INTRODUCTION

Tularemia, also known as ‘rabbit fever’ and ‘deerfly fever’, is a highly infectious bacterial disease caused by the aerobic Gram-negative coccobacillus Francisella tularensis. The disease may affect any mammal including rodents, rabbits, dogs, cats, horses and humans. Four subspecies of F. tularensis are identified: subsp. tularensis (AKA Type A), subsp. holarctica (AKA Type B), subsp. novicida and subsp. mediasiatica. F. tularensis subsp. tularensis (Type A) is the most common form in the United States and is the most pathogenic for humans: Type A subspecies is further subtyped as A1a, A1b, A2a, and A2b. A1b is the most pathogenic in humans with a mortality rate of 24%.

TRANSMISSION

F. tularensis can be transmitted by ingestion or inhalation of the organism or by direct cutaneous skin contact with infected tissues. It can also be transmitted via bite from biting insects. Ticks, especially Dermacentor variabilis (the American dog tick) and Amblyomma americanum (the Lone Star tick), serve as long-term reservoirs of infection as well as vectors and are the predominant vectors in the East and Midwest. Biting flies, which can serve as mechanical vectors when their mouthparts become contaminated while feeding on an infected host, are the principal vectors in California, Nevada and Utah; mosquitoes can also serve as mechanical vectors of the disease (Europe, Soviet Union). The organism is sustained in the environment by ticks (ticks maintain infection for life and can transmit the organism transovarially) and by infection of a wide range of wild mammals in which it often causes severe disease. F. tularensis also remains viable for months in water and for years in frozen rabbit meat. Most cases in cats and dogs are attributable to exposure to wild rabbits or rodents, especially ingestion of rabbit. Transmission can also occur from vector transmission or from bites or scratches from other animals with contaminated teeth or claws. Humans can be infected by being bitten or scratched by a dog or cat that has had contact with infected prey or possibly via aerosols from dogs’ coats after the dog have contacted infected animals.

OCCURRENCE

In the United States, tularemia occurs most commonly in Oklahoma, Kansas, Arkansas and Missouri but has been reported in virtually all states of the continental US. At the UI VTH Small Animal Clinic, the majority of cases have originated from Savoy, IL. Small foci of infection may maintained by tick-reservoir host transmission with epizootics of disease occurring when more virulent strains of the organism develop. Tularemia is a reportable disease in most states and is designated as a Notifiable Disease at the national level in the US (potential agent of bioterrorism). Natural disease usually occurs in late spring and summer. In humans, farming, hunting, landscaping and working with animals (veterinary practice, working with sheep, meat handling) are associated with increased risk for tularemia. Cats are far more susceptible than dogs: reports of naturally-occurring infection of dogs is rare. Disease is usually seen in outdoor or indoor/outdoor cats. At the UI VTH Small Animal Clinic, all cases of tularemia have been cats with an outdoor or indoor/outdoor lifestyle. Young animals are more susceptible and more likely to develop systemic (typhoidal) disease. All of the cats diagnosed at the Small Animal Clinic have been adult (> 1year of age).

PATHOGENESIS

Following inoculation, F. tularensis replicates locally then disseminates to regional lymph nodes. Subsequently, bacteremia may occur, allowing systemic spread to primarily reticuloendothelial tissues.
The organism is able to invade and survive within macrophages and is also capable of invading other non-phagocytic cell types, notably in the liver and lung, and incites a marked inflammatory response leading to host cell injury and necrosis. Clinical signs are often protean signs of inflammatory disease and may vary depending on which tissues are most affected. The incubation period in dogs and cats (1-5 days) appears to be much shorter than in humans (3 weeks).

Clinical disease in humans differs depending on the route of exposure and virulence of the infecting subspecies and subtype. Human tularemia is categorized as ulceroglandular (cutaneous inoculation, most common form), glandular, oculoglandular (conjunctival exposure), oropharyngeal (ingestion), typhoidal and pneumonic (inhalation or hematogenous spread to lungs, most severe form). Clinical disease in animals also varies depending on the route of inoculation of the agent. Dogs have been shown experimentally to develop acute febrile disease and mucopurulent oculonasal discharge lasting 5 days after ingesting infected tissue and transient ulceroglandular disease (fever, local pustules, regional lymphadenomegaly) following intradermal inoculation and septicemic (typhoidal) disease with focal abscessation, regional lymphadenomegaly followed by systemic spread (1 week following localized disease) with obvious illness, oculonasal discharge, cutaneous rash and high mortality following IM or SC inoculation. In cats, experimental exposure by feeding infected tissues resulted in systemic (typhoidal) disease in younger cats with development of generalized lymphadenomegaly and abscess formation in the liver and spleen, though some exposed cats showed no clinical disease. Intranasal or subcutaneous inoculation resulted in similar clinical manifestations with some cats also showing lung involvement (F. tularensis-positive bronchopneumonia).

CLINICAL FINDINGS

Tularemia in domestic cats is characteristically a severe acute febrile illness with rapid progression and a high mortality rate, though chronic infection (cat with chronic [1 year] draining cutaneous lesion) is reported. Cats typically show initial lethargy (often marked), anorexia, high fever (104-105°F) and dehydration. Ptyalism and acute shallow oral and/or lingual ulcers (oral exposure or ingestion of infected prey, especially rabbits) may be evident on initial examination or develop subsequently. Icterus, hepatomegaly, splenomegaly, vomiting, cutaneous abscesses and regional, abdominal or generalized lymphadenomegaly may be present. Hypothermia and bradycardia may occur terminally. A history of exposure to wild rabbits is frequent. Subclinical infection of cats with subsequent transmission to humans appears to occur.

