Zoonosis Update

Tularemia

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I know of no other infection of animals communicable to man that can be acquired from sources so numerous and so diverse. In short, one can but feel that the status of tularaemia, both as a disease in nature and of man, is one of potentiality.

—R. R. Parker, 1934[1]

Background

Tularemia, also known as rabbit fever and deerfly fever, is a bacterial zoonosis caused by the small, pleomorphic, gram-negative coccobacillus *Francisella tularensis*. The organism can infect numerous species of animals; in the United States, rodents and lagomorphs are the important epizootic hosts, and various species of ticks are important maintenance hosts and biologic vectors. Of 4 biogroups of the organism, 2 account for most clinical disease; these biogroups can be distinguished biochemically, epidemiologically, and by virulence testing. Jellison type A (*F tularensis* subsp *tularensis*) ferments glycerol, is highly virulent for laboratory rabbits, and is found predominately in North America; Jellison type B (*F tularensis* subsp *holarctica,* formerly susbsp *palaearctica*), which is less virulent than type A, is found throughout Europe and Asia but also in North America. *Francisella tularensis* subsp *mediaasiatica* is not known to cause infections in humans and is found in Central Asia. *Francisella novicida* was previously considered a separate species but is now classified as another biogroup of *F tularensis*. *Francisella tularensis* subsp *novicida* is of low virulence[2] and has been isolated from human patients with a tularemia-like illness in the United States and Canada.[3]

Tularemia was first described by McCoy in 1911 as a plague-like illness of California ground squirrels. In 1912, McCoy and Chapin[4] published a paper on the syndrome and the causative agent, which was originally called *Bacterium tularense* after Tulare County, where the work was done. The first described clinical case in which *F tularensis* was implicated as the etiologic agent occurred in 1914, when the oculoglandular form was reported in a restaurant worker in Cincinnati.[5] Edward Francis, a US Public Health Service surgeon, dedicated much of his scientific career to research on the organism, including classifying the various clinical manifestations of the disease, cultivating the organism, developing serologic tests, and elucidating its various mechanisms of transmission. In 1947, the agent was renamed *Francisella tularensis* in his honor.

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Epidemiology

Tularemia occurs throughout temperate regions of the Northern Hemisphere, including North America, continental Europe, the former Soviet Union, China, Korea, and Japan. The disease in humans is nationally notifiable in the United States and has been reported from all states but Hawaii. In the first half of the 20th century, tularemia infection in the United States was relatively common; the peak number of reported cases was 2,291 in 1939.[6] Since the 1950s, the number of reported cases has declined dramatically; a mean of 124 cases was reported annually between 1990 and 2000 (**Fig 1**). During this same period, over half of the human cases reported to the national Centers for Disease Control and Prevention were reported from Arkansas (23%), Missouri (19.4%), South Dakota (7%), and Oklahoma (6.6%; **Fig 2**). Cases have been reported in all months of the year, but most case onset is reported from May through August, corresponding to transmission via arthropod bites. Historically, a winter peak in incidence, associated with rabbit hunting, was also noticed. In humans, the incidence is highest in persons aged 5 to 9 years and in persons aged ≥ 75 years; males have a higher incidence in all age categories. Native Americans are disproportionately represented.[7]

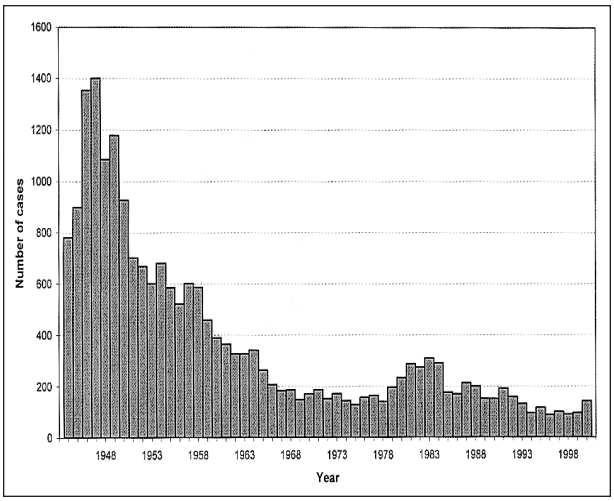

Figure 1—Number of reported human cases of tularemia by year—United States, 1944–2000.

