Journal of Microbiology and Infectious Diseases / JMID
2014; Special Issue 1: S17-S21
doi: 10.5799/ahinjs.02.2014.S1.0137

REVIEW ARTICLE

Tularemia (Rabbit Fever)

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ABSTRACT

Tularemia is a zoonotic disease caused by *Francisella tularensis*, an aerobic, sedentary and non-sporing gram negative bacillus. It is transmitted to people via the handling of an infected animal, contact with the body fluids of an infected animals, eating, drinking contaminated water or food, breathing aerosols or tick bite. Even though it is easily transmitted during the culture process, it is not transmitted human-to-human. *J Microbiol Infect Dis 2014; Special Issue 1: S17-S21*

Key words: Tularemia, *Francisella tularensis*, rabbit fever.

Tularemi (Tavşan Ateşi)

ÖZET

Tularemi, aerop, hareketsiz, sporsuz, gram negatif bir basil olan *Francisella tularensis*'in neden olduğu zoonotik bir hastalıktır. İnsanlara, enfekte bir hayvanın işlenmesi, enfekte hayvanın vücut sıvılarıyla temas, kontamine su veya besinlerin yenmesi, içilmesi aerosollerin solunması ya da kene ısırığı ile bulaşır. Kültür işlemi sırasında kolayca bulaşmasına rağmen, insandan insana bulaşmaz.

Anahtar kelimeler: Tularemi, *Francisella tularensis*, tavşan ateşi.

MICROBIOLOGY

Tularemia is a zoonotic disease caused by *Francisella tularensis*, an aerobic, sedentary and non-sporing gram negative bacilli.[1] *F. tularensis* is found in more than 100 animals in nature including rabbits, squirrels and rats. It persists for weeks in water and humid environments. This bacterium is highly virulent. 10-50 bacteria are enough for the disease to develop.

F. tularensis has two main biovars

• *F. tularensis* biovar tularensis (Type A) is very virulent, its biochemical properties are different (generates acid out of glycerol, has citrulline ureidase activity) and it is rampant in North America.

• *F. tularensis* biovar holarctica (Type B) has lower virulence, it is rampant in Europe and Asia.[2]

EPIDEMIOLOGY

Tularemia is a disease of the northern hemisphere (between the 30th and 71st latitudes). Reports have been received from North European counties with Bulgaria, Hungary, Austria and Germany ranking the first.

It is considered a biological weapon due to the resistance of the agent to the environmental conditions, the sensitivity of most people to the disease and the high virulence. It is estimated that 250.000 persons will be affected and 19.000 persons will die if 50 kg Francisella powder in virulent form is dispersed onto a city with a population of 5 million from the air.[3]

The disease is more frequent among males above the age of 30 although it develops in all age groups. Most of the cases witnessed in Western Europe and America are predators. However, water-born epidemics have been reported in Eastern Europe and Turkey. It may be transmitted to laboratory staff during bacteriological procedures.[4] The bacteria persist in water, hay or mud for weeks, not to say, months. Natural grass or potable water may be contaminated with *F. tularensis*.[5]

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Received: 10 February 2014, Accepted: 29 March 2014
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The incidence of tularemia is related to the socio-economic conditions. Generally speaking, it is more frequent in rural areas. Its incidence is increased during wars due to the deterioration of general conditions, compromised hygiene, and increased contact with rodents, ticks and rabbits. For example, an epidemic of 317 cases in Kosovo was reported in the years 1999-2000 during which the war prevailed.[6-8]

In Turkey, tularemia cases have been reported since 1936 (Thrace).[9] However, more detailed reports have been received from Bursa and its vicinity since 1988 and from Thrace, Marmara and Western Black Sea regions in recent years.[10-12] After that, tularemia cases were reported in Bolu Gerede, Çanakkale, Bilecik, Zonguldak, Samsun, Düzce, Gölcük, Sinop, Amasya, Zonguldak, Kastamonu, Bartın (Figure 1). Since the year 2009, several cases of patients from Çorum, Yozgat, Anakara and the vicinity have been reported. Furthermore, the majority of reports from Turkey are due to the contamination of water supply.[13]

