

TULAREMIA

Revised 7/17/2011

Tularemia is the zoonotic disease caused by the gram-negative coccobacillus *Francisella tularensis*. It is usually contracted through dog tick bites, or by eating or touching infected rabbits and rodents. *F. tularensis* is also considered a potential biological weapon due to its extreme infectivity. The disease it causes is now recognized as tularemia in most parts of the world, but it has been called: rabbit fever, deer-fly fever, and market men's disease in the United States; wild hare disease (yato-byo) and Ohara's disease in Japan; water-rat trappers' disease in Russia. Tularemia continues to be responsible for significant morbidity and mortality, despite the availability of numerous antibiotics active against the organism.

Bacteriology

F. tularensis requires cysteine or cystine (or another sulfhydryl source) for growth, and therefore will not grow on most routine solid media. It may be recovered with the use of glucose cysteine blood agar, thioglycolate broth, chocolate agar suitable for gonococcal growth, modified Thayer-Martin medium, or buffered charcoal-yeast agar. Of concern is the recognition that some strains of *F. tularensis* lack an overt requirement for cysteine or enriched medium for growth, leading the microbiology laboratory to suspect *Haemophilus* species because of the growth of an aerobic, gram-negative coccobacillus.

Visible colonies take 2 to 4 days to appear. Incubation at 35°C is optimal, and growth may be stimulated by an atmosphere of increased CO₂. The recovery of *F. tularensis* from contaminated specimens may be facilitated by the addition of penicillin, cycloheximide, or polymyxin B to the media. Virtually all *F. tularensis* strains are positive for β-lactamase.

F. tularensis is a hardy organism that can be spread with a small inoculum.

Epidemiology

Natural hosts

F. tularensis is capable of infecting hundreds of different vertebrates and invertebrates, but no more than a dozen mammalian species are important to its ecology in any geographic region. These include lagomorphs, particularly *Sylvilagus* and *Lepus* spp., and rodents such as voles, squirrels, muskrat, and beaver in North America; included in the former Soviet Union are voles, hamsters, mice, and hares.

Transmission to humans: Tularemia is a classic zoonosis capable of being transmitted by aerosol, direct contact, ingestion or via arthropods.

- Tick bite is the most common source of infection for people and herbivores is the bite of an infected tick.
- Ingestion: Persons who dress, prepare, or eat improperly cooked wild game are also at increased risk. Dogs, cats, and other carnivores may acquire infection from ingestion of an infected carcass.
- Inhalation of aerosolized organisms can produce a pneumonic form.

Human-to-human spread does not occur.

Bloodfeeding arthropods and flies are the most important vectors for tularemia in the United States. Ticks predominate in the central and Rocky Mountain states, whereas biting flies predominate in California, Nevada, and Utah. In contrast, mosquitoes are the most frequent insect vector in Sweden and Finland, and they also are important in the former Soviet Union. At least 13 species of ticks have been found to be naturally infected with *F. tularensis*, and transovarial passage may occur. The dog tick (*Dermacentor variabilis*), wood tick (*D. andersoni*), and Lone Star tick (*Amblyomma americanum*) are commonly involved in North America. The organism may be present in tick saliva or feces and may be inoculated either directly or indirectly into the bite wound. Several outbreaks of tickborne tularemia have involved *F. tularensis* biogroup *palaearctica* (type B), although this organism is more often linked to water, rodents, and aquatic animals; tick transmission traditionally has been associated with biogroup *tularensis* (type A). Tularemia in children in endemic areas of the U. S. is now most often associated with tick exposure in the summer.

Animal contact is another important mode of acquiring tularemia.

Tularemia is a bacterial septicemia affecting more than 250 species, including wild and domestic mammals, birds, reptiles, fish, and humans. Among domestic animals, sheep are the primary host, but clinical infection has been reported in dogs, cats, pigs, and horses; cattle appear to be resistant. Important wild animal hosts include cottontail and jack rabbits, beaver, muskrat & meadow voles in North America and other voles, field mice, and lemmings in Europe and Asia.

Skinning, dressing, and eating infected animals, including rabbits, muskrats, beavers, squirrels, and birds, have transmitted tularemia, occasionally resulting in large outbreaks in hunters. For example, hamster hunting was responsible for an epidemic in Eastern Europe.

Airborne transmission has occurred during these activities, as well as from contact with water, contaminated dust, and hay. Carnivorous animals may transiently carry *F. tularensis* in the mouth or on claws after killing or feeding on infected prey, whether or not they become infected. This is thought to be the mechanism by which domestic cats occasionally transmit tularemia. *F. tularensis* may survive for prolonged periods in water, mud, and animal carcasses even if frozen; however, cooking game meats thoroughly to the proper temperatures should minimize risk from ingestion. Contaminated water continues to be an important environmental source of tularemia.

