Chapter 24

TULAREMIA

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INTRODUCTION

Tularemia is a zoonosis caused by the Gram-negative, facultative intracellular bacterium, Francisella tularensis. The disease is characterized by fever, localized skin or mucous membrane ulceration, regional lymphadenopathy, and, occasionally, pneumonia.

In 1911, G. W. McCoy discovered the disease in Tulare County, California, as a cause of a plague-like illness in ground squirrels. An organism was isolated and named Bacterium tularense. The first bacteriologically confirmed case of human disease was reported in 1914. Edward Francis subsequently described transmission by deer flies via infected blood and coined the term tularemia in 1921. Transovarian transmission in ticks was reported in 1926. In 1959, the Soviets proposed changing the genus name to Francisella in recognition of the contributions of Edward Francis to the understanding of this disease.

F. tularensis has been considered an important biological warfare threat because of its very high infectivity after aerosolization.

THE INFECTIOUS AGENT

F. tularensis is a nonmotile, obligately aerobic, Gram-negative coccobacillus. There are two biovars:

- F. tularensis biovar tularensis is the most common isolate in the United States. It is recovered from rodents and ticks, and is highly virulent for rabbits and humans. It produces acid from glycerol and has citrulline ureidase activity.
- F. tularensis biovar palaearctica is more common outside the United States. It is recovered from water, mosquitoes, and aquatic mammals, and is relatively avirulent for rabbits and humans. It does not produce acid from glycerol, and does not have citrulline ureidase activity.

The subspecies are indistinguishable serologically, although they may be distinguished by 16S ribosomal ribonucleic acid (rRNA) analysis. A capsule has been reported that may contribute to virulence. F. tularensis may have a lipopolysaccharide (LPS), but the biological activity of the LPS has not been well characterized and its role in pathogenicity is unclear. No known toxins are produced.

THE DISEASE

Epidemiology

Tularemia occurs in North America, Europe, the Middle East, Russia, and Japan, but is rare in the United Kingdom, Africa, and Central and South America. In the United States, the disease is most prevalent in Arkansas, Illinois, Missouri, Texas, Virginia, and Tennessee, although cases have been reported from all states except Hawaii.

The principal reservoir of tularemia in North America is the tick; more than 10 species have been implicated. F. tularensis is maintained in tick populations by transovarial passage, and is probably transmitted to humans via feces since the bacterium has not been found in the tick salivary glands. The bacterium has been isolated from 55 other arthropods and more than 100 nonarthropods. In North America, the rabbit is the most common vertebrate associated with transmission of tularemia. In other areas of the world, such as the former Soviet Union, tularemia is maintained in water rats and other aquatic mammals. Pharyngitis, abdominal pain, and fever may result from the ingestion of contaminated water in these areas. With the disruption of normal sanitation during World War II, hundreds of thousands of civilians and large numbers of Russian troops contracted tularemia.

The reported incidence in the United States since 1967 has been fewer than 200 cases per year. This compares with 2,291 cases reported in 1939 and more than 1,100 cases per year during the 1940s. The decline in incidence may be due to a declining interest in rabbit hunting, less recognition of the disease by physicians, or inadvertent cure of the disease by physicians who treat febrile patients with aminoglycoside antibiotics.

Pathogenesis

F. tularensis is usually introduced into the host through breaks in the skin, or through the mucous membranes of the eye, respiratory tract, or gas-
Tularemia is caused by inhalation of aerosols containing virulent organisms, which can cause infection in humans. After inoculation, *F. tularensis* is ingested by and multiplies within macrophages. The host defense against *F. tularensis* is mediated primarily by (a) T-cell–independent mechanisms, which appear early (<3 days after infection), and (b) T-cell–dependent mechanisms, which appear later (>3 days after infection). In the T-cell–independent mechanisms, macrophages, which have ingested bacteria, secrete tumor necrosis factor–alpha (TNF-alpha). TNF-alpha stimulates natural killer (NK) cells to produce interferon-gamma (IFN-γ), which, in turn, feeds back on macrophages and stimulates the cells to kill intracellular bacteria through the production of nitric oxide. In the T-cell–dependent mechanism, macrophages present bacterial antigen in the context of the major histocompatibility complex (MHC-II) to cluster of differentiation 4+ (CD4+) T lymphocytes. These cells respond by proliferating and secreting TNF-alpha, IL-2, and IFN-γ, which stimulate the macrophages to kill intracellular bacteria. Cell-mediated immunity constitutes the major protective mechanism.

