



## **Tularemia September 2003**

Tularemia is the disease caused by *Francisella tularensis*.

Tularemia is a relatively modern disease, first described in the early 20<sup>th</sup> Century in Tulare County, California. Although less deadly than many other high priority biological weapon candidates, it causes severe incapacitation. Both the United States and former Soviet Union weaponized *F. tularensis* in their prior bioweapons program, and it was tested by the Japanese at the infamous Unit 731 in Manchuria during World War II.

In its natural form tularemia is a rare sporadic disease found primarily in moderate climates. It is endemic in the United States, Japan, Russia and Europe where it occasionally causes epidemics. There are approximately 125 cases reported annually in the U.S. since 1990, with the majority being reported from Midwestern states. Tularemia is a zoonotic infection of small mammals, particularly rabbits, that can be transmitted to humans via direct skin contact with infected animals, arthropod bites or aerosolization. Exposure by aerosol is the likely method that would be encountered in a bioterrorism event and has been reported after presumed aerosolization of infected animals by a lawn mower, illustrating the ease by which this route can cause disease. Overall mortality in the U.S. is less than 2%, but this rises to 30% to 60% for the typhoidal and pneumonic forms of disease when treatment is delayed.

Human tularemia occurs in 6 recognized forms, determined primarily by route of infection. Pneumonic tularemia that results from inhalation of aerosolized organisms is rare but is associated with the most severe disease. It should be noted that all forms of tularemia may develop secondary pulmonary features, but the designation of pneumonic tularemia should be confined to primary disease that is acquired via inhalation. The most common form of tularemia is ulceroglandular, accounting for 45-85% of U.S. cases. This results from inoculation of organisms into skin via arthropod bites or animal contact with subsequent local ulcer formation and lymphadenopathy in the proximal draining lymph nodes. Occasionally, lymphadenopathy occurs without an ulcer leading to the

designation of glandular disease. Oculoglandular disease occurs when *F. tularensis* is inoculated into the eye, and the oropharyngeal form most often occurs via ingestion of contaminated meat. The typhoidal form is marked by a lack of preceding skin ulcer, lymphadenopathy or pneumonia, similar in concept to the septicemic form of plague. It is thought that typhoidal disease primarily results from inhalation of organisms. A bioterrorism attack involving an aerosol of *F. tularensis* would be expected to cause primarily pneumonic disease, but all forms could be seen, particularly typhoidal.

The organism, *Francisella tularensis*, is a small, intracellular, aerobic pleomorphic Gram negative coccobacillus that is nonmotile and does not form spores. It has a thin envelope that allows it to live for weeks in cool, moist conditions. It stains very faintly on Gram stain, making it difficult to visualize in clinical specimens. Growth on culture is slow, generally taking 2-3 days to first appear, and it requires cysteine-enriched medium. There are 2 major strains, or biovars. Type A is the predominant strain in the U.S. and causes the most severe disease. Type B is found primarily in Europe and Asia, and mortality is rare.

The pathogenesis of *Francisella tularensis* is similar for all forms of tularemia. There is initial infection at the inoculation site. When the lung is the portal of entry, an acute bronchiolitis and pneumonitis leads to an aggressive immune response causing extensive suppuration and consolidation and eventual fibrosis. The pleura is also frequently involved manifested as pleural thickening and effusions. Organisms migrate to regional lymph nodes and can spread hematogenously to other organs where a similar suppurative immune response occurs if treatment is delayed. Severe systemic disease marked by sepsis, DIC, multiorgan failure and death can occur when the disease spreads hematogenously, which is most commonly seen with typhoidal and pneumonic forms.

All forms of tularemia are preceded by a common non-specific influenza-like illness characterized by the sudden onset of high fevers, chills, profuse sweats and myalgias often localizing to the lower back. Symptoms generally arise 2-5 days after exposure, but can be seen sooner in high dose aerosol exposure. The incubation period can uncommonly spread out to 3 weeks. Pleuropulmonary involvement including cough, chest pain and dyspnea occur in up to 40% of cases not exposed through inhalation. Interestingly, pulse/temperature dissociation, or relative bradycardia, is a relatively common, albeit nonspecific phenomenon seen in 40% of patients in one series, that may be helpful in differentiating tularemia from other diseases.