Environmental sources: In the summer of 2000, an outbreak of primary pneumonic tularemia occurred at Martha's Vineyard, Massachusetts. Confirmed cases had symptoms suggestive of primary pneumonic tularemia. Study of this outbreak of primary pneumonic tularemia implicates lawn mowing and brush cutting as risk factors for this infection.

Infection originated from surface water and crayfish in Spain. The presence of *F. tularensis*, both in the sewage-plant water and in the river crayfish, along with the association between the disease and hand injuries incurred on coming into contact with river water and mud at the fishing site or during crayfish cleaning.

Infectious Dose

F. tularensis is a virulent organism for susceptible species, including the accidental human host. Although the organism is reported to penetrate intact skin, most investigators believe that penetration occurs through sites of inapparent skin disruption. The infectious dose in humans depends on the portal of entry: 10 to 50 organisms when injected intradermally or when inhaled, and 10^8 organisms when ingested. That low numbers of bacteria can cause infection through the skin, mucous membranes, and airways helps to explain in part the extreme risk that *F. tularensis* poses to laboratory workers. In general, *F. tularensis* biogroup *tularensis* causes more severe disease than biogroups *palaearctica* and *novicida*. The molecular reasons underlying these differences in virulence are unknown at present.

Tularemia in the U.S.

Tularemia was very common in the United States before World War II. However, its incidence has declined steadily since the 1950s, and it has remained at less than 0.15 cases per 100,000 population since 1965. The summer peak corresponds to a greater number of tick-acquired cases, whereas the smaller peak

in late winter reflects an increased number of hunting-associated cases. Males account for up to 75% of cases, perhaps because of greater exposure opportunities.

Occupations that have been associated with an increased risk of tularemia are laboratory worker, farmer, veterinarian, sheep worker, hunter or trapper, and cook or meat handler.

The incubation period is 1-10 days in most species.

Clinical Description

The clinical consequences of *F. tularensis* infection depend on the virulence of the particular organism, the portal of entry, the extent of systemic involvement, and the immune status of the host. The result can range from asymptomatic or inconsequential illness to acute sepsis and rapid death. Patients who seek medical attention usually present with at least one of six classic forms of tularemia: ulceroglandular, glandular, oculoglandular, pharyngeal, typhoidal, and pneumonic. This somewhat artificial classification emphasizes only the predominant manifestations commonly encountered, and there is overlap in many patients.

Ulceroglandular tularemia has been the presentation in 21% to 87% of cases; tick bites and animal contacts are the usually recalled exposures. This is the form that is most quickly recognized as tularemia. The initial specific complaint is often of enlarged and tender localized lymphadenopathy. The inciting skin lesion may appear either before, simultaneously with, or from one to several days after the adenopathy. It starts as a red, painful papule in a region draining into the involved lymph nodes. The papule then undergoes necrosis, leaving a tender ulcer with a raised border. If untreated, the ulcer may take weeks to heal and leave a residual scar. Multiple lesions may occur, particularly in those with animal sources. The location of the ulcer generally reflects the mode of acquisition; animal contacts tend to yield ulcers on the hands and forearms, and tick bites tend to yield ulcers on the trunk, the perineum, the lower extremities, and the head and neck. The distribution of lymphadenopathy also reflects the exposure history, overall, cervical and occipital adenopathy is most common in children, and inguinal adenopathy is most common in adults. Skin changes over the involved nodes should suggest underlying suppuration. Some patients have a sporotrichoid presentation with ascending subcutaneous nodules. Lymphangitis is rare unless there is bacterial superinfection of the ulcer.

Glandular tularemia occurs when patients present with tender regional lymphadenopathy but without an evident cutaneous lesion. This form accounts for 3% to 20% of cases in the U.S., although 62% of cases in Japan have been of this type. Glandular tularemia represents essentially the same process as ulceroglandular disease, except that a skin lesion either healed before presentation, or was minimal or atypical and overlooked. Enlarged lymph nodes may persist for prolonged periods, and in some patients an exposure or prior febrile illness will be forgotten. For this reason, tularemia may not be considered in the initial differential diagnosis of some patients whose primary presentation is lymphadenopathy. In either ulceroglandular or glandular tularemia the lymph nodes may suppurate. When fluctuant, they should be needle-aspirated or surgically drained. The differential diagnosis of ulceroglandular and glandular tularemia includes pyogenic bacterial infections, cat-scratch disease, syphilis, chancroid, lymphogranuloma venereum, tuberculosis, nontuberculous mycobacterial infection, toxoplasmosis, sporotrichosis, rat-bite fever, anthrax, plague, and herpes simplex virus infection.

