### Tularemic Meningitis in the United States

**Diedre M. Hofinger, MD; Luzma Cardona, MD; Gregory J. Mertz, MD; Larry E. Davis, MD**

**Background:** Tularemia is a zoonotic disease caused by *Francisella tularensis*. Tularemia presents with various clinical illnesses, but meningitis is rare.

**Objectives:** To describe a patient who developed typhoidal tularemia with atypical acute meningitis and to review the pathogenesis, clinical and laboratory features, and antibiotic drug treatment of reported cases of tularemic meningitis.

**Design:** Case study and literature review.

**Setting:** University hospital, tertiary care center.

**Patient:** A 21-year-old healthy man who had recently worked as a professional landscaper in the Albuquerque, New Mexico, metropolitan area developed fever, malaise, headache, and a stiff neck.

**Main Outcome Measures:** *Francisella tularensis* cerebrospinal fluid culture, antibiotic sensitivity, transmission source, and outcome.

**Results:** The cerebrospinal fluid contained a lymphocytic pleocytosis, negative Gram stain, and *F. tularensis* isolation with chloramphenicol and streptomycin antibiotic sensitivities.

**Conclusions:** Although tularemia is uncommon and tularemic meningitis is rare in the United States, attention is drawn to the increasing number of cases in professional landscapers, the atypical cerebrospinal fluid picture, and unusual antibiotic sensitivities.

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**TULAREMIA IS A ZOONOTIC disease caused by an intracellular, gram-negative coccobacillus, *Francisella tularensis*, that occasionally causes meningitis.** There are 4 subspecies of *F. tularensis*, 3 of which are found in North America: *holarctica*, *tularensis*, and *novicida*. *Francisella tularensis* is transmitted to humans through several routes: by direct contact with infected animals (particularly rabbits and other rodents), by vectors (biting flies and ticks), by ingestion (contaminated water, raw milk, and undercooked meat), and by inhalation (aerosolized organisms from cutting grass or handling hay). There have been no reported cases of human-to-human transmission.

Tularemia presents with various clinical illnesses commonly classified as ulceroglandular or glandular, oropharyngeal, ocular-glandular, typhoidal, and pneumonic. We describe an unusual case of typhoidal tularemia with meningitis and review the reported cases of tularemic meningitis.
microagglutination testing. The serum antibody titer was 1:1024 by means of streptomycin sulfate, 1 g every 12 hours, for 14 days, sodium succinate, 1 g every 12 hours, and intravenous patient was treated with intravenous chloramphenicol by the New Mexico State health laboratory the negative coccobacillus that was confirmed to be to millimoles per liter, multiply by 0.0555.

The current serum glucose level was 128 mg/dL (to convert 2950 g/dL, and the Gram stain was negative. The con- glucose level was 28 mg/dL, the total protein level was 2660 g/dL. The concurrent serum glucose level was 123 mg/dL. Gram staining of CSF sediment was negative. Findings from chest radiography were normal. Magnetic resonance imaging showed cerebellar tonsillar herniation consistent with Chi-

The patient was initially treated with intravenous ceftri-

On hospital day 4, the initial CSF culture grew a gram-

Francisella tularen
tis is highly infectious, requiring as few as 10 inhaled bacteria to cause disease, making aeros-

The incubation period of tularemia is usually 3 to 6 days, but it may range from 1 to 14 days after inoculation. In patients with tularemia meningitis, signs and symptoms of meningitis typically developed 5 days after the onset of initial illness but ranged from 3 to 30 days. Seven pa-

The early clinical picture of tularemia meningitis may be relatively nonspecific. Most cases occur in late spring and summer,2 when individuals are exposed to infected arthropods (ticks and biting flies) or to aerosolized bacteria from handling hay, cutting brush, or mowing over dead infected animals.2,24 Occupational exposure has been reported in landscapers in Martha’s Vineyard in Massa-

Tularemia meningitis is rare; only 16 cases have been reported (Table). The worldwide incidence of tulare-

Before 1900 and 2005, 2000 human cases from 44 states were reported to the Centers for Disease Control and Prevention.21,22

In tularemia meningitis, patients usually had marked CSF pleocytosis, with a mean white blood cell count of 1788×10⁶/µL (range, 2-13 200×10⁶/µL). In contrast to most other causes of acute bacterial meningitis, in tulare-

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of Gram staining is unclear, it may reflect that an *F. tularensis* Gram stain is weak, is intracellular, or is in low numbers in the CSF (<10^3 colony-forming units/mL). Patients with tularemic meningitis had similar blood changes as patients with tularemia without meningitis. Some peripheral white blood cell counts were normal, but most were elevated (range, 3000-49,000/μL), with a mononuclear predominance.