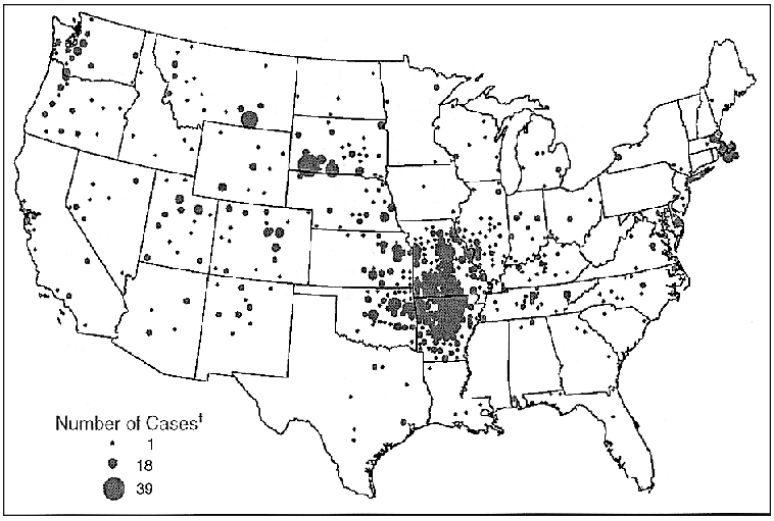

Figure 2—Reported cases* of tularemia—United States, 1990–2000. *Based on 1,347 human patients reporting county of residence in the lower continental United States. Alaska reported 10 cases in 4 counties during 1990–2000. †Circle size is proportional to the number of cases (range, 1 to 39).

Ecology

Francisella tularensis can infect a diverse population of animals, including more than 100 species of wild and domestic mammals as well as humans, 25 species of birds, and several species of amphibians and reptiles.[8] In the United States, lagomorphs (particularly *Sylvilagus* spp) are most commonly infected and important in the transmission of *F tularensis* to humans. Because ticks can maintain infection throughout their life cycle, they are not only important vectors but also important reservoirs of the disease. In the United States, tularemia outbreaks in humans have been associated with contact with muskrats[9] and beavers.[10] In addition to contact with lagomorphs, sporadic cases have been acquired through contact with squirrels,[11,12] sheep,[13] pheasants,[14] and nonhuman primates.[15] Epizootics have been reported in vole (*Microtus* spp),[16,17] beaver (*Castor canadensis*), and muskrat (*Ondatra zibethica*) populations.[10] Natural infection with *F tularensis* has also been recognized in wild-caught prairie dogs (*Cynomys ludovicianus*),[18] marmosets (*Callithrix jacchus*),[19] raptors,[20] quail,[21] mink and fox,[22] and numerous other species.[8]

Of domestic species, cats and dogs can acquire infection, although clinical illness is more common in cats. Dogs may serve as reservoirs for the organism or maintenance hosts for the tick vector.[23,24] Of livestock, sheep are most commonly affected; other livestock species may have serologic evidence of exposure to *F tularensis*, although clinical disease is rare. Infection in nonhuman primates has been reported[25-28] in a pet monkey and animals housed in zoos and laboratory facilities.

