Tularemia is a rare zoonosis caused by *Francisella tularensis*. Although many animals may be infected with tularemia, human infection most commonly occurs via an insect vector such as a tick or deer fly. In the US, most cases of tularemia occur in the summer in the south-central states, specifically Missouri, Arkansas, and Oklahoma. There are six major tularemia clinical syndromes each with different clinical presentations: ulceroglandular tularemia (42%-75% of all tularemia cases), glandular tularemia (15%-44% of all tularemia cases), oropharyngeal tularemia, ocuglandular tularemia, typhoidal tularemia, and pneumatic tularemia. The diagnosis of tularemia is typically made clinically, taking into account exposure history and clinical manifestations and confirmed by serologic testing. Aminoglycosides are the drugs of choice for the treatment of tularemia. Tularemia prevention is best accomplished by keeping away from dead or infected animals and avoiding ticks.

**ETIOLOGY AND EPIDEMIOLOGY**

Tularemia is a zoonotic infection caused by *F. tularensis*, a small, fastidious, aerobic gram-negative coccobacillus. There are four distinct subspecies of *F. tularensis*: however, disease is mainly caused by *F. tularensis* subspecies *tularensis* (type A) and *F. tularensis* subspecies *holarctica* (type B). Type A is more virulent and is primarily found in North America. Type B is found throughout the Northern Hemisphere, mainly in Europe and Asia, and causes milder infection than type A. *F. tularensis* is highly contagious; only a small inoculum is needed to produce disease.

More than 100 species of mammals have been noted to be infected with tularemia. This includes rabbits, hares, muskrats, prairie dogs, skunks, raccoons, rats, voles, squirrels, sheep, cattle, and cats. Disease transmission can occur via handling the carcass of an infected animal, via the bite of a infected animal, or via ingestion of meat from a diseased animal.

The bite of an insect vector such as a tick, deer fly, or flea can also transmit tularemia to humans. Insects become infected when they feed on an infected animal; ticks can also become infected by transovarian passage. In the United States, ticks are the most common and important insect vector of tularemia. Tick species that transmit tularemia to humans include *Amblyomma americanum* (lone star tick), *Dermacentor andersoni* (wood tick), and *Dermacentor variabilis* (dog tick).

Tularemia can also be caused by contact with aerosolized bacteria from mowing lawns, working on farms, or working in laboratories where *F. tularensis* is present. The disease can also be transmitted by drinking water contaminated with *F. tularensis*; this organism can survive in water and animal carcasses for long periods. Frozen rabbit meat has remained infective for greater than 3 years. Person-to-person transmission of tularemia does not occur.

In the US, 90 to 154 cases of tularemia have been reported yearly to the Centers for Disease Control and Prevention (CDC) from 2001 to 2010. Tularemia has been reported by every state except Hawaii. Arkansas, Oklahoma, and Missouri account for approximately 50% of the cases of tularemia reported in the US each year. Figure 1 (see page 289) is a CDC map detailing the locations of reported cases of tularemia from 2001 to 2010.
Tularemia presents most commonly in the summer, due to high tick activity, in the south-central US and peaks in the winter, the primary hunting season, in the northeastern US. Individuals at risk for developing infection include hunters, trappers, taxidermists, grounds maintenance workers, sheep herders/shearers, laboratory workers, those with tick exposure, and those living in or traveling to areas where tularemia is endemic. The highest incidence of tularemia occurs in children (and in adults older than age 75 years); boys have a higher incidence of infection than girls. The higher incidence in boys is most likely due to their greater participation in activities such as hunting that increase exposure to tularemia. Figure 2 (see page 290) shows the age and gender of reported tularemia cases from 2001 to 2010.

**CLINICAL SYNDROMES AND MANIFESTATIONS**

The incubation period of tularemia is 1 to 21 days, with an average of 2 to 5 days. There are six major tularemia clinical syndromes, which are classified by the portal of entry of the infection (see Table 1).

**Ulceroglandular Tularemia**

The most common syndrome, accounting for between 42% and 75% of all cases of tularemia, is ulceroglandular tularemia. This syndrome is characterized by a painful swollen papule at the portal of entry (skin) that becomes an ulcer. Tender lymphadenopathy is present proximal to the papule/ulcer (see Figure 3, page 291). Fever and malaise are commonly seen with ulceroglandular tularemia.