The differential diagnosis of mononuclear pleocytosis is broad. Viral infections, including herpes simplex virus, may cause a mononuclear predominance; however, it would be expected that the CSF would have an elevated glucose level. Other etiologies include *Mycobacterium* and *Cryptococcus*; however, these infections would be expected in immunocompromised hosts. Spirochete infections with *Treponema pallidum* or *Borrelia burgdorferi* may also cause mononuclear pleocytosis along with other infections, including *Brucella, Bartonella henselae*, and *Leptospira*. Our patient did not have risk factors for these diseases.

Isolation of *F. tularensis* is difficult and slow because *F. tularensis* is fastidious. Most isolates appear in 2 to 4 days, but it may take as long as 14 days to grow in culture. In our patient, CSF isolation required 4 days, but it may take as long as 14 days to grow in culture. It is important to notify the microbiology laboratory of suspected tularemia so that they will take appropriate safety precautions and hold the cultures longer. Routine clinical specimens require a biosafety level 2 laboratory, but further processing of initial isolates suspected of being

### Table. Case Histories of Tularemia Meningitis

<table>
<thead>
<tr>
<th>Source</th>
<th>Patient Sex/Age</th>
<th>Work</th>
<th>Presumed Source of Infection</th>
<th>Days From First Symptom to Meningitis</th>
<th>Worst CSF Findings, WBC/mm^3</th>
<th>Diagnosis</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Primary Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haiglip and O’Neil, 1931</td>
<td>M/45 y</td>
<td>Night watchman</td>
<td>Rabbit or squirrel</td>
<td>5</td>
<td>2100 (70% PMN)</td>
<td>Bacterial isolation: blood</td>
<td>None</td>
<td>Death</td>
<td>T</td>
</tr>
<tr>
<td>Bryant and Hirsch, 1931</td>
<td>M/48 y</td>
<td>Chef</td>
<td>Rabbit</td>
<td>8</td>
<td>400 (84% M)</td>
<td>Bacterial isolation: blood</td>
<td>None</td>
<td>Death</td>
<td>T</td>
</tr>
<tr>
<td>Hartman, 1932</td>
<td>M</td>
<td>Butcher</td>
<td>Rabbit</td>
<td>9</td>
<td>145 G (42 mg/dL)</td>
<td>Serology</td>
<td>Blood transfusion from survivor of tularemia</td>
<td>Death</td>
<td>T</td>
</tr>
<tr>
<td>Pand and Hatchett, 1937</td>
<td>F/12 y</td>
<td>None</td>
<td>Unknown</td>
<td>8</td>
<td>220 G (18 mg/dL)</td>
<td>Serology</td>
<td>None</td>
<td>Death</td>
<td>OP</td>
</tr>
<tr>
<td>David and Owens, 1944</td>
<td>F/5 y</td>
<td>None</td>
<td>Cat</td>
<td>11</td>
<td>2000 (99% M) G (18 mg/dL)</td>
<td>Bacterial isolation: blood</td>
<td>CSF, T</td>
<td>Death</td>
<td>T</td>
</tr>
<tr>
<td>Stuart and Pullen, 1945</td>
<td>M/34 y</td>
<td>Unknown</td>
<td>Unknown</td>
<td>5</td>
<td>960 (100% M) G (45.4 mg/dL) P (643 mg/cm^3)</td>
<td>Bacterial isolation: blood</td>
<td>None</td>
<td>Death</td>
<td>T</td>
</tr>
<tr>
<td>Fields, 1949</td>
<td>F/16 y</td>
<td>Unknown</td>
<td>Skinning rabbit</td>