Oculoglandular tularemia represents only 0% to 5% of cases. In this form, organisms have gained entry through the conjunctiva, either from contaminated fingers or from contaminated splashes and aerosols. Disease is bilateral in less than 12% of patients. Early complaints may include photophobia and excessive lacrimation. Examination shows lid edema and a painful conjunctivitis, with injection, chemosis, and small, yellowish conjunctival ulcers or papules in some patients. Associated tender lymphadenopathy may occur in the preauricular, submandibular and cervical regions. If the adenopathy is extensive and more prominent than the eye findings, this syndrome may be mistaken for mumps. Visual loss is rare, but complications include corneal ulceration, dacryocystitis and nodal suppuration. The differential diagnosis of

oculoglandular tularemia includes pyogenic bacterial infections, adenoviral infection, syphilis, cat-scratch disease, and herpes simplex virus infection.

Pharyngeal tularemia, another variant of ulceroglandular disease, is the result of primary invasion through the oropharynx. The source may be contaminated foods or water or contaminated droplets. This form represents 0% to 12% of cases and is being seen with increasing frequency in Japan. Children have been involved more often than adults and several family members may be affected simultaneously. It must be distinguished from the sore throat that may accompany any of the other major clinical forms of tularemia. In pharyngeal tularemia, the patient's predominant complaint is of severe throat pain. Exudative pharyngitis or tonsillitis is the rule, and one or more ulcers may be seen. A pharyngeal membrane has been described in some patients that is similar to a diphtheritic membrane. Cervical, preauricular, and retropharyngeal nodes may be involved, occasionally with abscess formation. The differential diagnosis includes streptococcal pharyngitis, infectious mononucleosis, adenoviral infection, and diphtheria. Tularemia should be suspected in an endemic area whenever a severe sore throat is unresponsive to penicillin therapy and routine diagnostic tests have been unrewarding.

Typhoidal tularemia refers to a febrile illness caused by *F. tularensis* that is not associated with prominent lymphadenopathy and does not fit into any of the other major forms. From 5% to 30% of cases are typhoidal, and they are the most difficult to diagnose. This form of tularemia may result from any mode of acquisition. Because the portal of entry is usually inapparent clinically, a history of outdoor activities with tick or animal exposure should be sought. Many patients have serious underlying chronic medical disorders; their presentation can be quite dramatic, with acute prostration and rapid death, or a protracted illness. For example, an adolescent boy with human immunodeficiency virus infection was diagnosed with typhoidal tularemia only after blood cultures grew the organism. His only possible exposure was a history of being licked by a diseased fawn with a cleft palate. The patient had a lengthy course with several relapses requiring prolonged antibiotic therapy with gentamicin and tetracycline. He never developed a positive serology, and this was thought to be a consequence of his severe immunocompromise (CD4 count of 0/mm³). Prominent symptoms of typhoidal tularemia may include any combination of fever with chills, headache, myalgias, sore throat, anorexia, nausea, vomiting, diarrhea, abdominal pain, and cough. Examination may reveal dehydration, hypotension, mild pharyngitis and cervical adenopathy, meningismus, and diffuse abdominal tenderness. Hepatomegaly and splenomegaly are found uncommonly in the acute stages and become more likely the longer the duration of illness. Diarrhea, a major manifestation only in typhoidal tularemia, is loose and watery, but only rarely bloody. Children may have more severe intestinal involvement, including focal areas of bowel necrosis. Secondary pleuropulmonary involvement is common in this form, with pulmonary infiltrates or pleural effusions being found in up to 45% of typhoidal cases; it is even more frequent in laboratory-acquired infections. Additional findings in severely ill patients may include hyponatremia, elevated creatine phosphokinase, myoglobinuria, pyuria, renal failure, and positive blood cultures. The differential diagnosis of typhoidal tularemia includes typhoid fever caused by *Salmonella* sp., brucellosis, *Legionella* infection, Q fever, disseminated mycobacterial or fungal infection, rickettsioses, malaria, endocarditis, and any other cause of prolonged fever without localizing signs.