**Glandular Tularemia**

Glandular tularemia, representing 15% to 44% of all cases of tularemia, presents with tender lymphadenopathy. Involved lymph nodes are most commonly axillary, inguinal, or cervical. The portal of entry with glandular tularemia is unknown but most likely is through the skin. Common additional symptoms include fever and malaise. The most common sites of lymph node involvement in a recent review of pediatric tularemia in Arkansas were head and neck (33%), followed by inguinal adenitis (30%).

In 50% of untreated cases of ulceroglandular or glandular tularemia, lymph nodes suppurate and drain. Lymph node suppuration can occur even in the setting of appropriate antibacterial therapy. Glandular tularemia is more common in children than adults; 44% of children compared with 16% of adults had primary glandular tularemia in a Missouri study of tularemia. Likewise, in a review of 30 cases of pediatric tularemia from 1996 through 2006 from Arkansas, the majority of children were younger than 6 years and had ulceroglandular or glandular disease.

**Oropharyngeal Tularemia**

Traditionally representing less than 5% of cases of tularemia, infection with oropharyngeal tularemia is established through the oropharyngeal mucosa, most commonly by eating undercooked meat from an infected animal. The hallmarks of oropharyngeal tularemia are severe pharyngitis (out of proportion to pharyngeal appearance), cervical lymphadenitis, and fever. Oral ulcers and/or an oropharyngeal pseudomembrane may be present. Cervical lymph nodes may suppurate and drain.

<table>
<thead>
<tr>
<th>Tularemia Syndrome</th>
<th>Characteristics</th>
<th>Portal of Entry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulceroglandular</td>
<td>Skin papule followed by ulcer, tender lymphadenopathy, fever</td>
<td>Skin</td>
</tr>
<tr>
<td>Glandular</td>
<td>Tender lymphadenopathy, fever</td>
<td>Unknown (likely skin)</td>
</tr>
<tr>
<td>Oropharyngeal</td>
<td>Severe pharyngitis, cervical lymphadenitis, fever</td>
<td>Oropharyngeal mucosa</td>
</tr>
<tr>
<td>Oculoglandular</td>
<td>Conjunctivitis, Parinaud’s oculoglandular syndrome</td>
<td>Conjunctiva</td>
</tr>
<tr>
<td>Typhodial</td>
<td>Fever of unknown cause, sepsis, myalgia, headache</td>
<td>Oropharyngeal mucosa or respiratory tract</td>
</tr>
<tr>
<td>Pneumonic</td>
<td>Pneumonia, fever</td>
<td>Respiratory tract</td>
</tr>
</tbody>
</table>

Figure 1. Reported cases of tularemia, United States, 2001 to 2010. One dot placed randomly within county of residence for each confirmed case. (From US Centers for Disease Control and Prevention)
Oculoglandular Tularemia

Oculoglandular tularemia was noted to cause 4% of all cases of tularemia in Missouri from 2000 to 2007. Nodular conjunctivitis, conjunctival inflammation, and edema are typically seen and corneal ulcers may occur. Regional lymphadenitis is also seen. Oculoglandular tularemia can manifest as Parinaud’s oculoglandular syndrome (conjunctivitis and painful ipsilateral preauricular lymphadenopathy). The conjunctiva is the portal of entry for oculoglandular tularemia and infection is usually caused by direct inoculation from infected fingers.

Typhoidal Tularemia

The portal of entry for typhoidal tularemia is either the oropharyngeal mucosa by ingestion (more common in children) or the respiratory tract by inhalation (more common in adults). Typhoidal tularemia is a serious illness that often presents with septic shock. Fever is present without localizing signs. Headaches, myalgias, pharyngeal pain, and diarrhea are common symptoms. Hepatomegaly and splenomegaly are usually seen. Given the nonspecific symptoms, a history of tularemia exposure is often needed before this diagnosis is considered.

Pneumonic Tularemia

Pneumonic tularemia is uncommon in children. In a Missouri study of 107 cases of tularemia, 4% of children compared with 39% of adults had primary pneumonic tularemia. Type A Francisella pneumatic tularemia has a high mortality rate and is the most severe form of tularemia. Symptoms include fever, cough, and chest pain. Pulmonary infiltrates, hilar adenopathy, and/or pleural effusions may be present. Via inhalation of aerosolized bacteria, the respiratory tract is the portal of entry for pneumonic tularemia.