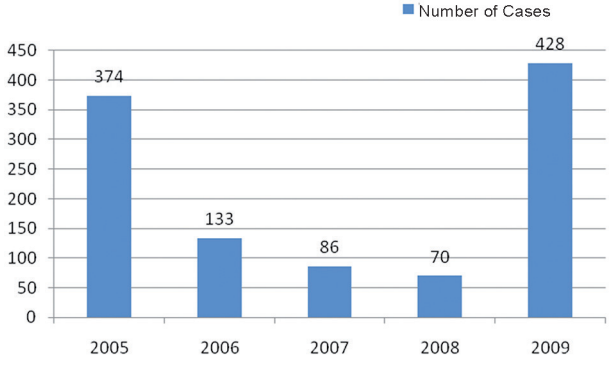

Figure 1. Tularemia cases of Turkey

CLINICAL CHARACTERISTICS

Tularemia may progress with no or mild symptoms whereas it may also result in pneumonia, severe sepsis or death. The major clinical forms of tularemia are oropharyngeal, ulceroglandular, glandular, oculoglandular, typhoid and pneumonic tularemia. In many patients, these clinical forms are intertwined. The clinical picture of the disease varies according to the point of entrance of the agent, whether there is systemic involvement and the bacterial virulence.[14,15]

The incubation period of the disease is circa 3-5 days (1-21 days). It starts suddenly with sore throat, weakness, loss of appetite, low-back pain, headache, trembling, febrility and sweating. Muscle pain, vomiting, sore throat and abdominal pain may develop. Fever-pulse discordance is identified in almost all of the patients. The symptoms vary according to the localization of the disease. The fever is reduced by itself within a few days. However, the other symptoms (loss of weight, fatigue and lymphadenomegaly) last for weeks (Figure 2).[14]

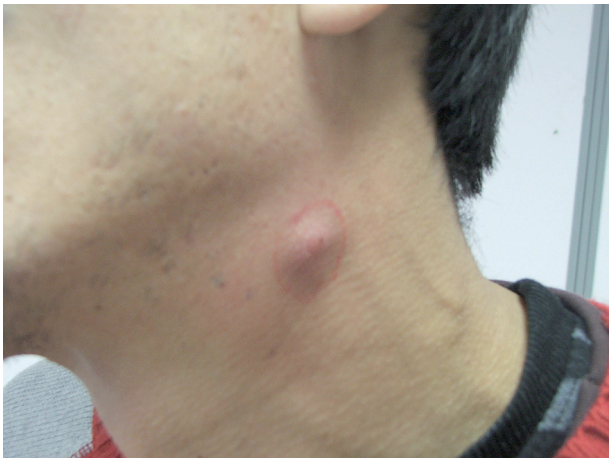

Figure 2. Cervical lymphadenopathy in a tularemia patient

Ulceroglandular tularemia

The clinical form with the highest incidence in the USA and European countries is the ulcerated glandular form. It is clinically characterized by fever, ulcer in the inoculation site and local lymphadenopathies. A small, tender, palpable papule in the first inoculation site of the bacterium goes through a rapid pustulization turning into an ulcer with sharp, necrotic edges. In addition to fever, there is also sensitivity in the lymphatic nodes of the lesion site. Generally speaking, the lymphatic notes in the axillary and inguinal sites are swollen and tender. Untreated ulcers heal with scars within months.[14,15]

Glandular Tularemia

Among all forms of tularemia, the incidence of glandular disease ranges between 3-20%. The glandular disease presents only with lymphadenopathy without any local lesions. The point of entrance of the bacteria cannot be located. Patients suffer from fever, weakness and fatigue.[5]