The role of humoral immunity and neutrophils in the host defense against *F. tularensis* is unclear. Specific immunoglobulins (IgG, IgA, and IgM) appear within 1 week of infection, and passive transfer of immune serum protects naive mice against challenge with attenuated vaccine strains. This protection, however, is not evident when mice are challenged with virulent wild-type strains. Although some of the antibodies produced are opsonic and facilitate phagocytosis by neutrophils, neutrophils are not efficient in killing ingested bacteria. Recent studies using animals depleted of neutrophils suggest that neutrophils are important in resistance to infection with attenuated strains, but the relevance of these findings to virulent wild-type tularemia is unknown. Overall, these data suggest that the humoral immune response plays a limited role in the host defense against naturally acquired infection.

**Clinical Manifestations**

Tularemia can be divided into the ulceroglandular (75% of patients) and the typhoidal (25% of patients) forms, based on the clinical signs. Patients with ulceroglandular tularemia have lesions on the skin or mucous membranes (including the conjunctiva), lymph nodes larger than 1 cm in diameter, or both. Patients with typhoidal tularemia, on the other hand, present with lymph nodes smaller than 1 cm in diameter and without skin or mucous membrane lesions. This simplified scheme is suggested instead of the more-complicated, previous classification (ie, ulceroglandular, glandular, oculoglandular, typhoidal), because it is more in keeping with the clinical, pathophysiological, and prognostic aspects of the disease.

After an incubation period of 3 to 6 days, patients with the ulceroglandular form of the disease develop a constellation of symptoms consisting of fever (85%), chills (52%), headache (45%), cough (38%), and myalgias (31%). The fever is often accompanied by a pulse–temperature disassociation (ie, the pulse increases less than 10 beats per min per 1°F increase in temperature above normal). Patients may also complain of chest pain, vomiting, arthralgia, sore throat, abdominal pain, diarrhea, dysuria, back pain, or stiff neck.

A cutaneous ulcer occurs in approximately 60% of patients and is the most common sign of tularemia. Ulcers are generally single lesions of 0.4 to 3.0 cm in diameter, with heaped-up edges (Figure 24-1). Lesions associated with infection acquired from mammalian vectors are usually located on the upper extremities, whereas lesions associated with infection acquired from arthropod vectors are usually located on the lower extremities. Ulcerative lesions are almost always accompanied by regional lymphadenopathy.
with the vector is the same as for ulcerative lesions.\textsuperscript{19} Enlarged lymph nodes may become fluctuant, drain spontaneously, or persist for as long as 3 years.\textsuperscript{22}

Pharyngitis may occur in up to 25% of patients with tularemia.\textsuperscript{15,22,47,48} The posterior pharynx may not be inflamed; however, there may be erythema, exudate, petechiae, hemorrhage, or ulcers. On occasion, patients with pharyngitis may also develop a retropharyngeal abscess or suppuration of regional lymph nodes.\textsuperscript{47,49–51} Pneumonia commonly accompanies pharyngitis, perhaps reflecting acquisition of the disease by the aerosol route.

