Tick-Borne Diseases, Tularemia

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Synonyms and related keywords: Francisella tularensis, ulceroglandular, glandular, oculoglandular, oropharyngeal, pneumonic, typhoidal, rabbit fever, vector-borne disease

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Background: First described in Japan in 1837, tularemia is an infectious disease caused by the gram-negative pleomorphic bacterium, *Francisella tularensis*. The disease name relates to the description in 1911 of a plaguelike illness in ground squirrels in Tulare County, California, and the subsequent work performed by Dr Edward Francis. In 1928, Francis described his personal experience with more than 800 cases.

*F tularensis* is found worldwide in more than 100 species of wild animals, birds, and insects. It produces an acute febrile illness in humans. The route of transmission and factors relating to the host and the organism influences the presentation.

Pathophysiology:

Categories of tularemia

Some authorities classify tularemia into 2 groups, which include the far more common ulceroglandular form (in which local or regional symptoms and signs predominate) and the more lethal typhoidal form (in which systemic symptoms dominate the clinical picture). However, tularemia generally is divided into 6 forms: ulceroglandular, glandular, oculoglandular, oropharyngeal, pneumonic, typhoidal; each form reflects the mode of transmission. The organism gains access to the host by means of inoculation into skin or mucous membrane, inhalation, or ingestion.

Ulceroglandular form (70-80% of cases): The organism enters through a scratch, abrasion, or tick or insect bite and spreads via the proximal lymphatic system. Within the ulceroglandular form, more differentiation exists. A subcutaneous inoculum of as few as 10 organisms can cause disease.

Glandular form: No ulcer is present, and the organism is presumed to have gained access to the lymphatic system and/or bloodstream through clinically unapparent abrasions.

Oculoglandular form (1% of cases): The organism
enters through the conjunctiva from either a splash of infected blood or rubbing the eyes after contact with infectious materials (eg, blood from a rabbit carcass).

Oropharyngeal form (rare): This form occurs after ingestion of eating undercooked rabbit meat containing the organism.

Pneumonic form (uncommon): This form occurs when the organism is inhaled. This form is observed in laboratory workers and, occasionally occurs naturally. Pneumonia also occurs in 10-15% of patients with ulceroglandular tularemia and in one-half of those patients with typhoidal tularemia.

Typhoidal (or septicemic) form (10-15% of cases): This form is more severe than the others and often includes pneumonia. Ingestion may be the mode of transmission; however, in most cases, the portal of entry remains unknown.

**Incubation**

After an incubation period of 3-4 days (range, 1-14 d), a papule develops, and a high fever develops. The papule evolves into an ulcer associated with regional lymphadenopathy. Some patients infected by a second, less virulent strain (type B), have less dramatic presentations.

**Carriers**

Although numerous animals and insects can carry *F. tularensis*, rabbits and ticks (especially *Dermacentor* and *Amblyomma* species) most commonly are implicated in human cases. The deer fly is another classic, although less common, vector.

**Frequency:**

- **In the US:** A few hundred cases of tularemia are reported annually in the US. As with most such diseases, the majority of cases are likely unreported or misdiagnosed. Although sporadic cases occur in all states, those with highest prevalence are Arkansas, Illinois, Missouri, Texas, Oklahoma, Utah, Virginia, and Tennessee.
The frequency of tularemia has decreased markedly over the last 50 years, and a shift from winter disease (usually from rabbits) to summer disease (more likely from ticks) has occurred.

- Internationally: Tularemia is found worldwide, but the incidence is unknown.

Mortality/Morbidity: Untreated, tularemia has a mortality rate of 5-15%; this rate is even higher with the typhoidal form. Appropriate antibiotics lower this rate to about 1%.

Sex: Biologically, no sex bias exists; however, young to middle-aged men may be more likely to engage in activities (e.g., associated with tick bites, rabbit and wild game exposure) that predispose them to tularemia.

History:

- The general history for tularemia may include fever, chills, myalgias, and malaise. Occasionally patients with tularemic meningitis, pericarditis, peritonitis, endocarditis, and osteomyelitis have symptoms that correspond to each form of the disease, as follows:

  - Ulceroglandular and glandular forms
    - Patients have ulcers at the sites of inoculation.
    - In rabbit-associated cases, ulcers usually are on the fingers or hands.
    - In tick-associated cases, common sites include the groin, axillae, and trunk. Swollen regional glands reflect this same geographic pattern. Infected nodes are painful.

