forming Gram-negative coccobacillus, ***Francisella tularensis*** (formerly *Pasteurella tularensis*). The generic name refers to Edward Francis, a scientist who devoted many years of his life to studying the disease. The species name refers to Tulare County in California, an area where tularemia occurs regularly. There are three biovars, *F. tularensis tularensis* (biovar A, syn. nearctica), *F. tularensis holarctica* (biovar B, syn. palearctica) and *F. tularensis novicida* (biovar C).

In humans, infection with type A has a much more serious course than with type B. Type A is mainly found in rabbits and rodents. Type B is found more in animals that live near water and is predominant in Eurasia. Type A is predominant in North America, although it is sometimes found in Central Europe. Biovar C is a germ with low virulence, found in North America.

**Infections in Europe or Russia tend to have a much milder course than infections in the New World.** Type A is fatal to guinea pigs and rabbits, unlike type B. Serologically there is no difference between the three forms. Both phagocytosing cells and non-phagocytosing cells can be invaded. **Intracellular multiplication** occurs. Specific exotoxins such as in anthrax have so far not been demonstrated. There is however an **endotoxin**, similar to other Gram-negative pathogens. The disease has been studied for possible use as a **biological weapon**.

## Transmission

The infection is restricted to certain areas and **only occurs in the Northern Hemisphere**: Mexico, USA, Canada, Scandinavia, eastern Europe and in Russia as far as Siberia. Cases

which occurred in Utah led to the name “Pahvant Valley fever”. There are few infections in Japan, where the disease is known as “yatobyoo”. In 1939 some 2300 cases were reported in the USA, but since then the number of infections has fallen substantially. In 1966-67 there was an epidemic with more than 600 cases in Sweden. In the period 1999-2000, 327 cases were reported in post-war Kosovo. In the New World, cottontail rabbits and jackrabbits form an important reservoir, hence the common name “**rabbit fever**”. Other animals such as dogs and cats, sheep, squirrels, skunks, beavers, muskrats and even birds can be infected. Prairie dogs can become chronic carriers. **Various occupations** are at an increased risk of tularemia: hunters, butchers, veterinary surgeons, and furriers. There have been no reports of person-to-person transmission. Transmission is by **inhalation, ingestion, inoculation or contamination through direct contact** with infected material, including water. Although the pathogen does not form spores -unlike anthrax- the bacterium can **survive for 2-6 months in mud, water and carcasses**.

Transmission can be by the bite of hard **ticks, fleas** or **horseflies** such as tabanids (“deer fly fever”). These arthropods first infect themselves by sucking the blood of an infected animal. With ticks there is transovarian transmission. The pathogen is present in small numbers in tick saliva and in greater numbers in tick faeces. The ticks that are notorious for transmitting *Francisella tularensis* in the USA are *Dermacentor andersoni* (Rocky Mountain wood tick), *D. variabilis* (American dog tick), *D. occidentalis* (Pacific coast dog tick) and *Amblyomma americanum* (Lone Star tick). **Skin contact** with the infected tissue of an animal that has for example been hunted and skinned is dangerous. The disease can occur after **eating infected** meat. Racoons, snakes or coyotes can carry the bacteria in their mouths.

Domestic animals or wild animals that have had direct contact with an infected animal can cause infection in man. Transmission by **aerosol** is possible. Transmission can occur by breathing in contaminated **dust** that has been whipped up, such as by a grass cutter or brush cutter. By this route the pathogen is extremely infectious. This was one of the reasons why tularemia was studied as a bio warfare agent. Fewer than 50 bacteria are enough to cause pulmonary infection. The infectious dose by the oral route is much higher: 10<sup>8</sup> organisms.

## Clinical aspects

The disease occurs in different clinical forms. Its presentation depends on the route of infection, the size of the inoculum, the virulence of the organism and the immune status of the patient.

**Ulceroglandular form.** About 80-90% of cases are of this form. The point of entry may be the site where an arthropod has bitten. Microtraumata with small tissue defects in the skin form a point of entry. After an incubation period of 2-4 days (1-10, exceptionally 21) there is **suddenly high fever with rigors**, together with headache, nausea, vomiting and pronounced malaise and fatigue. A primary red, slightly itching and slightly painful skin **papule** is observed. This soon becomes pustular and necrotic. The ulcer is usually on the hands. Afterwards there is **local lymphadenopathy** (buboes) with swelling of the epitrochlear and/or axillar lymph nodes. If inoculation occurs on a leg, there are swollen inguinal/femoral lymph nodes. Oral infection results in cervical lymphadenopathy. The lymph nodes may **suppurate** and drain to the skin. A non-specific roseola-like maculopapular rash appears in 20% of cases. Rarely there is erythema nodosum.

**Oculoglandular form** (1%). With inoculation in the conjunctiva, for example due to dirty fingers, severe **painful conjunctivitis** develops, followed by swelling of the ipsilateral lymph nodes. Keratitis and corneal ulceration may follow. If the pre-auricular nodes are swollen, this is called **Parinaud's oculoglandular complex**. This is to be distinguished from cat-scratch disease, tuberculosis, sporotrichosis, sarcoidosis and syphilis. [P.S. Do not confuse the term with Parinaud's syndrome, a neurological entity with vertical gaze abnormalities due to lesions in the dorsal part of the midbrain, the colliculi superior.]

A **purely glandular** form can occur, but this is rare (2%). It is a form consisting of local lymphadenitis without a primary skin lesion. Sometimes there is cervical adenopathy, which suggests oral ingestion of the pathogens.

**Oropharyngeal form**, with stomatitis and/or severe inflammation of the throat (pharyngitis, tonsillitis) that can resemble diphtheria, together with cervical lymphadenopathy.