**TABLE 2.** Differential Diagnoses for the Various Clinical Syndromes of Tularemia

<table>
<thead>
<tr>
<th>Ulceroglandular and Glandular Tularemia</th>
<th>Oropharyngeal Tularemia</th>
<th>Oculoglandular Tularemia</th>
<th>Typhoidal Tularemia</th>
<th>Pneumonic Tularemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em> lymphadenitis</td>
<td>Streptococcal pharyngitis</td>
<td>Bartonella</td>
<td>Bacterial sepsis</td>
<td>Typical and atypical bacterial pneumonia</td>
</tr>
<tr>
<td><em>Staphylococcus pyogenes</em> lymphadenitis</td>
<td>Diphtheria</td>
<td>Sporotrichosis</td>
<td>Malaria</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Viral pharyngitis</td>
<td>Tuberculosis</td>
<td>Brucellosis</td>
<td>Legionnaire's disease</td>
</tr>
<tr>
<td>Non-tuberculous mycobacterium</td>
<td>Syphilis</td>
<td>Q fever</td>
<td>Q fever</td>
<td></td>
</tr>
<tr>
<td>Bartonella</td>
<td>Coccidioidomycosis</td>
<td>Rickettsial diseases</td>
<td>Fungal pneumonia</td>
<td></td>
</tr>
<tr>
<td>Anthrax</td>
<td>HSV</td>
<td>Ehrlichiosis</td>
<td>Viral pneumonia</td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infectious mononucleosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sporotrichosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Lymphogranuloma venereum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2.** Reported tularemia cases in the United States by age and gender, 2001 to 2010. (From US Centers for Disease Control and Prevention®)
Mortality and Prognosis

Mortality is less than 1% for all types of tularemia except typhoidal and pneumonic. Lymph node suppuration is the most common complication of tularemia. The risk of lymph node suppuration increases if there is a delay in beginning appropriate antibacterial therapy. Treatment failure is also more common if appropriate antibacterial therapy is delayed.

Other possible complications include sepsis, disseminated intravascular coagulation, renal failure, acute respiratory distress syndrome (ARDS), rhabdomyolysis, jaundice, hepatitis, meningitis, encephalitis, endocarditis, pericarditis, peritonitis, osteomyelitis, splenic rupture, and thrombophlebitis. Subcutaneous nodules and various rashes (maculopapular, erythema, erythema multiforme, pustular lesions) have also been described in individuals with tularemia.

Common differential diagnoses for the various clinical syndromes of tularemia are listed in Table 2 (see page 290).

Diagnosis

The diagnosis of tularemia is usually made clinically, taking into account exposure history and clinical manifestations and confirmed by serologic testing. Serologic testing was diagnostic in 77% of children with tularemia in Arkansas from 1996 to 2006.

Standard agglutination tests, tube agglutination (TA), and microagglutination (MA), for tularemia are commercially available. Agglutinating antibodies usually are not detectable until the second week of illness. Therefore, effective antibiotic therapy should not be withheld while awaiting results of serologic testing.

Acute and convalescent serum testing should be obtained at least 2 weeks apart. A presumptive diagnosis of tularemia can be made if a single serum antibody titer is at least 1:160 by TA or at least 1:128 by MA; however, this can also represent past infection. Diagnosis is confirmed if there is a fourfold or higher increase in titer between acute and convalescent serology with one specimen having a minimum titer of 1:160 by TA or 1:128 by MA. Of note, cross-reactivity may occur because of antibodies to Brucella, Legionella, Salmonella, Yersinia, or other gram-negative bacteria.

Diagnosis is also confirmed by isolation of F. tularensis in blood, body fluids, or tissue. F. tularensis is a fastidious bacterium that rarely is seen on Gram’s staining. The bacteria grows best on culture media supplemented by cysteine. Health care providers should alert microbiology laboratory personnel if tularemia is suspected, as it is highly infectious, and laboratory workers have a high risk of acquiring infection. Cultures of F. tularensis should be done only in a biosafety level 3 (BSL-3) laboratory.

Polymerase chain reaction (PCR) assays for the diagnosis of tularemia are very sensitive but are not commercially available. The white blood cell count may be normal or elevated, with a predominance of neutrophils, in children with tularemia. C-reactive protein and erythrocyte sedimentation rate are typically elevated; liver function tests may also be elevated. Chest X-ray findings in pneumonic tularemia may include hilar lymphadenopathy, pulmonary infiltrates, pleural effusions, and/or empyema.

In the US, tularemia is a nationally notifiable disease; cases should be reported to the local department of health.