  - Glandular form
    - This form is distinguished from the ulceroglandular form by the absence of an
ulcer
  - The bacterium presumably gains entry via microscopic abrasions.

- Oculoglandular form
  - The patient has a painful, red eye, often with purulent exudate.
  - Swollen glands may occur in submandibular, preauricular, or cervical areas.

- Oropharyngeal form
  - Produced from eating undercooked infected meat, this form is associated with a sore throat, abdominal pain, nausea, vomiting and diarrhea, and occasionally, GI bleeding.
  - Abdominal pain is caused by mesenteric adenopathy, and bleeding results from intestinal ulcerations.

- Pneumonic form
  - In this form, produced by inhalation of organisms or by hematogenous spread from ulceroglandular or typhoidal disease, patients have a dry cough, dyspnea, and pleuritic chest pain.
  - Some patients with tularemic pneumonia have systemic symptoms without these respiratory complaints.

- Typhoidal (septicemic) form
  - *F. tularensis*, bacteremia causes this form and produces fevers, chills, myalgias, malaise, and weight loss.
  - The absence of an ulcer or lymphadenopathy makes diagnosis difficult.

**Physical:** Physical findings in tularemia vary with the
mode of presentation.

- Findings common to most cases are fever, tender hepatosplenomegaly, and in about 20% of patients, a generalized maculopapular rash that occasionally becomes pustular.

- In 1 series, erythema nodosum occurred in 4 of 88 cases.

- The ulcer forms at the site of skin entry of the organism. The location varies with the vector.
  - The lesion starts as a tender papule that evolves into an ulcer with sharply demarcated borders and exudate.
  - The base changes from yellow to black.
  - Regional nodes are edematous and tender, can become fluctuant, and may drain spontaneously.

- Ocular findings may include unilateral intensely injected conjunctiva with purulent exudate, ulcerations and nodules on the palpebral conjunctiva, preauricular and cervical adenopathy, and corneal ulceration.

- Exudative and membranous pharyngitis with regional adenopathy may be observed with the oropharyngeal form.

- In the pneumonia form, rales are sometimes heard, but normal findings at lung examination are not uncommon.

- Physical findings associated with pericarditis, peritonitis, meningitis, and osteomyelitis can be observed.

**Causes:** Tularemia is caused by infection with the bacteria *F. tularensis.*
Other Problems to be Considered:

Psittacosis
Brucellosis

Lab Studies:

- Results of standard blood tests are nondiagnostic.

- The WBC count usually is normal or elevated. No consistent abnormality is found in other components of the CBC.

- In 1 series, urinalysis revealed pyuria in nearly one quarter of the cases in one series.

- Serum chemical analysis reveals elevation of at least 1 test of hepatic function in about 50% of patients. An elevated creatine kinase level is associated with rhabdomyolysis and is a poor prognostic sign.

- Examination of the spinal fluid occasionally reveals an elevated protein level or a few WBCs.

- Findings with routine blood cultures usually are normal because the organism has unique growth requirements. Similarly, while the organism is present in the ulcers, it rarely grows in cultures.
The sputum of patients with tularemic pneumonia usually is white and does not reveal the pathogen.

Imaging Studies:

- A chest radiograph is indicated, because roughly 30% of patients with tularemic pneumonia do not have respiratory symptoms.

Other Tests:

- Definitive diagnosis usually is established with serologic testing.
  
  - A 4-fold increase in the titer or a single titer of 1:160 or more is the common threshold, although this varies with the laboratory.
  
  - One study revealed that no patient had a diagnostic titer before the 11th day of illness, but nearly all had one by day 16. Therefore, in interpreting the result, one must factor in the timing of the serologic test.
  
  - Rabbit handlers and others may have an asymptomatic elevation in antitularemic antibody titers without disease; thus, the elevated titer in the absence of clinical tularemia does not establish a diagnosis.

Emergency Department Care:

- Tularemia must be considered in patients with fever and regional lymphadenopathy, particularly when an ulcer or conjunctivitis is present.

- The typhoidal form presents as a nonspecific febrile illness with little to suggest tularemia in the absence of a careful epidemiologic history taking. In patients with this form of the disease, other potentially life-threatening infections should be considered and excluded or treated as appropriate.

- Supportive care with fluids and antipyretics may be indicated.

Consultations: Consultation with an infectious disease specialist often is indicated.
The goal of therapy is eradication of tularemia with antibiotics.