The lower respiratory tract is involved in 47% to 94% of patients.\textsuperscript{13,52,53} The variability in these figures is probably due to the variable use of chest radiographs during patient evaluations. Patients present with nonproductive or productive cough, and less commonly with pleuritic chest pain, shortness of breath, or hemoptyis. Examination of the sputum is not helpful for making the diagnosis of tularemia pneumonia. Chest radiographs show that approximately 50% of patients have pneumonia, and 1% or fewer have hilar adenopathy without parenchymal involvement. Pleural effusions are seen in 15% of patients with pneumonia. Interstitial patterns, cavitary lesions, bronchopleural fistulae, and calcifications have been reported in patients with tularemia pneumonia (Figure 24-2).\textsuperscript{53–62} Approximately 30% of patients with ulceroglandular tularemia and 80% of patients with typhoidal tularemia have pneumonia. The higher incidence of pneumonia in patients with typhoidal tularemia probably accounts for the higher mortality associated with this form of the disease.\textsuperscript{13}

Other, infrequent clinical syndromes associated with tularemia include pericarditis, enteritis, appendicitis, peritonitis, erythema nodosum, and meningitis.\textsuperscript{13,22,63–66}

Patients usually do not have abnormalities in the hematocrit, hemoglobin, or platelet levels. The peripheral white blood cell count may range between 5,000 and 22,000 cells per microliter, but it is usually only mildly elevated. Differential blood cell counts are usually normal, although patients may have a lymphocytosis late in the disease.\textsuperscript{13,67} Patients may have microscopic pyuria, which may lead to the erroneous diagnosis of a urinary tract infection.\textsuperscript{13,68} Mild elevations in lactic dehydrogenase, serum transaminases, and alkaline phosphatase are commonly seen. Some patients may experience rhabdomyolysis associated with elevations in the serum creatine kinase and urinary myoglobin levels.\textsuperscript{69} The cerebrospinal fluid is usually normal, although mild abnormalities in protein, glucose, and blood cell count have been reported.\textsuperscript{13}

![Fig. 24-2. Chest roentgenogram of tularemia pneumonia showing bilateral infiltrates. Photograph: Courtesy of William Beisel, M.D., Colonel, Medical Corps, US Army (Ret).](image)

### Diagnosis

Tularemia can be diagnosed by recovery of \textit{F. tularensis} in culture, or from serologic evidence of infection in a patient with a compatible clinical syndrome. Although the organism is difficult to culture,\textsuperscript{24,25,53,70} it can be recovered from blood, ulcers, conjunctival exudates, sputum, gastric washings, and pharyngeal exudates.\textsuperscript{23,70} Recovery may be possible even after the institution of appropriate antibiotic therapy.\textsuperscript{23} The organism grows poorly on standard media. On media containing cysteine or other sulfhydryl compounds (e.g., glucose cysteine blood agar, thioglycollate broth), \textit{F. tularensis} appears as small, smooth, opaque colonies after 24 to 48 hours of incubation at 37°C. The bacterium has occasionally been recovered on charcoal yeast extract (CYE),\textsuperscript{71} or Thayer-Martin agar,\textsuperscript{72} or from radiometric detection systems if the media are subcultured onto chocolate agar.\textsuperscript{73,74} The organism can readily be recovered from animals inoculated with infectious materials, but
Tularemia is a zoonotic disease caused by infection with the Gram-negative, facultative intracellular bacterium, *Francisella tularensis*. The organism is highly infectious by both the cutaneous and aerosol routes. Naturally occurring tularemia occurs most commonly in its ulceroglandular form; pa-
tients present with a cutaneous ulcer or mucous-membrane lesion and regional tender lymphadenopathy. The typhoidal form occurs in 25% of naturally occurring cases; patients present with systemic symptoms without local lesions or marked lymphadenopathy. Pneumonia occurs in up to 80% of patients with typhoidal tularemia.

A biological warfare attack with aerosolized \textit{F. tularensis} would probably produce pneumonia with or without accompanying mucous membrane lesions. Diagnosis is usually established by serology, as the organism is difficult to culture. The treatment of choice is streptomycin, with other aminoglycoside drugs being reasonable alternatives. Immediate postexposure antibiotic prophylaxis with tetracycline prevents disease. A live, attenuated vaccine, available as an Investigational New Drug, is effective against aerosol infection.

REFERENCES