Francisella tularensis does not form spores but can survive in water, soil, and decaying animal carcasses. The organism has been isolated from water and mud samples stored at 7°C for as long as 14 weeks, in tap water for as long as 3 months, and in dry straw litter for at least 6 months.[8]

Mode of Transmission

Francisella tularensis is highly infectious, and as few as 10 to 50 organisms inhaled or injected intradermally can reliably cause disease in humans.[29,30] Natural transmission of *F tularensis* to humans can occur through various modes—the most common in the United States are via an arthropod bite, such as that of a tick or deerfly,[31] and through direct contact with infected tissues. There are numerous reports[32-39] of acquisition of tularemia through direct contact with infected cats, through breaks of the skin (cat bite or scratch), and in at least 1 instance where no abrasion or wound was recalled.[35] Clinical illness in cats is not necessary for transmission to occur.[39] It has been speculated that dogs can mechanically transmit the bacterium after mouthing an infected animal or becoming wet with contaminated water[40]; in 1 instance, inhalation of the organism occurred while shearing a dog.[41] Human cases have resulted from contact with *F tularensis*-infected sheep,[6,13] including contact during shearing. *Francisella tularensis* can also be transmitted to humans by ingestion of the organism in contaminated food or drink, after exposure to contaminated water, and through inhalation. People who mow lawns or cut brush in tularemia-endemic areas may be at increased risk of pneumonic tularemia.[42] Laboratory transmission of *F tularensis* occurs readily because the organism is easily aerosolized, sometimes simply by opening a culture plate; at 1 time tularemia was second only to viral hepatitis as an occupationally acquired infection of laboratory workers.[43] Person-to-person transmission of *F tularensis*, even in cases of pneumonic tularemia, has not been convincingly documented, although specimens obtained from ulcers or buboes should be considered infectious.

In the United States, the most common tick vectors of tularemia are the American dog tick (*Dermacentor variabilis*), the Lone Star tick (*Ambloyomma americanum*), and the Rocky Mountain wood tick (*D andersoni*), although other ticks are known to be naturally infected.[44] Deerflies, and possibly other biting arthropods such as mosquitoes, can mechanically transmit the organism. Dogs and cats acquire infection through the bite of an infected arthropod or by ingestion of, or direct contact with, infected tissues.

Because of the high infectivity of *F tularensis*, its relative ease of dissemination, and its potential to cause severe disease, the organism is classified as a Category A agent of bioterrorism.[45] *Francisella tularensis* could be used as a biologic weapon if aerosolized or used to contaminate food or water. The Johns Hopkins University Working Group on Civilian Biodefense believes that the greatest adverse medical and public health consequences would be realized following the intentional release of aerosolized *F tularensis*.[46]

Clinical Signs

In humans, tularemia is characterized by acute

febrile illness that commonly includes other nonspecific symptoms such as malaise, chills, headache, and myalgia. Following a typical incubation period of 3 to 5 days (range, 1 to 14 days), people infected with *F tularensis* develop 1 of 6 clinical syndromes that depend on the portal of entry. The most commonly occurring syndrome in the United States is the ulceroglandular form of the disease in which an ulcer develops at the site of cutaneous or mucous membrane inoculation, accompanied by regional lymphadenopathy. The glandular form of the disease lacks an ulcer. The oropharyngeal and oculoglandular syndromes have signs localized to the oropharynx and eye, respectively. The primary pneumonic form is rare but is the most severe, with an untreated mortality rate of up to 60%.[47] Chest radiography may reveal various interstitial infiltrates with only minimal pulmonary symptoms and no obvious abnormalities detected during physical examination. Other chest radiographic findings include hilar adenopathy, pleural effusion, or miliary nodules. The typhoidal form of the disease has no localizing signs and can be a diagnostic challenge. All forms of tularemia can progress to secondary pleuropneumonia, meningitis, or sepsis; the latter can progress to shock or death. Without treatment, symptoms can persist for weeks to months, and overall mortality in untreated humans infected with Type A *F tularensis* is 5 to 15%; the overall case-fatality rate of tularemia in the United States is currently less than 2%.[46]

Clinical manifestations of the disease in animals are as diverse as in humans; like humans, animals typically have signs of acute febrile illness. Cats may be more susceptible to tularemia than dogs, and the clinical picture of naturally acquired tularemia in domestic animals is best described in that species,[38,48-51] although it is probably underdiagnosed.[49] Tularemia in cats can range from nonclinical infection to mild illness with lymphadenopathy and fever to severe overwhelming infection and death.[52] In addition to fever, cats develop with signs that can include anorexia, dehydration, listlessness, lymphadenopathy, draining abscesses, oral or lingual ulceration, pneumonia, hepatomegaly, splenomegaly, and icterus. The WBC count may be normal, high, or low, compared with reference values; other laboratory findings may include a left shift, thrombocytopenia, toxic neutrophils with changes ranging from mild to severe, high serum transaminase activity, and hyperbilirubinemia. Antemortem diagnosis has been made by serology and culture of bone marrow and lymph node aspirates. An extensive review of the disease in cats is available.[52]

