Tularemia

by Brandy Guillory

Disease Etiology:

Tularemia (tulaeremia) is a disease of both animals and humans. Infection is caused by the bacterium Francisella tularensis. There are other subspecies of this bacterium: F. tularensis holartica; F. tularensis mediiasiatica; F. tularensis novicida; and F. tularensis philomiragia. These strains are not as virulent, and are limited to specific regions in the world.

Disease Transmission and Reservoirs:

"Tularemia is highly infectious, and can enter the body through the eyes, mouth, skin, throat, and lungs." Humans and animals, such as rodents, rabbits and hares, are the reservoirs for Tularemia. There are various routes of transmission for the bacteria. It can be transmitted by dog ticks (Dermacentor variabilis), wood ticks (Dermacentor anderson), lone start ticks (Vambyromma americanum), and deer flies (Chrysops spp.). It can be transmitted to humans through skin contact with infected animal tissue. Other exposures occur by inhalation of dust or aerosols contaminated with F. tularensis bacteria, or by ingestion of contaminated water. Tularemia is also considered a bioterrorism threat in aerosol form. There is no documented cases of person to person transmission of this disease.

Specific Tests for Identification:

Tularemia can be mistaken for several other types of diseases (Staphylococcal, Streptococcal, Anthrax, Toxoplasmosis, Influenza, and several more). "When the epidemiology is suggestive, tularemia should be considered in any case of fever of unknown origin." Blood cultures, serology, chest x-ray, and Polymerase chain reaction (PCR) are the most common diagnostic tests for this disease. Skin ulcer scrapings, lymph node biopsies, or sputum, are the optimal methods to directly isolate the bacteria. F. tularensis is a difficult organism that requires an enriched medium for growth. Cysteine glucose blood agar has been the medium of choice, however, chocolate agar and nonselective buffered charcoal yeast extract agar have also been successful for organism growth. PCR assays appear to offer advantages over the direct culture of bacteria. In an experimental infection of mice, 83% of blood samples, taken after 24 hours of exposure, were positive by PCR. However, bacteria could only be cultured in 48% of the samples. This success also extended to clinical samples. A study of swab samples taken from lesions in 40 human cases (ulceroglandular), the PCR assay was positive in 73% of the samples. Only 25% of the samples were positive with bacteria cultures. In addition, PCR was able to identify F. tularensis in a sample that had not been identified by culture or serology in parallel study.

Signs and Symptoms:

The incubation period for Tularemia is 3-5 days from exposure. Signs and symptoms usually depend on route of entry (eyes, skin, mouth, lungs). Symptoms include: fever, headache, chills, joint pain, ulcers on the skin, pneumonia, sweating, weight loss, and eye irritation. Symptoms appear rather suddenly, and usually last several weeks. Site specific symptoms take on certain forms, such as glandular tularemia, and oropharyngeal tularemia. Glandular forms are a result of tick or fly bites, animal bites, or direct exposure to the eye(s). This form makes up approximately 95% of reported cases.
Lymph node enlargement in a human case of glandular tularemia.[2]

Primary ulcer in a human case of ulceroglandular tularemia.[2]

**History:**

There is evidence that Tularemia in humans occurred in the early nineteenth century in the United States, Russia, Japan, and Norway.[6] In 1911, George W. McCoy and Charles W. Chapin, of US Public Health Services, began examining thousands of rats and ground squirrels to “detect foci of suspected plague infections in San Francisco.”[6] They encountered an infection with lesions early in their investigation. “A year later, they isolated the causative organism of this plague-like disease from California ground squirrels and named it *Bacterium tularense*” (after Tulare County where they performed the work). McCoy and Chapin developed “agglutination and complement fixation tests to aid in diagnosis.” The first confirmed case of human tularemia occurred in 1914 in Cincinnati, OH.[6]