Pneumonic tularemia refers to an illness whose initial presentation is dominated by pulmonary infection. This is found in 7% to 20% of all tularemia cases. It may result from direct inhalation of the organism or from secondary hematogenous spread to the lung. Primary pneumonic tularemia is a risk for certain occupations, including sheep shearers, farmers, and laboratory workers. Cases also have been described as resulting from common exposure in a more casual setting. Although secondary pneumonia may complicate any of the syndromes already discussed, Evans and colleagues found pneumonia to be most frequent in typhoidal (83%), and ulceroglandular (31%) diseases. Scofield and associates reported that patients with pneumonic involvement were more likely to be older, to recall no exposure, to present with typhoidal illness, to have positive cultures, to stay hospitalized longer, and to have a higher mortality rate. From 25% to 30% of patients have radiographic infiltrates without any clinical findings of pneumonia. Common symptoms include fever, cough, no or minimal sputum production, substernal tightness, and pleuritic

chest pain. Hemoptysis may occur but is uncommon. Physical examination may be nonspecific or may reveal rales, consolidation, and a friction rub or signs of effusion. Some patients need mechanical ventilation, and adult respiratory distress syndrome may complicate the course of any form of tularemia. Routine examination of sputum does not help to suggest the diagnosis. However, a false-positive direct fluorescent antibody stain for *Legionella* on bronchoscopy specimens has been reported. Infected pleural fluid is exudative, negative on Gram stain, and usually contains more than 1000 leukocytes/mm³; cells are predominantly lymphocytes, but neutrophilic effusions may occur. Pleural effusions seen with tularemia frequently mimic those seen with tuberculosis. Similar findings for both include a lymphocyte-rich exudative pleural effusion and a high adenosine deaminase concentration. Granulomas may be found on pleural biopsy and may be confused with tuberculosis. Acute radiographic changes may include subsegmental or lobar infiltrates, hilar adenopathy, pleural effusion, and apical or miliary infiltrates; less common changes include ovoid densities, cavitation, and bronchopleural fistula. Secondary pneumonias are more likely to involve the lower lobes and be bilateral, perhaps because of their hematogenous origin. Healing usually occurs without residual changes, but fibrosis and calcifications may result. Therefore, tularemia may manifest as an enigmatic community-acquired atypical pneumonia that does not respond to routine therapies. The differential diagnosis of pneumonic tularemia includes *Mycoplasma pneumoniae* pneumonia, *Legionella* infection, *Chlamydia pneumoniae* infection, Q fever, psittacosis, tuberculosis, the deep mycoses, and many other causes of atypical or chronic pneumonias

Secondary skin rashes are an underappreciated part of tularemia and may be found in up to 35% of cases. They usually appear within the first two weeks of symptoms, but in a minority are delayed. Rash is more common in women than in men. Cutaneous changes may include diffuse maculopapular and vesiculopapular eruptions, erythema nodosum, erythema multiforme, acneiform lesions, and urticaria. Although any type of secondary rash may be part of any form of tularemia, erythema nodosum has been found to occur most commonly with pneumonic tularemia.

A review of tularemia in Sweden focused on reports of oropharyngeal tularemia, bacteremia, and meningitis. Tularemia was not in the initial differential diagnosis of these infections, but was considered only after patients failed to respond to standard therapy for more common causes. This suggests that even in endemic regions tularemia may not be detected, or may be diagnosed only after a prolonged delay. The clinical manifestations of infections caused by *F. tularensis* biogroup *novicida* are less well characterized than for the other biogroups, but are similar to those previously described. *F. philomiragia* has caused pneumonias, sepsis, peritonitis, and meningitis. This organism predominantly infects patients with host defenses impaired by chronic granulomatous disease, near-drowning in salt water or estuaries, or myeloproliferative disorders.

Complications

Suppuration of involved lymph nodes is currently the most common complication of tularemia, and this may occur even after specific antibiotic therapy. Patients with severe disease may manifest disseminated intravascular coagulation, renal failure, rhabdomyolysis, jaundice, and hepatitis. Meningitis, encephalitis, pericarditis, peritonitis, osteomyelitis, splenic rupture, and thrombophlebitis have become very rare since antibiotic therapy has become available. The cerebrospinal fluid (CSF) in meningitis almost always shows a mononuclear cell pleocytosis, with a high protein concentration and hypoglycorrhacia.

Tularemia may lead to months of debility in some patients, usually associated with late lymph node suppuration and/or persistent fatigue. Features that are associated with a worse prognosis include increasing age, serious coexisting medical conditions, symptoms of a month or longer before treatment, significant pleuropulmonary disease, typhoidal illness, renal failure, a delay in the diagnosis, and inappropriate antibiotic therapy. Overall death rates in the antibiotic era have been 4% or less, but were as high as 33% before the introduction of streptomycin as treatment.