Natural infection in dogs has been reported rarely. In 1 instance, a 13-month-old dog that had ingested a wild rabbit the week prior had an acute onset of anorexia, pyrexia, and lymphadenopathy (including necrotizing tonsillitis). The disease was self-limiting with only supportive treatment. A diagnosis of tularemia was confirmed by a > 4-fold increase in paired serum titers. All laboratory findings, with the exception of high plasma fibrinogen concentration, were within normal reference ranges.[53] Dogs experimentally infected with *F tularensis* develop similar illness to that acquired by natural infection, and puppies may be more susceptible than young adult dogs. Dogs fed infected tissues developed a 5-day illness with fever and mucopurulent discharge from the nose and eyes. Intradermal inoculation resulted in transient illness characterized by fever, pustules at the inoculation site, and regional lymphadenopathy.[54] Despite the relative dearth of reports of clinical illness in dogs, there is ample evidence in the literature of seroconversion in dogs,[23,24,40,55,56] suggesting that natural infection in dogs is not a rare event, but resultant illness is inapparent or mild.

Outbreaks of tularemia in sheep have been reported[6] in Montana and Idaho and can result in substantial morbidity and mortality. Outbreaks generally occur in association with reduced body condition following severe winter weather, a decreased plane of nutrition, and heavy tick infestations. Affected sheep were reported to have high rectal temperatures, low body weight, regional lymphadenopathy, and diarrhea.[57] There is abundant seroevidence of natural infection in cattle,[55,56,58-60] although a definitive clinical syndrome has not been described. In several situations, concomitant tick paralysis was observed in infected herds; however, in at least 1 epidemic, tularemia was definitively diagnosed in 2 sick calves.[60] A mare and 5 foals were reported to have developed tularemia, 2 of which died from the disease. The infected horses were febrile and dyspneic, had signs of depression and incoordination, and were infested with ticks; 1 of the 2 foals that died had no signs of illness. Seroconversion in surviving horses was detected, and *F tularensis* was isolated from tissues collected at necropsy.[61] Livestock may be more important as maintenance hosts of the tick vectors rather than as reservoirs of infection.

Naturally occurring tularemia has occurred in nonhuman primates including squirrel monkeys (*Saimiri sciureus*), black and red tamarins (*Sanguinus nigricollis*), talapoins (*Cercopithecus talapoin*), and a lowland gorilla (*Gorilla gorilla gorilla*).[25-28] These animals have developed various nonspecific signs including depression, lethargy, anorexia, vomiting and diarrhea, generalized lymphadenopathy, pale mucous membranes, and cutaneous petechiae; several animals died acutely.

Clinical illness is recognized in wild lagomorphs and rodents and is generally evidenced as lethargy and sluggishness in its terminal phase. Because sick and dying animals are easily preyed upon, transmission of *F tularensis* to predator species is facilitated.

Pathogenesis and Pathologic Features

After entering the host, *F tularensis*, which is facultatively intracellular and multiplies within macrophages, disseminates via a hematogenous route to organs throughout the body.[2] Although rarely detected, bacteremia may be common early in infection. Bacteria and cell debris from capillary endothelium can lead to necrotic foci in the liver, spleen, lymph nodes, lung, and bone marrow as a result of thrombotic development. The initial response primarily by neutrophils subsequently includes lymphocytes, macrophages, and epithelioid cells. Lesions have been mistaken for tuberculosis because of the occasional caseating granuloma

formation.[2] Humoral immunity develops between the second and third week after infection, with IgG, IgM, and IgA appearing almost simultaneously. Humoral immunity, however, provides insufficient protection against virulent infection, and cell-mediated immunity, which develops a week before humoral immunity, is more important because of the intracellular nature of the organism.[2]

