syndromes, the most common of which consists of an ulcerative lesion at the site of inoculation, with regional lymphadenopathy and lymphadenitis. Systemic manifestations, including pneumonia, typhoidal tularemia, meningitis, and fever without localizing findings, pose a greater diagnostic challenge.

ETIOLOGY AND EPIDEMIOLOGY

F. tularensis is a class A bioterrorism agent **(Chap. 261e)**. With rare exceptions, tularemia is the only disease produced by *F. tularensis*—a small (0.2 μm by 0.2–0.7 μm), gram-negative, pleomorphic, nonmotile, non-spore-forming bacillus. Bipolar staining results in a coccoid appearance. The organism is a thinly encapsulated, nonpiliated strict aerobe that invades host cells. In nature, *F. tularensis* is a hardy organism that persists for weeks or months in mud, water, and decaying animal carcasses. Dozens of biting and blood-sucking insects, especially ticks and tabanid flies, serve as vectors. Ticks and wild rabbits are the source for most human cases in endemic areas of the southeastern United States. In Utah, Nevada, and California, tabanid flies are the most common vectors. Animal reservoirs include wild rabbits, squirrels, birds, sheep, beavers, muskrats, and domestic dogs and cats. Person-to-person transmission is rare or nonexistent.

The four subspecies of *F. tularensis* are *tularensis*, *holarctica*, *novicida*, and *mediasiatica*. The first three of these subspecies are found in North America; in fact, subspecies *tularensis* has been isolated only in North America, where it accounts for >70% of cases of tularemia and produces more serious human disease than other subspecies (although, with treatment, the associated fatality rate is <2%). The progression of illness depends on the infecting strain's virulence, the inoculum size, the portal of entry, and the host's immune status.

Ticks pass *F. tularensis* to their offspring transovarially. The organism is found in tick feces but not in large quantities in tick salivary glands. In the United States, the disease is carried by *Dermacentor andersoni* (Rocky Mountain wood tick), *Dermacentor variabilis* (American dog tick), *Dermacentor occidentalis* (Pacific Coast dog tick), and *Amblyomma americanum* (Lone Star tick). *F. tularensis* is transmitted frequently during blood meals taken by embedded ticks after hours of attachment. It is the taking of a blood meal through a fecally contaminated field that transmits the organism. Transmission by ticks and tabanid flies takes place mainly in the spring and summer. However, continued transmission in the winter by trapped or hunted animals has been documented.

Tularemia is most common in the southeastern United States; Arkansas, Missouri, and Oklahoma account for more than half of all reported cases in this country. Small outbreaks in higher-risk populations (e.g., professional landscapers cutting up brush, mowing, and using a leaf blower) have been reported. Although the irregular distribution of cases of tularemia makes worldwide estimates difficult, increasing numbers of cases have been reported between latitudes 30° and 71°N (the Holarctic region) in the Northern Hemisphere. Cases of tularemia have been reported from Europe, Turkey, Canada, Mexico, and Asia. If the disease is caused by subspecies *tularensis*, the clinical manifestations are similar to those in the United States. However, in areas where tularemia is due largely to subspecies *holarctica*, oropharyngeal disease is common. Disease acquisition results from the consumption of water contaminated by live organisms shed by animals (e.g., muskrats, beavers). Subspecies *holarctica* is known to cause milder disease than other subspecies and responds well to fluoroquinolones, especially ciprofloxacin.

PATHOGENESIS AND PATHOLOGY

The most common portal of entry for human infection is through skin or mucous membranes, either directly—through the bite of ticks, other arthropods, or other animals—or via inapparent abrasions. Inhalation or ingestion of *F. tularensis* also can result in infection. *F. tularensis* is extremely infectious: Although $>10^8$ organisms are usually required to produce infection via the oral route (oropharyngeal or gastrointestinal tularemia), as few as 10 organisms can result in infection when injected into the skin (ulceroglandular/glandular tularemia) or inhaled (pulmonary tularemia). After inoculation into the skin, the organism multiplies locally; within 2–5 days (range, 1–10 days), it produces an erythematous, tender, or pruritic papule. The papule rapidly enlarges and forms an ulcer with a black base (chancriform lesion). The bacteria spread to regional lymph nodes, producing lymphadenopathy (buboes). All forms can lead to bacteremia with spread to distant organs, including the central nervous system.

Tularemia is characterized by mononuclear cell infiltration with pyogranulomatous pathology. The histopathologic findings can be quite similar to those in tuberculosis, although tularemia develops more rapidly. As a facultatively intracellular bacterium, *F. tularensis* can parasitize both phagocytic and nonphagocytic host cells and can survive intracellularly for prolonged periods. In the acute phase of infection, the primary organs affected (skin, lymph nodes, liver, and spleen) include areas of focal necrosis, which are initially surrounded by polymorphonuclear leukocytes (PMNs). Subsequently, granulomas form, with epithelioid cells, lymphocytes, and multinucleated giant cells surrounded by areas of necrosis. These areas may resemble caseation necrosis but later coalesce to form abscesses.

Conjunctival inoculation can result in infection of the eye, with regional lymph node enlargement (preauricular lymphadenopathy, Parinaud's complex). Aerosolization and inhalation or hematogenous spread of organisms can result in pneumonia. In the lung, an inflammatory reaction develops, including foci of alveolar necrosis and cell infiltration (initially polymorphonuclear and later mononuclear) with granulomas. Chest roentgenograms usually reveal bilateral patchy infiltrates rather than large areas of consolidation. Pleural effusions are common and may contain blood. Lymphadenopathy occurs in regions draining infected organs. Therefore, in pulmonary infection, mediastinal adenopathy may be evident, whereas patients with oropharyngeal tularemia develop cervical lymphadenopathy. In gastrointestinal or typhoidal tularemia, mesenteric lymphadenopathy may follow the ingestion of large numbers of organisms. (The term *typhoidal tularemia* may be used to describe severe bacteremic disease, irrespective of the mode of transmission or portal of entry.) Meningitis has been reported as a primary or secondary manifestation of bacteremia. Patients may also present with fever and no localizing signs.

IMMUNOLOGY

Although a complete and widely accepted understanding of the protective immune response to *F. tularensis* is lacking, significant advances in the study of natural and protective immunity have been made in recent years and may ultimately result in a vaccine candidate. Complete genomic sequencing and the availability of attenuated *F. tularensis* strains developed through genetic manipulation are facilitating research that will expand our knowledge in this area.

A number of investigators have studied various models and proposed various hypotheses regarding the induction of protective immunity to *F. tularensis*. Although further research is needed, synergy between humoral and cell-mediated immune (CMI) responses appears to be critical in inducing effective immune protection. Elucidation of the molecular mechanisms for the organism's evasion of the host response, pathogen-associated molecular patterns, and effective host immune protection has led to novel vaccination strategies tested in animal models. Antibodies to Fc receptors on antigen-presenting cells have been shown to be protective in animal models of pulmonary tularemia, resulting in both mucosal and CMI responses. This enhanced understanding of mucosal and serum antibodies in combination with a targeted CMI response holds great promise for future vaccine development.

CLINICAL MANIFESTATIONS

Tularemia often starts with a sudden onset of fever, chills, headache, and generalized myalgias and arthralgias **(Table 195-1)**. This onset takes place when the organism penetrates the skin, is ingested, or is inhaled. An incubation period of 2–10 days is followed by the formation of an ulcer at the site of penetration, with local inflammation. The ulcer may persist for several months as organisms are transported via the lymphatics to the regional lymph nodes. These nodes enlarge and may become necrotic and suppurative. If the organism enters the bloodstream, widespread dissemination can result.