**Gastrointestinal form** follows eating infected meat. Mesenterial lymphadenopathy,

abdominal pain, nausea, vomiting, diarrhoea and intestinal blood loss from intestinal ulcers occur.

**Typhoidal form.** Here sepsis with abdominal pain predominates. Myalgia and joint pain may occur but are unspecific. **Disseminated necrotic foci** are found throughout the body (1 mm to 8 cm in diameter). The **systemic toxicity** is pronounced. Delirium can occur. Splenomegaly and perisplenitis can arise. A full blood count reveals a normal or raised leukocyte count. Mediastinitis, meningitis, peritonitis and lung abscess can occur as complications but are rare. Tularemia is a rare cause of “fever of unknown origin”.

**Pulmonary tularemia.** Tularemia is a rare cause of **atypical pneumonia as well as fulminant pneumonia**. Primary pulmonary tularemia progresses rapidly with fever, cough, dyspnoea and a burning feeling under the sternum. Pleural effusions and pleuritic pain can occur. On a chest X-ray there are poorly defined infiltrates and the concave lining of pleural fluid can be seen. Mediastinal lymphadenopathy can occur. Pneumonia does not always have to be primary but can be secondary (cfr similar situation in plague).

### **Differential diagnosis:**

Depending on the clinical presentation, several other diseases can also be considered. The clinical picture of a **febrile syndrome of sudden onset with a skin lesion and swollen lymph nodes after contact with a possibly infected animal**, could be:

- ulceroglandular tularemia (*Francisella tularensis*), but also
- bubonic plague (*Yersinia pestis*) or
- cutaneous anthrax (*Bacillus anthracis*).
- Skin infection with pyogenic bacteria such as *Streptococcus pyogenes* and *Staphylococcus aureus* are in most cases not difficult to diagnose.
- Rat bite fever, also known as “sodoku” is caused by *Spirillum minus* and can follow a bite from an infected rat. Relapsing fever, skin lesions and joint pain are important.
- Dog bites are often infected with *Capnocytophaga canimorsus*.
- Scrub typhus (*Orientia tsutsugamushi*) occurs in Asia (geographically different area from tularemia). Here the lymphadenopathy is less pronounced.
- Swimming pool granuloma caused by *Mycobacterium marinum* may be a possibility, but its

course is less rapid, and the general condition is excellent.

- Cat-scratch fever (*Bartonella henselae*) is a more difficult differential diagnosis.
- Sporotrichosis can mimic tularemia.

**Oropharyngeal tularemia** must be distinguished from diphtheria, severe streptococcal pharyngitis, actinomycosis, lymphoma, tuberculosis and Plaut-Vincent pharyngitis.

**Atypical pneumonia due to tularemia** can resemble infections caused by *Coxiella burnetii*, *Legionella pneumophila*, *Chlamydia psittaci*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae* and even *Histoplasma capsulatum*. Fulminant pneumonia can resemble anthrax, pneumonic plague, SARS and pulmonary hantaviriosis caused by the Sin Nombre virus.

**Typhoidal tularemia** may resemble typhoid fever (*Salmonella typhi*), brucellosis (*Brucella* sp), typhus (rickettsioses such as Rocky Mountain spotted fever) and ehrlichioses. The latter two should be especially considered if it is known that the person has been bitten by a tick. If granulomata are present tuberculosis and sarcoidosis can be brought into the differential diagnosis of tularemia. Haverhill fever is caused by *Actinobacillus muris* (= *Streptobacillus moniliformis*) and can follow a rat bite or by drinking milk infected with rat urine. In practice the diagnosis of Haverhill fever can only be confirmed by identifying the pathogen in a culture.

## Diagnosis

*Francisella tularensis* type A is a **level 3 pathogen**. As the bacterium is highly infectious, it is dangerous to try to isolate it in a standard laboratory (culturing skin lesions, sputum, pleural fluid, blood culture). Laboratory infections have been described. It is not an easy bacterium to culture. Clinical samples can be examined quickly with fluorescing antibodies.

**Serology** is important. In some patients antibodies are positive after one week but in other patients it takes three weeks before antibodies can be detected. This can lead to false-negative results early in the disease. In the right context a single raised value of 1/160 can suggest the diagnosis. There is a limited cross-reactivity with *Brucella* and *Legionella* bacteria. These antibodies play a minor role in protection. It is predominantly primary (polymorphonuclear) and cellular immunity which is responsible for protection. The T-

lymphocyte-dependent protection develops over the course of 2-4 weeks. Initially a lesion contains many neutrophils.

A biopsy of a cutaneous lesion may be pathologically similar to tuberculosis, but the evolution of tularemia is far more rapid. There is **granuloma** formation with epitheloid cells, lymphocytes and polynuclear giant cells. PCR exists for the bacterium.

## Treatment

The pathogen is sensitive to **gentamicin**, **streptomycin** and to **fluoroquinolones** and **doxycycline**. Tularemic meningitis can be managed with an aminoglycoside combined with chloramphenicol or doxycycline. If the patient is pregnant gentamicin is still the recommended treatment. If treatment is given soon after infection, mortality remains low. Skin wounds require local care. In the case of ocular tularemia moist dressings, eyedrops with homatropine and dark glasses are recommended.

## Prevention

Avoid **ticks and insect bites** (protective clothing, repellents, permethrin). Wear gloves and masks **when touching wild animals** (e.g. the fieldwork of a biologist) particularly if these are rabbits in an endemic area. Shot game must be very thoroughly cooked before it can be eaten. The previously used vaccine prepared from the live vaccine strain (LVS) of *F. tularensis* subspecies *holarctica* is no longer available because of concerns about its unknown mechanisms of attenuation and stability. Using leaf blowers to clear gardens, streets or parks in areas with tularemia is not advised (airborne transmission via contaminated dust).