**Drug Category: Antibiotics** -- Empiric antimicrobial therapy must be comprehensive and should cover all likely pathogens in context of the clinical setting. In treating tularemia, streptomycin is the drug of choice. Although less experience exists with other aminoglycosides, gentamicin also appears to be effective.

Although aminoglycosides are the drugs of choice, reports of patients who have responded well to fluoroquinolones (prior to tularemia being suspected) exist. In addition, in vitro susceptibility testing shows that the quinolones have great promise in treating tularemia. Thus, this class of drug may be an alternative in patients who cannot tolerate aminoglycosides. Also, many practitioners are using newer fluoroquinolones as monotherapy for community acquired pneumonia.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Streptomycin sulfate -- Aminoglycoside antibiotic recommended when therapeutic agents with less potential hazard are ineffective or contraindicated.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Dose</td>
<td>1-2 g IM divided bid for 7-14 d or until the patient is afebrile for 5-7 d; not to exceed 2 g/d</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>20-40 mg/kg/d IM for 7-14 d or until patient is afebrile; not to exceed 0.75-1 g</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity; non–dialysis-dependent renal insufficiency</td>
</tr>
<tr>
<td>Interactions</td>
<td>Nephrotoxicity may be increased with aminoglycosides, cephalosporins, penicillins, amphotericin B, and loop diuretics</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>B - Usually safe but benefits must outweigh the risks.</td>
</tr>
<tr>
<td>Precautions</td>
<td>Narrow therapeutic index; not intended for long-term therapy; caution in renal failure not treated with dialysis; caution with myasthenia gravis, hypocalcemia, and conditions that depress neuromuscular transmission</td>
</tr>
</tbody>
</table>

| Drug Name | Gentamicin (Garamycin, Gentacidin) -- Aminoglycoside used as an alternative to streptomycin. Less experience exists with this agent. Dosing regimens are numerous and adjusted based on creatinine clearance and changes in volume of distribution, as well as body space into which the agent must distribute. Follow each regimen by at least a trough level drawn on the third or fourth dose, 0.5 h before dosing; may draw a peak level 0.5 h after the 30-min infusion. |

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<thead>
<tr>
<th>Drug Name</th>
<th>Tetracycline (Sumycin) -- Second DOC. Duration of treatment of &lt;2 wk is associated with greater risk of relapse. Only potential advantage is its ability to cover other coexisting tick-borne pathogens. Inhibits bacterial protein synthesis by binding with 30S and possibly 50S ribosomal subunits of susceptible bacteria.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult Dose</td>
<td>500 mg PO bid or 250 mg PO qid for 7-14 d</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>&gt;8 years: 10-20 mg/lb/d (25-50 mg/kg) PO divided qid</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity; severe hepatic dysfunction</td>
</tr>
<tr>
<td>Interactions</td>
<td>Bioavailability decreases with antacids containing aluminum, calcium, magnesium, iron, or bismuth subsalicylate; can decrease effects of oral contraceptives, causing breakthrough bleeding and increased risk of pregnancy; tetracyclines can increase hypoprothrombinemic effects of anticoagulants</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>D - Unsafe in pregnancy</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>&lt;5 years with normal renal function: 2.5 mg/kg/dose IV/IM q8h &gt;5 years: 1.5-2.5 mg/kg/dose IV/IM q8h or 6-7.5 mg/kg/d divided q8h; not to exceed 300 mg/d with adjustments for renal function prn</td>
</tr>
<tr>
<td>Adult Dose</td>
<td>5 mg/kg/d IV/IM q6-8h</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity; non-dialysis-dependent renal insufficiency</td>
</tr>
<tr>
<td>Interactions</td>
<td>Coadministration with other aminoglycosides, cephalosporins, penicillins, and amphotericin B may increase nephrotoxicity; aminoglycosides enhance effects of neuromuscular blocking agents (prolonged respiratory depression may occur); coadministration with loop diuretics may increase auditory toxicity of aminoglycosides; possible irreversible hearing loss of varying degrees may occur (monitor regularly)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>B - Usually safe but benefits must outweigh the risks.</td>
</tr>
<tr>
<td>Precautions</td>
<td>Narrow therapeutic index; not intended for long-term therapy; caution in renal failure not treated with dialysis, myasthenia gravis, hypocalcemia, and conditions that depress neuromuscular transmission; adjust dose in renal impairment</td>
</tr>
<tr>
<td>Precautions</td>
<td>Photosensitivity may occur with prolonged exposure to sunlight or tanning equipment; reduce dose in renal impairment; consider drug serum level determinations in prolonged therapy; tetracycline use during tooth development (last one-half of pregnancy through age 8 y) can cause permanent discoloration of teeth; Fanconi-like syndrome may occur with outdated tetracyclines</td>
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<tr>
<td>Drug Name</td>
<td>Chloramphenicol (Chloromycetin) -- Insufficient data on the use of chloramphenicol in tularemia exist. This agent is a distant third choice. Binds to 50 S bacterial-ribosomal subunit and interferes with or inhibits protein synthesis. Is effective against gram-negative and gram-positive bacteria.</td>
</tr>
<tr>
<td>Adult Dose</td>
<td>50-100 mg/kg/d PO/IV divided q6h; not to exceed 4 g/d</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>50-75 mg/kg/d PO/IV divided q6h</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Documented hypersensitivity</td>
</tr>
<tr>
<td>Interactions</td>
<td>Concurrently with barbiturates, chloramphenicol serum levels may decrease, while barbiturate levels may increase, causing toxicity; manifestations of hypoglycemia may occur with sulfonylureas; rifampin may reduce serum levels, presumably through hepatic enzyme induction; may increase effects of anticoagulants; may increase serum hydantoin levels, possibly resulting in toxicity; levels may be increased or decreased</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>D - Unsafe in pregnancy</td>
</tr>
<tr>
<td>Precautions</td>
<td>Use only for indicated infections or as prophylaxis for bacterial infections; serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, granulocytopenia) can occur; perform baseline and periodic blood studies approximately every 2 d during therapy; discontinue upon appearance of reticulocytopenia, leukopenia, thrombocytopenia, anemia or findings attributable to chloramphenicol; adjust dose in liver or kidney dysfunction; caution in pregnancy at term or during labor because of potential toxic effects on fetus (gray syndrome)</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Levofoxacin (Levaquin) -- May be a useful agent to treat tularemia.</td>
</tr>
<tr>
<td>Adult Dose</td>
<td>500 mg PO qd</td>
</tr>
<tr>
<td>Pediatric Dose</td>
<td>Children: Not recommended Adolescents: 250 mg PO qd</td>
</tr>
</tbody>
</table>
Contraindications