Treatment

Antibiotic therapy should be initiated as soon as tularemia is suspected, rather than awaiting results of serologic testing. The illness may be prolonged, complications are more likely to occur, and treatment failure is more frequent if antibiotic therapy is delayed. Relapse is possible even after appropriate antibiotic therapy. Jarisch-Herxheimer reactions can occur with antibacterial therapy.

Streptomycin and Gentamicin

The aminoglycosides streptomycin and gentamicin are the drugs of choice for the treatment of tularemia. However, only streptomycin is approved by the US Food and Drug Administration for the treatment of tularemia. A literature review of in vitro susceptibilities, cure rates, and relapse rates of antibiotics used to treat adult and pediatric cases of tularemia showed that cure rates were highest and relapse rates lowest for streptomycin. However, gentamicin was noted to have similar efficacy to streptomycin.

Given the limited availability of streptomycin in the US, gentamicin, considered the best alternative, is typically used for treatment of tularemia. Twenty-eight of 30 children with tularemia seen at Arkansas Children’s hospital between 1996 and 2006 were treated with gentamicin; only one child had treatment failure with persistent lymphadenitis. Of note, that child had symptoms of tularemia for 30 days prior to...
initiation of therapy with gentamicin, making treatment failure more likely.

The recommended pediatric dose of gentamicin for treatment of tularemia is 5 mg/kg divided every 8 or 12 hours and the typical treatment course with aminoglycosides is 10 days. However, extension of therapy may be indicated for severe disease or for those children with prolonged symptoms prior to diagnosis. Aminoglycoside levels should be monitored closely during therapy due to potential ototoxicity and nephrotoxicity. Once-daily gentamicin has been reported to be successful for the treatment of adults with glandular tularemia, but no data are available on the efficacy of once-daily gentamicin for the treatment of tularemia in children.

**Alternative Antibiotic Therapies**

Alternative antibiotic therapies for tularemia include doxycycline and ciprofloxacin. Relapse is more common in patients treated with tetracyclines (12%) than gentamicin (6%).

Therefore, doxycycline is not recommended as a first-line therapy for tularemia. In addition, a longer treatment course (14 days) is recommended due to the increased relapse rate.

Unless the benefits outweigh the risks, doxycycline should not be given to children younger than 8 years for the treatment of tularemia because of the potential for teeth staining.

Ciprofloxacin has been shown to have efficacy in the treatment of tularemia. For example, a Swedish study documented the successful treatment of 12 children with ulceroglandular tularemia with oral ciprofloxacin. However, most studies on fluoroquinolone efficacy have been done in Europe where *F. tularensis* subspecies *holarctica* (type B) predominates. *F. tularensis holarctica* causes far less severe disease than *F. tularensis tularensis*, the major causative agent of tularemia in North America.

Ciprofloxacin is not recommended for the treatment of tularemia in children younger than 18 years because of the potential for joint and/or cartilage injury. Beta-lactams, clindamycin, and trimethoprim-sulfamethoxazole are not effective for the treatment of tularemia.

**PREVENTION**

Tularemia prevention is best accomplished by steering clear of infected animals and insect vectors. Common sense strategies include avoiding dead or sick animals and areas that are tick-infested.

For hunters or abattoir workers, animals should not be skinned with bare hands; gloves and eye protection are indicated when removing animal skin. All wild game should be cooked thoroughly before eating. Patients should be counseled to not drink untreated water. When mowing the lawn, care should be taken to avoid mowing over any sick or dead animals.

When engaging in outdoor activities, to prevent bites from tick and deer flies, protective clothing such as long pants tucked into socks and long sleeves should be worn. Insect repellents that contain DEET (diethyltoluamide) provide protection against ticks but need to be reapplied frequently. Formulations that contain 10% to 30% DEET can be used in children 2 months and older. Children should be checked for ticks frequently, especially in the warmer months, in tularemia-endemic areas. Ticks should be removed as soon as possible using tweezers, not fingers, by grabbing the tick as close to the skin surface as possible, then pulling straight up. Hands should be washed immediately after removing a tick.

As there is no evidence for person-to-person transmission of tularemia, isolation of infected individuals is not indicated.

Although tularemia is a rare zoonosis, pediatricians need to be aware of this infection as the diagnosis is typically made clinically based on the appropriate exposure history and the classic clinical manifestations of the various tularemia syndromes. Pediatricians in the south-central US are ever vigilant for this infection. Pediatricians across the US should be on the lookout for tularemia in children who have traveled to endemic areas, especially during summer months.

**REFERENCES**