<td>155</td>
<td>330 (70% M) G (25 mg/dL) P (730 mg/cm^3)</td>
<td>Bacterial isolation: blood</td>
<td>CSF serology</td>
<td>Recovered with sequelae</td>
<td>T</td>
</tr>
<tr>
<td>Hutton and Everett, 1965</td>
<td>M/60 y</td>
<td>Unknown</td>
<td>Tick</td>
<td>9</td>
<td>2620 (63% PMN) G (39 mg/dL) P (174 mg/dL)</td>
<td>Bacterial isolation: blood</td>
<td>CSF, T</td>
<td>Recovered</td>
<td>T</td>
</tr>
<tr>
<td>Lovell et al, 1986</td>
<td>M/13 mo</td>
<td>None</td>
<td>Cat scratch</td>
<td>59</td>
<td>13,200 (100% M)</td>
<td>Bacterial isolation: blood</td>
<td>Chloramphenicol</td>
<td>Recovered</td>
<td>T</td>
</tr>
<tr>
<td>Harper et al, 1986</td>
<td>M/18 mo</td>
<td>None</td>
<td>Unknown</td>
<td>8</td>
<td>3470 (96% M) G (33 mg/dL) P (205 mg/dL)</td>
<td>Bacterial isolation: blood</td>
<td>Chloramphenicol</td>
<td>Recovered</td>
<td>T</td>
</tr>
<tr>
<td>Hill et al, 1990</td>
<td>M/64 y</td>
<td>Unknown</td>
<td>Unknown</td>
<td>7</td>
<td>290 (60% M) G (32 mg/dL) P (350 mg/dL)</td>
<td>Bacterial isolation: blood</td>
<td>Chloramphenicol, rifampicin, gentamicin</td>
<td>Recovered</td>
<td>T</td>
</tr>
<tr>
<td>Alfers and Ayers, 1990</td>
<td>M/19 y</td>
<td>Construction</td>
<td>Rabbit</td>
<td>7</td>
<td>2127 (100% L) G (30 mg/dL) P (115 mg/dL)</td>
<td>Bacterial isolation: blood</td>
<td>Chloramphenicol, streptomycin, chloramphenicol</td>
<td>Recovered</td>
<td>T</td>
</tr>
<tr>
<td>Pittman, 1996</td>
<td>M/5 y</td>
<td>None</td>
<td>Rabbit</td>
<td>3</td>
<td>2 Shunt fluid 75 (90% L) G (59 mg/dL) P (23 mg/dL)</td>
<td>Bacterial isolation: blood</td>
<td>Chloramphenicol, streptomycin followed by tetracycline</td>
<td>Recovered</td>
<td>T</td>
</tr>
<tr>
<td>Rodgers et al, 1998</td>
<td>F/4 y</td>
<td>None</td>
<td>Unknown</td>
<td>9</td>
<td>1570 (66% L), G (34 mg/dL) P (120 mg/dL) 2 (62% M) G (25 mg/dL) P (48 mg/dL)</td>
<td>Bacterial isolation: blood</td>
<td>Chloramphenicol, doxycycline</td>
<td>Recovered</td>
<td>T</td>
</tr>
<tr>
<td>Weiner et al, 2004</td>
<td>M/17 mo</td>
<td>None</td>
<td>Tick</td>
<td>Unknown</td>
<td>2926 (94% PMN) G (33 mg/dL) P (1800 mg/dL) 1416 (73% L) G (41 mg/dL) P (286 mg/dL)</td>
<td>Bacterial isolation: blood</td>
<td>Chloramphenicol, streptomycin, doxycycline</td>
<td>Recovered</td>
<td>T</td>
</tr>
<tr>
<td>Gangal, 2007</td>
<td>F/51 y</td>
<td>Unknown</td>
<td>Rabbit</td>
<td>30</td>
<td>245 Bacterial isolation: blood</td>
<td>Chloramphenicol, streptomycin, doxycycline</td>
<td>Recovered</td>
<td>T</td>
<td></td>
</tr>
<tr>
<td>Present study</td>
<td>M/21 y</td>
<td>Landsnapper</td>
<td>Rabbit</td>
<td>7</td>
<td>3000-49,000×10^6/μL</td>
<td>Bacterial isolation: blood</td>
<td>None</td>
<td>Death</td>
<td>T</td>
</tr>
</tbody>
</table>

Abbreviations: CSF, cerebrospinal fluid; G, glucose; L, lymphocyte; M, monocyte; OP, oropharyngeal; P, protein; PMN, polymorphonuclear cell; T, typhoidal; UG, ulceroglandular; WBC, white blood cell.