Typhoidal Tularemia

A patient with typhoidal tularemia generally presents with fever the cause of which is unknown. Pa-

tients have an intoxicated appearance. They suffer from headache, nausea, diarrhea and fever without lymphadenopathy. Signs of multiple organ involvement (pneumonia, meningitis, hepatitis, carditis, relative bradicardia, nephropathy, etc.) appear. It is highly difficult to diagnose if there no history of tick bite or epidemiological information are available. Blood culture positivity is frequent.[1]

OCULOGLANDULAR TULAREMIA

The bacteria enter through the conjunctival sac by means of contaminated fingers, contaminated water and aerosols. It is mostly one-sided. The eyelids are swollen and painful. It causes a yellow nodule and ulcer in the conjunctiva. The affected lymphatic nodes are generally in the head and neck. Its incidence among all forms of tularemia is less than 5%.[15]

Oropharyngeal disease

It is the most frequently encountered clinical form in Turkey.[11,16,17] The bacteria enters through the mouth and pharyngeal mucosa. It often originates from contaminated water or food. Fever, sore throat, exudative pharyngitis, pharyngeal ulcers and swollen lymphatic nodes are observed (Figure 3). Hyperemia or yellow-white colored pseudo-membranes appear around the tonsils. The patients are mostly attempted to be treated with a beta-lactam antibiotic based on the diagnosis of cryptic angina. The most frequent complication in the oropharyngeal form is the suppuration developing in the lymphatic nodes (Figure 4).

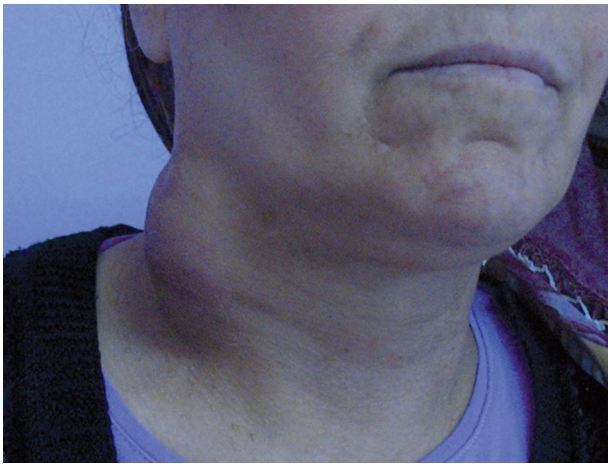

Figure 3. Tularemic lympadenopathy

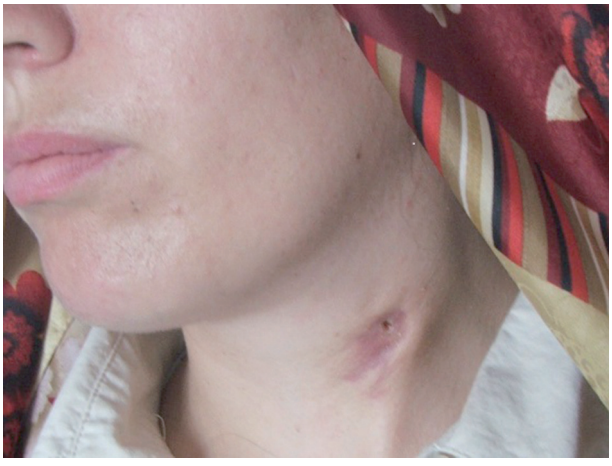

Figure 4. Suppurated lymphatic node in oropharyngeal disease

Pneumonic form

Ten percent of all tularemia cases are in the pneumonic form. The agent is ingested via inhalation. Patients develop fever, weakness, dry cough, substernal and pleural pain, dyspnea and sore throat. Hemoptysis may also develop. Consolidation and pleural effusion in the lungs may be identified via imaging. 1/3 of the cases have hilar lymphadenopathy. Phlegm analysis and gram staining of the phlegm are generally inutile for diagnosis. The pathological signs identified via bronchoscope generally cannot be differentiated from tuberculosis or sarcoidosis.[18] In pleural biopsy, granulomatous inflammation is mostly identified and this situation is generally interpreted in favor of tuberculosis.[19] Bioterrorism-related tularemia generally presents with pneumonia.