Recovery from tularemia is thought to confer protective immunity for life, although a few recurrent infections have been documented. Most recurrences have been clinically mild ulceroglandular disease, and

systemic symptoms have been uncommon. Therefore, previously infected individuals are not candidates for vaccination or preemptive antibiotic therapy after a known exposure.

Laboratory Tests

The diagnosis of tularemia ultimately rests on clinical suspicion. Results of routine laboratory testing are nonspecific. The leukocyte count and sedimentation rate may be normal or elevated. Thrombocytopenia, hyponatremia, elevated serum transaminases, increased creatine phosphokinase, myoglobinuria, and sterile pyuria are occasionally found.

The organism is rarely seen on Gram-stained smears or in tissue biopsies and does not grow in routinely plated cultures. However, *F. tularensis* may be recovered from blood, pleural fluid, lymph nodes, wounds, sputum, and gastric aspirates when processed on supportive media. Because of this and its severity, lab technicians should be notified if tularemia is suspected.

Isolations by blood culture using more sensitive radiometric techniques have included *paleartica* strains. The nonradiometric blood culture medium also supports the growth of *F. tularensis*. Methods for rapid diagnosis that show future promise include direct fluorescent antibody staining of smears and tissues, antigen detection in urine, RNA hybridization with a 16S ribosomal probe, and polymerase chain reaction (PCR). Animal inoculation is rarely performed at present, in part because this requires biosafety level 3 facilities; however, biosafety level 2 is sufficient for laboratory handling of clinical materials.

The use of PCR is appealing in that smears and cultures are usually negative, standard microbiologic isolation may be hazardous to laboratory personnel, and serologic diagnosis may take several weeks to confirm. Initial studies done in murine and other animal models showed that PCR was an effective modality for diagnosing infection with *Francisella*. Sjostedt and colleagues tested wound swabs from infected patients and found a 73% sensitivity with PCR using a 17-kD lipoprotein *F. tularensis* gene and 50% sensitivity with primers to the 16S rDNA gene. Dolan and associates were able to show that PCR on lymph node aspirates was positive even after antibiotic therapy was initiated. Therefore, PCR may prove useful for diagnosing tularemia in patients already receiving suppressive empiric antibiotic therapy

Serologic studies are the most common way that the diagnosis of tularemia is confirmed. Antibodies to *F. tularensis* may be demonstrated by tube agglutination, microagglutination, hemagglutination, and enzyme-linked immunosorbent assay (ELISA). Standard tube agglutination titers are usually negative in the first week of illness, are positive in most patients by the end of two weeks, and peak after four to five weeks. The microagglutination assay is up to 100-fold more sensitive than tube agglutination. Both IgM and IgG antibody titers may persist for longer than a decade after infection, limiting the value of a single positive result. A presumptive diagnosis is supported by an acute agglutination titer of 1:160 or more in the face of compatible disease but may also reflect remote infection. Definitive serologic diagnosis requires a fourfold or greater rise in titer between acute and convalescent specimens; serologies may need to be repeated at seven-to-ten day intervals before a rise is demonstrated. Antibodies may cross-react with *Brucella* spp., *Proteus* OX19, and *Yersinia* spp., but titers to *F. tularensis* are almost always higher, and dithiothreitol treatment of the serum eliminates most of these other reactions. False-positive heterophile agglutinins also rarely occur during tularemia. Tests for cell-mediated immunity such as lymphocyte blastogenesis and delayed hypersensitivity skin test reactivity may be positive earlier than serologies, but standardized antigen preparations are not commercially available.

Detection in the environment

Its wide distribution in the environment poses a challenge for understanding the transmission, ecology, and epidemiology of the disease. A multitarget real-time TaqMan PCR assay capable of rapidly and accurately detecting *F. tularensis* in complex specimens was developed. The sensitive and specific nature of this rapid multitarget TaqMan assay provides a valuable new tool that with future evaluations can be used for analyzing clinical specimens, field samples during bioterrorism threat assessment, and samples from

outbreaks and for improving our understanding of the ecology and environmental prevalence of *F. tularensis*.

Treatment

The drug of first choice for the treatment of all forms of tularemia except meningitis is **streptomycin**, although gentamicin is an acceptable substitute.