* a Serology indicates serum agglutination or CSF agglutination.
F. tularensis usually requires a biosafety level 3 laboratory to protect laboratory personnel. Diagnosis of F. tularensis DNA by means of polymerase chain reaction assay is also available for the diagnosis of tularemia; however, blood may contain compounds capable of inhibiting the assay.

Because of the difficulties in culturing or directly detecting the bacteria, most cases of tularemia are diagnosed by demonstrating a diagnostic rise in serum antibodies to F. tularensis. Antibodies to F. tularensis can be detected approximately 2 weeks after the onset of symptoms. Latex agglutination, microagglutination, hemagglutination, and enzyme-linked immunosorbent assay tests are commercially available. A polymerase chain reaction on tissue specimens has been developed but is not widely available. Real-time polymerase chain reactions on samples other than tissue are currently under investigation. Due to the time delays in establishing a firm diagnosis, the decision to treat in many patients has to be made on clinical suspicion. In our patient, no acute serologic testing was performed because the patient’s CSF culture was positive for F. tularensis, but the convalescent antibody titer at 8 months was 1:1024 by means of microagglutination testing.

Treatment for tularemic meningitis differs from the usual antibiotics given for bacterial meningitis. Ceftriaxone and other β-lactam antibiotics commonly used for empirical treatment of meningitis may be ineffective, as was the case in our patient. For tularemic meningitis, chloramphenicol and streptomycin is the regimen of choice. Gentamicin sulfate is an alternative if streptomycin is not available, but some studies suggest higher relapse rates for patients with tularemia who are treated with gentamicin vs streptomycin. Gentamicin was used in 2 of 17 patients with tularemic meningitis with successful treatment. Chloramphenicol was used in 7 of the 17 patients who were treated successfully; however, it should be used in conjunction with an aminoglycoside. Chloramphenicol is bacteriostatic and aminoglycosides are bactericidal, and the use of streptomycin, in particular, has been associated with lower relapse rates. Doxycycline has successfully cured tularemic meningitis in combination with an aminoglycoside and is effective in the treatment of tularemia in animal models. Ciprofloxacin has also shown to treat tularemia in animal models and has successfully treated 2 cases of human tularemia without meningitis. In the cases summarized in the Table, tularemic meningitis was most often successfully treated with streptomycin and chloramphenicol for 7 to 21 days.

In conclusion, our patient is typical in that he had recently worked as a professional landscaper performing high-risk activities that included mowing, brush cutting, and using a blower. He is also typical in that his diagnosis was delayed and he had poor response to empiric meningitis treatment with intravenous ceftriaxone. It is unknown whether the asymptomatic Chiari type 1 malformation noted on magnetic resonance imaging in our patient had any role in allowing F. tularensis to enter the meninges from the bloodstream. The outcome of tularemic meningitis is good if the diagnosis is made early, the correct antibiotics are given, and the patient does not have overwhelming bacterial sepsis or organ failure. Deaths have occurred in the patient series from misdiagnosis, use of inappropriate antibiotics, and occurrence during the era before antibiotics.

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Author Contributions: All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Hofinger, Cardona, Mertz, and Davis. Acquisition of data: Hofinger, Cardona, Mertz, and Davis. Analysis and interpretation of data: Hofinger, Mertz, and Davis. Drafting of the manuscript: Hofinger, Cardona, and Davis. Critical revision of the manuscript for important intellectual content: Hofinger, Mertz, and Davis. Administrative, technical, and material support: Hofinger. Study supervision: Mertz and Davis.

Financial Disclosure: None reported.

REFERENCES


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**Announcement**

**Calendar of Events**

On the Calendar of Events site, available at http://pubs.ama-assn.org/cgi/calendarcontent and linked off the home page of the Archives of Neurology, individuals can submit meetings to be listed. Just go to http://pubs.ama-assn.org/cgi/cal-submit/ (also linked off the Calendar of Events home page). The meetings are reviewed internally for suitability prior to posting. This feature also includes a search function that allows searching by journal as well as by date and/or location. Meetings that have already taken place are removed automatically.