On postmortem examination of cats, hepatomegaly, splenomegaly, or both have been observed. Multiple small grayish, yellow, or white foci of necrosis are commonly found in the spleen, liver, and lungs.[38,51] Lymph nodes may be up to 2 times normal size, and hepatic necrosis and multifocal fibrinonecrotic pneumonia may also be evident[38,51]; involvement of Peyer's patches has also been described.[51]

In a report[25] of tularemia in tamarins and talapoins, necropsy findings in all monkeys included splenomegaly, a slight excess of abdominal fluid, small focal areas of caseous necrosis in the spleen and liver, fibrinous exudates attached to serosal and pleural surfaces, enlarged and edematous mesenteric lymph nodes, and mild intraluminal intestinal hemorrhage. Cutaneous petechiae and hemorrhage in the lungs, adrenal glands, gastrointestinal tract, meninges, and on the epicardium were observed in 2 squirrel monkeys,[26] and hemorrhagic colitis was noted in a lowland gorilla.[27]

Diagnosis

The most common method used to diagnose tularemia is detection of agglutinating antibodies in the serum by tube agglutination, microagglutination, hemagglutination, and ELISA,[2] although antibody may not be detected until the second or third week of illness. Definitive diagnosis of tularemia is made from the isolation of *F tularensis* from clinical specimens such as blood, exudates, or biopsy material from a lesion or lymph node. *Francisella tularensis* is a strict aerobe, and culturing it requires media supplemented with sulfhydral compounds (cysteine or cystine) for optimal growth; therefore, it will not grow on most conventional laboratory media but can be successfully recovered by use of glucose cysteine blood agar, thioglycolate broth, chocolate agar suitable for gonococcal growth, modified Thayer-Martin medium, or buffered charcoal-yeast agar. The optimal temperature for growth is 35°C, and colonies may take 2 to 4 days to appear.[2] On glucose cysteine blood agar, colonies are gray and can reach 4 mm in diameter, with the medium turning greenish; morphologic characteristics of the colony can vary by strain and within strains.[8] Other diagnostic tests include fluorescent assays on clinical specimens and the polymerase chain reaction. *Francisella tularensis* is rarely detected on Gram-stained smears.

For the surveillance of human disease, confirmatory laboratory evidence of tularemia is culture of the bacterium or detection of a 4-fold change of titer between acute and convalescent serum samples obtained 2 to 4 weeks apart. Presumptive diagnosis of tularemia can be made by detecting *F tularensis* antigens with fluorescent assays or by a single high antibody titer. Most state public health laboratories in endemic states can test specimens for tularemia. Commercial and reference laboratories may also provide diagnostic services, but because of the highly infectious nature of the organism, laboratories should at a minimum be **biological safety level II (BSL-2)** and practice **biological safety level III (BSL-3)** safety procedures.

Treatment

In humans, the treatment of choice for tularemia is streptomycin, but gentamicin is a suitable alternative. Other agents used in the treatment of *F tularensis* infection are tetracyclines and chloramphenicol, which is indicated for tularemia meningitis. Because tetracyclines and chloramphenicol are bacteriostatic, it is important to treat for a full course of 14 days to minimize the risk of relapse when these agents are used. There is growing evidence that the fluoroquinolones are effective in the treatment of tularemia,[32,62-67] and ciprofloxacin (or doxycycline) administered orally is recommended by the Working Group on Civilian Biodefense in the event of a mass casualty setting following a bioterrorist event.[46] *Francisella tularensis* produces β-lactamase and, thus, is resistant to the beta-lactam class of antimicrobials. Despite good in vitro susceptibility to the cephalosporins, there have been reports of treatment failures following treatment with ceftriaxone.[68] *Francisella tularensis* has various degrees of in vitro susceptibility to macrolide antimicrobials; there are at least 2 reports of the successful use of erythromycin,[69,70] but macrolides are not recommended for the treatment of tularemia.