- 7.5 to 10 mg/kg IM q 12 hours for 7 - 14 days
- or 15 mg/kg IM q 12 hours for first 3 days, followed by ½ dose to complete treatment.
- In very sick patients, 15 mg/kg q 12 hours may be given throughout a 7-to-10-day course.
- The pediatric regimens for streptomycin are similar: 30 to 40 mg/kg/day intramuscularly in two divided doses for a total of 7 days; or 40 mg/kg/day intramuscularly in two divided doses for the first three days, followed by 20 mg/kg/day intramuscularly in two divided doses for the next four days.

Doses greater than 2 g/day of streptomycin in adults do not increase efficacy.

The first few days of streptomycin rarely may induce a Jarish-Herxheimer–like reaction, with an increase in symptoms and a transient drop of the serum agglutination titer.

Gentamicin has proved to be effective therapy. A review of the literature revealed that gentamicin was effective for treatment except that the relapse and failure rates were higher with gentamicin, compared with historical rates for streptomycin. In pediatric patients, gentamicin was shown to be effective for treatment of tularemia without relapse or failure. Gentamicin is given intravenously at a dose of 3 to 5 mg/kg/day in divided doses for 7 to 14 days, with desired peak serum levels of at least 5.0 µg/ml. The efficacy of single-daily dosing has not been studied. The doses of both streptomycin and gentamicin need to be adjusted for renal insufficiency.

Doxycycline had a much higher relapse rate compared with the aminoglycosides. Tetracycline and chloramphenicol are bacteriostatic for *F. tularensis*, and this accounts in part for the high rate of relapse after treatment with these agents. Tetracycline should not be used in children younger than eight years of age, during pregnancy, or during lactation. Tetracycline is most effective in adults when given as 2 g/day in divided oral doses for at least 14 days, a suggested oral regimen in children is 30 mg/kg/day, to a maximum of 2 g/day, in divided doses for the same duration. Doxycycline may also be used and provides the convenience of twice-daily dosing. In general, chloramphenicol should not be chosen to treat tularemia because of its potentially serious toxicity and the availability of more effective alternatives with less dangerous potential side effects. However, chloramphenicol, 50 to 100 mg/kg/day intravenously in divided doses, may be added to streptomycin to treat meningitis. When used in the past for other forms of tularemia, the oral dose of chloramphenicol has been 30 to 50 mg/kg/day in three or four divided doses for at least 14 days. The oral preparation is no longer available in the United States.

Penetration of these drugs into the cerebrospinal fluid is poor and erratic and may be inadequate in tularemic meningitis. Pittman reported a central nervous system shunt infection caused by *F. tularensis* that was successfully treated with intrathecal gentamicin. An additional 13 cases of tularemic meningitis in children have been documented. Successful treatment generally included combinations of streptomycin and chloramphenicol. The most recent case was successfully treated with a combination of intravenous gentamicin and oral doxycycline.

Drugs with well-established clinical efficacy have exhibited achievable minimal inhibitory concentrations (MIC) against *F. tularensis* on in vitro susceptibility tests. Other agents with relatively low MICs include erythromycin, rifampin, cefoxitin, cefotaxime, ceftriaxone, ceftazidime, most aminoglycosides, and several fluoroquinolones except cinoxacin. The effectiveness of these drugs in treating tularemia is not fully established. In fact, ceftriaxone has failed in several patients treated as outpatients. Erythromycin has been used successfully in a few patients who were thought to have *Legionella* infections. However, resistance to erythromycin has been described in *F. tularensis* strains from outside of North America. Case

reports also suggest that ciprofloxacin, norfloxacin, and imipenem are effective in some patients. A monoclonal antibody to the LPS of *F. tularensis* and serum from vaccinated people are effective passive therapies for murine infection, offering the future hope of immunotherapeutic agents for tularemia. Surgical therapies are limited to drainage of abscessed lymph nodes and chest tube drainage of empyemas.

Surveillance

Tularemia is a condition reportable within 24 hours of diagnosis.

Case Definition

Clinical description: An illness characterized by several distinct forms, including the following:

- Ulceroglandular: cutaneous ulcer with regional lymphadenopathy
- Glandular: regional lymphadenopathy with no ulcer
- Oculoglandular: conjunctivitis with preauricular lymphadenopathy
- Oropharyngeal: stomatitis or pharyngitis or tonsillitis and cervical lymphadenopathy
- Intestinal: intestinal pain, vomiting, and diarrhea
- Pneumonic: primary pleuropulmonary disease
- Typhoidal: febrile illness without early localizing signs and symptoms

Clinical diagnosis is supported by evidence or history of a tick or deerfly bite, exposure to tissues of a mammalian host of *Francisella tularensis*, or exposure to potentially contaminated water.