DIAGNOSIS

Routine laboratory test results are mostly normal. Leukocytosis, thrombocytopenia and increased hepatic enzyme are observed.[20] *F. tularensis* affects the skin, mucosa, respiratory system and gastrointestinal system. The ability of bacteria to persist in macrophage enables it to cause granulomatous inflammation. The infection spreads to the lymphatic nodes, spleen, lung and pleura. The histopathological signs of biopsy samples are very similar to those of tuberculosis.

Even though the culture is the gold standard for the laboratory diagnosis of tularemia, a laboratory setting with special safety precautions (bio-safety level 3) is necessary due to its extremely contagious

character.[1] *F. tularensis* may be isolated from the patients at an early stage. Therefore, appropriate samples should be collected when one meets a patient that complies with the description of a suspected case. The samples taken should be consigned to the laboratory in an appropriate transport medium (such as Amies activated carbon, Stuart and Carry-Blair). There is a higher chance for bacteria isolation in media with Cysteine. In recent years, it has become important to demonstrate the site-specific genes of the bacteria in clinical samples by using the polymerase chain reaction (PCR) method.[21]

For the diagnosis of tularemia, serology (tube agglutination test or micro-agglutination test) is often used. 89-95% of the patients develop antibodies within two weeks after the onset of symptoms. It is enough for the antibody titer to be 1:160 and above for the diagnosis.[1] The diseases that should be considered in differential diagnosis of the tularemia disease are presented in Table 1.

Table 1. Differential diagnosis of tularemia

Ulceroglandular form	Mycobacterium marineum infection Cat scratch disease Herpes simplex virus lesions Syphilis Lymphogranuloma venorum Anthrax
Pneumonic form	Community-acquired pneumonia Psittacosis Legionellosis Q fever
Glandular and Typhoidal forms	Thyphoid Brucellosis Ehrlichiosis
Oropharyngeal form	Adenoviral pharyngitis Infectious Mononucleosis Streptococcal pharyngitis Diphtheria

TREATMENT

It is recommended that the treatment is started early. The recovery period of the patients for whom the treatment starts late becomes longer. There is a higher risk of suppuration in the lymph glands in treatments that are started after the second and third week of the disease.

The first option for treatment includes antibiotics, aminoglycosides. Streptomycin (2x1 g IM) or gentamycin (5 mg/kg 1x1, IM or IV) should be administered to the patients for 10 days.[22] Even though alternative antibiotics are chloramphenicol, tetracycline and quinolone, the risk of relapse in patients receiving them is higher as compared to chloramphenicols.[23]

Aminoglycoside and doxycycline combinations are recommended as immunosuppressives for cases with severe prognosis (meningitis, pericarditis, pneumonic and typhoidal forms, etc.).

Penicillin, cephalosporin, rifampicin, cotrimoxazole and clindamycin are not used for treatment.[24] There might lymph suppuration even in patients that received treatment for the appropriate duration and at the correct dose. It may take time for the lymph glands to become smaller. This situation does not require initiating a new antibiotic treatment.

Protection and Control

The direct and indirect contact with ticks and wild animals should be minimal. Gloves should be worn while handling hunted animals such as rabbits, etc. One of the most ideal methods to prevent oropharyngeal contamination is the chlorination of water supply. Since tularemia is not transmitted between people, the patients do not need to be isolated. Standard personal protective measures are adequate for collecting samples and disposing of patient discharge in the acute phase. If there is risk of aerosolization during these processes, personal protective equipment such as masks and gloves should be used.[25]

The mortality is around 30% if the pneumonic and typhoidal forms remain untreated. The mortality today is below 1% in cases that are properly treated. In Turkey, tularemia is in the Group C that includes diseases that must be obligatorily reported. The reporting should be done using the special informing form when a case is identified.

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