Defervescence in humans with tularemia has been noted within 48 hours of treatment with streptomycin or tetracycline.[29,30] Because no systematic trials have been performed to assess treatment of tularemia in animals, the treatment options for animals should be extrapolated from human recommendations (**Appendix**).

Public Health Implications

Despite its relative rarity, veterinarians should consider a diagnosis of tularemia in animals that have a febrile illness with or without lymphadenopathy in an area where the disease is endemic. Standard precautions, used for both patient care and postmortem examination, should reduce the risk of transmission of tularemia from animals to humans. Local or state health departments may be useful resources regarding management of exposures to animals suspected of having tularemia. Medical advice should be sought promptly if fever or other signs compatible with tularemia develop in a person exposed to an animal with tularemia. Pet owners should be educated about the value of a good tick control program in the prevention of tularemia and other tick-borne diseases.

Occupations with an increased risk of tularemia infection are veterinarian, laboratory worker, farmer, sheep worker, hunter or trapper, cook or meat handler,[2] and landscaper.[42] Laboratories processing clinical specimens should at a minimum be BSL-2 and practice BSL-3 safety procedures. Vaccination with an attenuated live vaccine was previously available for laboratorians and others at high risk of tularemia under an Investigational New Drug protocol but is not currently available. Hunters and those who skin, dress, and eat

wild game, in particular rabbits, should wear gloves when handling carcasses, disinfect their equipment following use, and cook all meat thoroughly. People should be advised not to handle sick or dead animals.

Humans and animals with tularemia, and animal die-offs in rodent and lagomorph populations, should be reported to local or state health authorities. Because of the possibility for use as a bioterrorism agent, human and animal outbreaks of tularemia require prompt investigation by public health authorities. Epidemiologic and laboratory support can be obtained by contacting the local or state health department or the national Centers for Disease Control and Prevention, Bacterial Zoonoses Branch, at (970) 221-6400.

Summary

Tularemia is a rare but potentially fatal disease that develops in numerous wild and domestic animals, including lagomorphs, rodents, cats, and humans. The disease occurs throughout much of the United States and should be considered in the differential diagnosis of acute febrile illness, particularly when risk factors such as contact with wild mammals or tick exposure are present. Veterinarians may be at increased risk of acquiring tularemia from contact with infected animals, but standard precautions should greatly reduce this risk. Outbreaks of tularemia warrant investigation, especially given the possibility of the use of *F tularensis* as an agent of bioterrorism.

Appendix

Suggested antimicrobials for the treatment of tularemia in cats and dogs.* Because no systematic trials have been performed to assess treatment of tularemia in animals, the treatment options for animals should be extrapolated from human recommendations

Antimicrobials	Dosage
Gentamicin†,‡	6.6 mg/kg (3 mg/lb), IM, IV, or SC, q 24 h or divided q 12 h or 8 h
Doxycycline§,¶	5 mg/kg (2.3 mg/lb), PO, q 24 to 12 h
Chloramphenicol¶	Cats: 50 mg/kg (22.7 mg/lb), PO or IM, q 12 h Dogs: 100 mg/kg (45.5 mg/lb) initially, then 50 mg/kg, PO or IM, q 8 h
Enrofloxacin‡,#	2.5 mg/kg (1.1 mg/lb), PO or IM, q 12 h

*Dosages adapted from the Formulary of the Colorado State University Veterinary Teaching Hospital, May 1998. †Streptomycin is the treatment of choice for tularemia in humans, but is not widely available; gentamicin is considered a suitable alternative to streptomycin, although it is not approved for this purpose. Adjust dosage for animals with renal failure. ‡Treatment with gentamicin or enrofloxacin should be continued for 10 days. §Approved for the treatment of tularemia in humans. ¶Because doxycycline and chloramphenicol are bacteriostatic, treatment should be given for 14 days to minimize risk of relapse. #Fluoroquinolones are not approved for the treatment of tularemia in humans; however, there is growing evidence these agents are effective in the treatment of tularemia in humans.

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