Laboratory criteria for diagnosis:

Presumptive:

- Elevated serum antibody titer(s) to *F. tularensis* antigen (without documented fourfold or greater change) in a patient with no history of tularemia vaccination or
- Detection of *F. tularensis* in a clinical specimen by fluorescent assay

Confirmatory

- Isolation of *F. tularensis* in a clinical specimen or
- Fourfold or greater change in serum antibody titer to *F. tularensis* antigen

Case classification:

Probable: a clinically compatible case with laboratory results indicative of presumptive infection

Confirmed: a clinically compatible case with confirmatory laboratory results

Intervention

The purpose of investigation is to identify and confirm suspected cases, to determine the source of infection (chiefly to rule out a bioterrorism event), and to search for any contacts that may have been exposed.

- Upon receipt of a report of a case of tularemia, contact the physician and/or hospital to confirm the diagnosis.
- Identify the source of infection (occupation, insect bite, contaminated food, aerosol, bioterrorism)

Antibiotic prophylaxis after potential exposures of unknown risk, such as tick bites, is not recommended. Streptomycin given in the incubation period after experimental inoculation successfully aborts illness, but the bacteriostatic oral drugs do not. Documented exposures from laboratory accidents may be treated preemptively with intramuscular streptomycin. The value of the oral fluoroquinolones for this purpose is unknown. Liposome-encapsulated ciprofloxacin delivered by aerosol inhalation was highly effective in the treatment of respiratory *F. tularensis* infection in mice. The data indicate that this treatment might be

effective in humans as postexposure prophylaxis for aerosol exposure to the organism. The efficacies of doxycycline and ciprofloxacin also were examined in the murine model. These antibiotics, given separately 48 hours before challenge and continued through five days after challenge, were protective against intraperitoneal infection; however, mice succumbed once the antibiotics were withdrawn. If the antibiotics were extended to 10 days after challenge, relapse was much less likely to occur. When antibiotics were begun 24 hours after exposure instead of prophylactically, there was a four-fold and ten-fold decrease in efficacy for doxycycline and ciprofloxacin, respectively. The results of these experiments could be useful if *F. tularensis* is continued to be viewed as a possible weapon of biological warfare.

Immunization

Vaccines prepared from killed *F. tularensis* are ineffective, in part because they only induce an antibody response. A live vaccine based on an attenuated strain of *F. tularensis* (LVS), originally obtained from the former Soviet Union, has been developed in the United States. The LVS vaccine is an attenuated, live *F. tularensis* strain that occurs in two colony phenotypes, one of which is immunogenic and has major importance for the induction of protective immunity. A new vaccine lot has been used and has shown to be immunogenic in humans.

This vaccine induces cell-mediated and humoral immunity, is effective in preventing typhoidal disease, and reduces the severity of ulceroglandular disease but does not prevent it. Vaccination may be considered for persons who will be working with *F. tularensis* and for anyone else with repeated occupational exposures. The vaccine, an investigational agent, is available with a monitoring fee through an Investigational New Drug protocol from Headquarters, United States Army Medical Research and Materiel Command, Fort Detrick, Frederick, Maryland 21702-5012, U.S.A.

Prevention of Transmission

- Avoiding exposure to the organism is the best prevention of tularemia.
- Wild animals should not be skinned or dressed using bare hands, or when the animal appeared ill. Gloves, masks, and protective eye covers should be worn when performing such tasks and when disposing of dead animals brought home by household pets.
- Wild game should be cooked thoroughly before ingestion.
- Wells or other waters that are contaminated by dead animals should not be used.
- The most important measure to avoid tick bites in infested areas is wearing clothing that is tight at the wrists and ankles and that covers most of the body. Chemical tick repellants also may be of benefit. Frequent checks should be made for attached ticks so that they may be removed promptly; this must not be done with bare hands, and care should be taken not to crush the tick.

Hospital Precaution and Isolation

Hospitalized patients with tularemia do not need special isolation because person-to-person spread does not occur, and even in the pre-antibiotic era secondary cases were not found. Standard universal precautions for contaminated secretions are adequate when handling drainage from wounds or eyes.

Other Francisella:

Francisella novicida

F. novicida, often referred to as *F. tularensis* subsp. *novicida*, is rarely attributed to human infection and is not readily recognized in most clinical laboratories. Because of the unreliable results of phenotypic identification methods, unfamiliarity of the bacterium and close genetic relatedness among *Francisella* spp., the organism can be misidentified, thus leading to inappropriate management.

There were two cases of infection in Louisiana in 2010, both in severely immune-compromised individuals, leading to death for one of the two.