Naturally-occurring tularemia in dogs is rare. Transient signs of lethargy, anorexia, high fever, peripheral/mandibular lymphadenomegaly, multifocal draining abscesses, myalgia, ocular discharge, conjunctivitis, uveitis and tonsillitis may be seen. Sudden death following possible inhalation exposure (sniffing a dead infected rabbit) has been reported but cause of death was not documented.

LABORATORY AND IMAGING FINDINGS

In cats, abnormalities in the CBC are common but variable: neutrophil counts may be normal, profoundly decreased or elevated with toxic changes to neutrophils; moderate to marked elevations in bands may be present; lymphopenia and thrombocytopenia (as low as 40K) are common. Elevations of ALP and ALT are common and hyperbilirubinemia is less commonly present. Azotemia, hypoglycemia and electrolyte abnormalities may occur. Splenomegaly, hepatomegaly and/or lymphadenomegaly may be evident on abdominal imaging studies and sternal lymphadenomegaly and pulmonary changes (focal alveolar changes, nodular interstitial pattern) may be noted on thoracic radiographs. Cytologic examination of lymph node aspirates may show lymphoid hyperplasia, pyogranulomatous inflammation with increased macrophages and/or supplicative lymphadenitis with degenerate neutrophils. F. tularensis organisms are small and stain poorly so are rarely identified on routinely stained cytological preparations but may be evident as intracellular coccobacilli.
MD Ridgway  Tularemia

DIAGNOSIS

Definitive diagnosis of tularemia is established by demonstrating the *F. tularensis* organism via immunological techniques, molecular techniques or culture. Immunological techniques include direct immunofluorescent antibody (IFA) staining of aspirates of affected tissues or direct IFA or immunoperoxidase staining of tissue collected at necropsy. Negative results do not rule out tularemia and recent antibiotic administration may cause false negatives. On the other hand, IFA may be positive in samples that are negative on culture. Molecular techniques include polymerase chain reaction (PCR) and, uncommonly, fluorescence in situ hybridization (FISH). PCR assays are sensitive and rapid and pose low risk to laboratory staff relative to culture techniques. PCR may be applied to blood, tissue aspirates and tissue necropsy samples. Culture of blood, exudates, aspirates of affected lymph node or tissues or of tissue collected at necropsy poses significant risk to laboratory personnel and must be conducted at selected (Biosafety Level 2) laboratories. Isolation of the organism requires special media and recent antibiotic treatment may cause false negatives. The delay in diagnosis of 2 or more days for cultures to grow followed by confirmation of the identity of the organism immunological or molecular techniques is likely to negatively impact outcomes because of delayed initiation of specific treatment.

Serologic testing for antibodies to *F. tularensis* by microscopic agglutination (MA), IFA or ELISA techniques can identify exposure but may be negative early in infection: a negative result does not rule out tularemia. Additionally, a positive result indicates exposure not active infection: acute and convalescent titers (after 3 weeks because specific antibody may not appear until 3 weeks post-infection) showing a four-fold increase in antibody levels is necessary for serologic diagnosis of tularemia. Serology is not practical in confirming acute disease as cats may die prior to appearance of specific antibody.

Necropsy findings include regionally or generally enlarged lymph nodes, sometimes with associated draining tracts; splenomegaly; hepatomegaly; multifocal small yellow or gray lesions (caseous necrosis) in liver, spleen, lung and, uncommonly, heart; icterus; and sometimes intestinal hemorrhage. Organisms are not readily seen in lesions and special staining or immunological techniques are required to confirm the presence of organisms associated with post-mortem lesions.

TREATMENT

Affected animals must be managed under strict isolation procedures for at least the first 3 days following initiation of specific treatment and require intensive supportive care as well as administration of antimicrobial drugs effective against *F. tularensis*. Gentamicin (IV, IM or SC 5-7mg/kg q24h for 14 days) is considered the drug of choice for treatment of tularemia. Doxycycline and fluoroquinolones are alternative antimicrobials for treating tularemia but are associated with more treatment failures than the aminoglycosides and should be administered for 2-3 weeks, though there is little objective data to direct these recommendations in animals.

PROGNOSIS

Though specific data regarding outcomes in feline tularemia are limited, cats with acute tularemia often die unless tularemia is diagnosed and treated specifically. In cats diagnosed early and treated with appropriate antibiotics and supportive care, outcomes may be excellent. Some owners elect euthanasia of affected cats due to the zoonotic/public health concerns and cost of intensive care required for these cats.

PREVENTION

There is currently no licensed vaccine available, though there is continuing strong interest in vaccine development for prevention of human disease given the organism’s potential as a bioterrorism agent. Prevention centers on avoiding exposure by preventing access to infected animals (indoor lifestyle), rodent control, and prevention of tick bites by consistent use of acaricides.
Infected animals may transmit tularemia to humans by direct contact of infected body fluid or tissue with the human’s skin, uncommonly by bites and scratches, and rarely by carrying infected vectors into the human’s environment. For veterinary professionals, recognition of potential cases of tularemia (cat with acute high fever, lymphadenomegaly, oral/lingual ulceration, draining skin or lymph node lesions, history of potential exposure/outdoor lifestyle, contact with wild rabbit) and use of appropriate protective procedures (gloves and goggles, safe handling of biological materials from patient, isolation procedures) are imperative to prevent zoonotic disease. Onset of flu-like illness in a human within a few weeks of potential exposure to an affected animal should prompt the person to seek immediate medical care, advising the attending physician of the possibility of exposure to \textit{F. tularensis}. 