In 1928, Dr. Edward Francis, also from US Public Health Services, determined the cause of deer-fly fever was from *Bacterium tularense*. Because of his extensive knowledge and contributions to the disease, the organism was later renamed *Francisella tularensis*. Based on Dr. Francis’ analysis of 800 cases, four clinical types of *F. tularensis* were recognized in 1929. Decades later, in 1947, Francis added three more types (meningeal, oropharyngeal, and pulmonary).[6]

In 1930’s and 40’s, large water-borne outbreaks occurred in Europe and Soviet Union. Russian scientists recognized two subspecies of *F. tularensis* in 1959 (*F. tularensis* biovar tularensis [type A] and *F. tularensis* biovar palaearctica [type B]). Type A is the most common in North America, and is highly virulent in both animals and humans.[6] Type B is thought to be the cause of human tularemia in Europe and Asia. It is mostly “avirulent in humans, but can cause disastrous epizootics in its main reservoirs, the water rat and vole rat.”[6]

Tularemia is chiefly endemic in Europe and Asia. The largest recorded epidemic of pneumonic tularemia occurred from 1966-1967 in Sweden.[6] There were over 2,700 reported cases of human tularemia during this epidemic; this is close to half the total number of cases reported in Sweden from 1931-1993.

In the 1950’s and 60’s there was a large interest in the pathogen due to its ability to be highly infectious and transmissible by aerosol. This rendered tularemia a potential “biothreat agent.”[8] It had the highest priority in offensive programs of the United States and Soviet Union. After the termination of these programs (late 1960’s), the interest in *F. tularensis* drastically declined. Little to no research was conducted until the 21st century, after a number of outbreaks in Kosovo, Spain, and Scandinavia.[8] Since, there has been a renewed interest, and an increase in active *Francisella* researchers.[8]

**Virulence Factors:**

Very few virulence factors have been identified in *F. tularensis.[9][5]* This is due in part by the lack of research performed since the 1960’s. Fatality rate in tularemia cases is less than 5% without treatment, and less than 1% with treatment.[3]
**Pathogenesis:**

There is little understood of the genetic means of pathogenesis of *F. tularensis*. The bacteria are able to survive and replicate in macrophages.[9] A virulence factor, MgIA, “regulates the transcription of genes necessary for intracellular growth, including those located within the *Francisella* Pathogenicity Island (FPI).” FPI genes are responsible for intramacrophage growth and virulence, and “appear to encode a protein secretion system.”[9] The exact function of individual FPI proteins is yet to be determined.

**Treatment:**

Antibiotics are the course of treatment for tularemia.[1][2][5] Gentamicin is the most successful, but ciprofloxacin has also been used to treat the disease. *F. tularensis* has been noted to resist treatment with erythromycin, which should not be used. There is a concern in treating pregnant patients, due to the fact that both gentamicin and ciprofloxacin are not approved for administration by the Food and Drug Administration. The benefit versus the side effects must be evaluated before treatment. In this case, ciprofloxacin is the option, with an individualized treatment period.[2]

**Prevention/Vaccines:**

A live vaccine strain (LVS) has been developed, but has not been approved in the United States.[5][10] To date, it is the only successful vaccine against tularemia.[5] To prevent possible exposure, individuals should use insect repellent with 20-30% deet when working outdoors, hunting, camping, and/or hiking. Wear long sleeve shirts, pants, and long socks to prevent ticks and fly bites. Do not touch dead animals/carcasses, and wear dust masks while working outside to prevent inhalation of bacteria. Wear gloves when handling animals, especially rodents (rabbits, muskrats, prairie dogs, etc), and cook game meat thoroughly.[10]

**Local Cases/Outbreaks:**

In 2012, there were 149 reported cases of tularemia in the United States.[7] During 2003 - 2012, the state of Texas only had six reported cases of tularemia.[7]

**Global Cases/Outbreaks:**

In 2002, there was a tularemia outbreak in the Kosovo region of Yugoslavia. There were 715 reported cases, with only 170 cases confirmed by laboratory analysis.[6][8]

**Sources:**