After the initial flu-like prodrome, primary pneumonic tularemia can have variable manifestations from mild disease to fulminant pneumonia with sepsis. Patients usually present with fever, minimally productive cough, pleuritic pain and dyspnea. Hemoptysis is occasionally present and leukocytosis is common. Chest radiographs typically show lobar and often bilateral patchy infiltrates with pleural effusions and sometimes hilar adenopathy. Secondary pneumonic tularemia has similar findings in addition to the features coinciding with the primary disease process. The differential diagnosis for pneumonic tularemia includes other atypical pneumonias including pneumonic plague. Ulceroglandular tularemia is characterized by a solitary painful ulcer at the inoculation

site that starts as a maculopapular lesion 2 days after the prodromal illness appears and progresses to a pustule then a slow-healing ulcer with raised edges. Painful lymphadenopathy with overlying erythema usually appears proximal to the inoculation site, but is not always present.

This photo shows the typical skin ulcer of ulceroglandular tularemia.

A high index of suspicion is required to diagnose tularemia as there are no readily available rapid and specific confirmatory tests. Gram stains are rarely helpful, culture lacks specificity and takes several days to grow and serological testing is retrospective only. Blood cultures are rarely positive, but sputum and pharyngeal washings have higher yields for *F. tularensis*. Fluorescent antibody assays (DFA), PCR and immunohistochemical assays can give a presumptive diagnosis within hours but are usually only available at reference labs.

The treatment of choice is streptomycin at 1gram IM bid in adults, which has proven clinical efficacy with nearly 100% cure rates and is FDA-approved for this indication. The second choice is gentamicin with near 90% cure rates and greater convenience because it can be given intravenously and once daily. Failures with aminoglycosides are usually related to insufficient duration of therapy, severe comorbid illnesses, or delay in treatment initiation. Alternatives such as doxycycline and tetracycline are effective, however, they have a higher risk of relapse and must be continued for a longer course of therapy.

Chloramphenicol is another effective option that should be considered if meningitis is suspected, however its high relapse rate precludes monotherapy. Ciprofloxacin has been shown to have very good success anecdotally in several cases, with no reported failures and only one relapse. An advantage of the tetracyclines and fluoroquinolones is that they can be directly converted to oral therapy upon clinical improvement. Beta-lactams and macrolides are clinically ineffective and should be avoided, despite good in vitro activity for ceftriaxone. Ten days is a sufficient duration of therapy for aminoglycosides, whereas ciprofloxacin should be continued for 14 days. Doxycycline, tetracycline and chloramphenicol treatment durations should be 14-21 days.

For persons who quickly become aware of a suspected exposure to aerosolized *F. tularensis*, such as in a laboratory accident or an announced bioterrorism attack, oral doxycycline or ciprofloxacin should be given for prophylaxis for 2 weeks. In a more likely scenario where a bioterrorism release is not discovered until after the first cases present, then it is recommended that all potentially exposed persons be monitored for development of a fever without initiation of antibiotics as the incubation period is generally short. An active treatment regimen of antibiotics should be started immediately if a temperature over 38° C occurs during a 14 day period after presumed exposure. Persons in contact with tularemia patients do not require prophylaxis unless they were at risk for the original exposure themselves, as there is no known person-to-person transmission.

A live, attenuated vaccine is available that is primarily used by researchers exposed to *F. tularensis*. The precise efficacy is unknown, but it is thought to reduce the incidence of typhoidal disease, and the severity of ulceroglandular. Because of the short incubation period of tularemia, and the time required to develop an immune response from immunization, use of the vaccine is not recommended as post-exposure prophylaxis.

There has been no documented person-to-person transmission of tularemia, even in the pre-antibiotic era. Thus, standard precautions are sufficient for patient handling in hospital settings. While clinical specimens can be handled with routine procedures, pure culture of *Francisella tularensis* is a danger to laboratory workers, with several reported cases of inhalationally acquired typhoidal or pneumonic infection. Thus, cultures with colonial growth require handling in BSL-2 conditions in a safety cabinet. Therefore, when tularemia is suspected the microbiology lab should be alerted prior to receiving the specimens to be cultured.