

Zoonosis Update

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, 1934¹

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 predominantly in North America; Jellison type B (*F tularensis* subsp *holarctica*, formerly subsp *palaeartica*), 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 virulence² 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 Chapin⁴ 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, devel-

oping serologic tests, and elucidating its various mechanisms of transmission. In 1947, the agent was

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

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 muskrats⁹ 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 reported²⁵⁻²⁸ 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 deer-fly,³¹ and through direct contact with infected tissues. There are numerous reports³²⁻³⁹ 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 water⁴⁰; 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

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 tularemia 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%.⁶⁷ 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 tularemia is 5 to 15%; the overall case-fatality rate of tularemia in the United States is currently less than 2%.⁶

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,^{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 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.

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 tularemia develop similar illness to that acquired by natural infection, and puppies may be more susceptible than young adult dogs. Dogs

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 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 sero-evidence 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. 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 tularemia 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 (*Leontideus nigriceps*), 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 tularemia to predator species is facilitated.

Pathogenesis and Pathologic Features

After entering the host, tularemia which is facultatively intracellular and multiplies within macrophages, disseminates via a hematogenous route to organs throughout the body. 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.

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.⁵³

In a report²⁵ of tularemia in tamarins and talapoins,

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

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