- Documented hypersensitivity

Interactions

- Antacids, iron salts, and zinc salts may reduce serum levels; administer antacids 2-4 h before or after taking fluoroquinolones; cimetidine may interfere with metabolism of fluoroquinolones; levofloxacin reduces therapeutic effects of phenytoin; probenecid may increase levofloxacin serum concentrations; may increase toxicity of theophylline, caffeine, cyclosporine, digoxin (monitor digoxin levels); may increase effects of anticoagulants (monitor PT)

Pregnancy

- C - Safety for use during pregnancy has not been established.

Precautions

- In prolonged therapy, periodically evaluate organ system functions (eg, renal, hepatic, hematopoietic); adjust dose in renal function impairment; superinfections may occur with prolonged or repeated antibiotic therapy

Further Outpatient Care:

- Any patient being treated as an outpatient for tularemia should undergo close follow-up, preferably with a primary care physician.

Deterrence/Prevention:

- When hunting rabbits or skinning or preparing rabbit carcasses, great care must be taken to avoid touching the rabbit blood and flesh. Touching one’s eyes should be avoided while performing these activities. Hands should be washed thoroughly afterwards.

- For other suggestions for avoiding tick bites, see Tick-borne Diseases, Introduction.

Complications:

- Pneumonia
- Hemoptysis
- Lung abscess
- Respiratory failure
- Rhabdomyolysis
- Renal failure requiring dialysis

**Prognosis:**

- Roughly 5-15% of untreated patients die of the disease.
- Factors associated with increased mortality include typhoidal presentation, elevated creatine kinase levels, renal failure, late diagnosis, or other serious comorbidities.

**Patient Education:**

- See [Deterrence/Prevention](#).

**Medical/Legal Pitfalls:**

- Failure to consider this treatable and potentially fatal infection is a major pitfall.
  - When the ulceroglandular form is present, the physician is more likely to consider tularemia.
  - The typhoidal form, which is more deadly, has few clues for the diagnosis, unless the physician routinely searches for the epidemiologic clues.

**BIBLIOGRAPHY**

- Schmid GP, Kombliatt AN, Connors CA, et al: Clinically mild tularemia