Microbiology

Similarities between *F. tularensis* and *F. novicida*: Comparative studies of various properties of *Francisella tularensis* (= *Pasteurella tularensis*) and *F. novicida* were performed. The two organisms are very similar morphologically. Growth of both was markedly enhanced by addition of cystine to media, but *F. novicida* is less fastidious than *F. tularensis*. The virulence of *F. novicida* for mice and cavy is lower than that of fresh isolates of *F. tularensis*. In complement-fixation tests, some cross-reaction occurred when rabbit antisera were used; complement-fixation tests with cavy antisera were specific. Agglutination tests with sera from both rabbits and cavy were specific. Nonliving vaccines of the two organisms (extracts, whole dead cells) conferred no cross-protection to mice; living attenuated vaccines conferred cross-protection which was more transitory than was specific protection. Passive cutaneous anaphylaxis (PCA) tests were highly specific. Absorption of antisera with homologous organisms removed all PCA reactivity, while absorption with heterologous organisms left it almost intact. Hemagglutination and hemagglutination-inhibition tests were specific. It was concluded that the two organisms are sufficiently similar to belong in the same genus but sufficiently different to be retained in separate species.

Epidemiology

There is no clear explanation regarding route of acquisition and the pathogenic role of this organism. Additionally, there is no evidence for human-to-human transmission.

Immunosuppression and severe liver failure are important risk factors to contracting the disease.

Clinical picture

A clinical diagnosis of *Francisella* infection is highly nonspecific. Given that the organism is believed to be of low virulence, particularly that it does not pose a substantial risk for immunocompetent persons, its role as a human pathogen remains controversial.

Laboratory diagnosis

F. novicida is not considered to have a fastidious growth requirement. The standard protocol of five-day incubation for automated blood culture is supposedly sufficient for detection of *F. novicida* bacteremia. Identification of *F. novicida*, however, is often difficult because the bacterium can be easily misidentified as a non-*Francisella* species or as a highly pathogenic *F. tularensis*. It was also indicated that this organism could not be detected by a direct fluorescent antibody test used for the identification of *F. tularensis* types A and B.

Treatment

Most strains were susceptible to aminoglycosides, quinolones, and tetracyclines. Some cases were successfully treated with flucloxacillin and doxycycline, followed by dicloxacillin and doxycycline. Some reports suggest that piperacillin/tazobactam and other β -lactams are generally considered ineffective in vivo against *Francisella* spp. and likely result in therapeutic failure.

Prevention

The high risk for laboratory-acquired tularemia when handling *F. tularensis* cultures does not seem to exist for *F. novicida*. Prophylactic treatment is unnecessary because these isolates are not known to cause laboratory-acquired infections.

Francisella philomiragia

Francisella philomiragia is a rare gram-negative, halophilic coccobacillus with bizarre spherical forms on primary isolation.

A case of *F. philomiragia* bacteremia in a 24-year-old patient with chronic granulomatous disease was reported. Identification of *F. philomiragia* was problematic with conventional tests but was done correctly and rapidly by kit 16S ribosomal DNA sequencing.

The patient was a 24-year-old man with chronic granulomatous disease (CGD). At the age of 2.5 years he was operated on for a hepatic abscess with *Staphylococcus aureus*. Follow-up investigations on his granulocyte function showed a profound defect in the intracellular bactericidal activity against *S. aureus*. Repeated studies of the respiratory burst function all showed nearly complete absence of activity. The patient was put on prophylactic treatment with trimethoprim-sulfamethoxazole and later dicloxacillin, on which he remained well without serious infections. One month prior to the admission he was treated successfully with penicillin for pneumonia. During a vacation in Turkey, where he had gone swimming in the sea and taken mud baths, he developed a high fever. The fever continued after his return from vacation and was accompanied by cough and expectoration. Three days before admission to the hospital he had a fever of 39°C and treatment with cefuroxime was initiated. His general condition deteriorated rapidly and he was admitted in shock at the intensive care unit with bilateral interstitial pneumonia with pleural effusion and splenomegaly. Treatment with high doses of erythromycin, ciprofloxacin, and metronidazole was initiated. The next day when gram-negative coccobacilli grew in blood cultures, the treatment was supplemented with meropenem, interferon, and filgrastim (Neupogen). The patient developed multiorgan failure and disseminated intravascular coagulation and died after four days. An autopsy was not performed.

F. philomiragia caused septic shock with multiorgan failure despite the administration of antibiotics to which the organism was sensitive (cefuroxime, ciprofloxacin, erythromycin, and meropenem) plus interferon and filgrastim. Identification of the organism as *F. philomiragia* is difficult.