Bioterrorism Agent Fact Sheet

Tularemia/*Francisella tularensis*

Disease

Naturally occurring tularemia is a zoonotic disease that is transmitted to humans via contact with infected animals or from the bite of arthropods that have fed on infected animals. It is caused by the highly infectious, slow-growing, aerobic, non-sporulating, Gram negative coccobacillus *Francisella tularensis*. As few as 10-50 organisms are sufficient to cause disease if inhaled or inoculated into the skin. Discovered in the early 20th century, the disease has caused multiple sporadic outbreaks but no large epidemics. It is endemic in rural areas in moderate climates, particularly in the midwestern United States. Over the last decade, annual incidence has been less than 200 cases nationwide. Pneumonic tularemia is considered one of the diseases most likely to be encountered in a bioterrorism event. Intentional aerosol release should be suspected if cases occur in nonendemic areas when no discernible risk factors for exposure are identified. Outbreaks of any form of tularemia should be rapidly investigated to rule out a bioterrorism event. There are six forms of tularemia, classified by clinical presentation and determined by route of exposure:

- **Pneumonic tularemia**

  Although up to half of all tularemia cases present with lung involvement from hematogenous spread of systemic infection (secondary pneumonic), this term is generally used to describe infection in the lung as a result of direct inhalation of aerosolized bacteria (primary pneumonic), which is not associated with skin ulcers or lymphadenopathy. Primary pneumonic accounts for <5% of all tularemia cases, but is associated with the highest mortality of 30-60% when untreated. This form is the most likely to be seen in a bioterrorism setting, but can also be seen after handling infected animals or contaminated soil.

- **Typhoidal tularemia**

  Presents as severe systemic disease without skin ulcers, lymphadenopathy or pneumonia. Any route of infection possible. 5-15% of tularemia cases. Mortality similar to pneumonic. Could be seen in bioterrorism setting, but less likely than pneumonic.

- **Ulceroglandular tularemia**

  Characterized by skin ulcer and regional lymphadenopathy. Occurs via contact with an infected animal (particularly rabbits) or by arthropod (particularly tick) bite. Most common natural form of disease, 50-85%. Mortality <5%.

- **Glandular tularemia**

  Regional lymphadenopathy without a skin ulcer. Approx. 10% of cases. Mortality similar to ulceroglandular.

- **Oculoglandular tularemia**

  Conjunctivitis and local lymphadenopathy following inoculation into the eye. Theoretically possible from aerosol or from direct contact with infected material. <5% of cases. Mortality similar to ulceroglandular.

- **Oropharyngeal tularemia**

  Pharyngitis and cervical lymphadenopathy following ingestion of inadequately cooked meat from an infected animal. <5% of cases. Mortality similar to ulceroglandular.

Tularemia

Clinical Features of Tularemia

All forms of disease:

Tularemia can vary in severity, from asymptomatic to fulminant, depending on inoculation dose, host factors and route of infection. *F. tularensis* readily grows at the inoculation site, and is then carried to regional lymph nodes where suppurative lymphadenopathy generally develops. Bacteremia usually follows, especially if untreated, leading to hematogenous spread of infection to multiple organs, including the lungs. Clinically, a nonspecific, flu-like follows an incubation period of 2-5 days (range 1-14 days), consisting of sudden onset of fever, chills and malaise and usually lower back pain/myalgias, headache and temperature/pulse dissociation. Nearly half of all cases develop pulmonary symptoms such as cough - usually nonproductive and chest pain. Leukocytosis is common. The most severe cases develop sepsis and multiorgan failure.

Pneumonic tularemia:

A nonproductive or minimally productive cough, pleuritic chest pain and dyspnea are common. Auscultation of the lungs is often normal, although pleural rubs are not uncommon. Chest radiograph abnormalities must be present to qualify as pneumonic. Findings include patchy, often bilateral infiltrates, and effusions.

Typhoidal tularemia:

Characterized by severe constitutional symptoms and prostration, frequently with GI symptoms. There are no ulcers or detectable lymphadenopathy, and no radiographic abnormalities. Along with pneumonic, it is the most likely form to lead to sepsis, DIC and multiorgan failure.

Ulceroglandular/Glandular tularemia:

A painful papule appears at inoculation site, which may lead to an ulcer. Regional, tender lymphadenopathy develops proximal to inoculation site.

Diagnosis

There are currently no widely available rapid confirmatory diagnostic tests for tularemia. A presumptive diagnosis can be made quickly based on presenting symptoms if there is a high index of suspicion. Blood, sputum, biopsy specimens, pleural fluid, conjunctival exudates and pharyngeal washings may all be obtained to aid in diagnosis.

Presumptive diagnosis:

• Appropriate clinical presentation (see right), especially important in outbreak setting. Suspicion should be particularly high in the setting of a large number of previously healthy persons presenting with a severe pneumonia with or without skin ulcers and lymphadenopathy, associated with temperature/pulse dissociation and pleural involvement, not responding to typical pneumonia antibiotics.

• Several tests including fluorescent antibody detection assays, PCR, immunohistochemical stains, and antigen detection assays may be available at reference laboratories.

Confirmatory diagnosis:

• Microbiologic: *F. tularensis* can be cultured from any infected fluids, however the sensitivity is low, even on specific cysteine-enriched media. Also, because of the high risk of exposure to this organism in culture, some microbiology laboratories do not set up cultures if tularemia is suspected. Gram stain is usually negative.

• Serologic: Serum agglutinin antibody assays and enzyme linked immunosorbent assays (ELISA) are of limited use in acute infection because antibody levels are generally not detected until two weeks after infection.

Treatment

Treatment should be initiated as soon as a diagnosis of tularemia is suspected, and should not be delayed for confirmatory testing. Cure rates are high if antibiotics are started prior to development of severe illness, and survivors have no long term sequelae. Naturally-occurring *F. tularensis* exhibits reliable susceptibility patterns, however, unusual resistance patterns could be a concern in a bioterrorism event.

Until sensitivities are known, treat as follows: continue treatment for 10-14 days if aminoglycosides or fluoroquinolones are used, or up to 21 days for other agents. Intravenous therapy can be switched to the oral equivalent (when available) upon clinical improvement and the patient's ability to eat and absorb medications. Intensive supportive care will be required for severe cases.

• **Adults**

streptomycin 1 g IM q 12 hrs (should be avoided in pregnant or lactating women)
gentamicin 3-5 mg/kg IV/IM q day

• **Children**

streptomycin 15 mg/kg IM q 12 hrs, maximum 2 grams per day
gentamicin 2.5 mg/kg IV q 8 hrs

Alternative therapies include:

ciprofloxacin (very active in vitro, limited clinical data)
doxycycline (high risk of relapse if duration <21 days)
chloramphenicol (high risk of relapse, but best for meningitis)

Noneffective therapies include:

Beta-lactams (including 3rd generation cephalosporins) and macrolides

In mass casualty incidents, parenteral administration may not be feasible; substitution with oral antibiotics, as recommended for post-exposure prophylaxis, may be necessary.

Infection Control

Although *F. tularensis* is highly infectious, no person-to-person transmission has been documented. Standard precautions are suggested for patient care. Because of its infectiousness in pure culture, however, the microbiology lab should be alerted if tularemia is suspected. Routine procedures with microbiologic specimens requires BSL-2 handling, while higher risk procedures involving large volumes or potential aerosolization require BSL-3 handling.

Decontamination

F. tularensis can live for weeks in cold, moist conditions. However, an aerosol release would likely be completely dispersed within a few hours after release, and secondary aerosolization is thought to be extremely unlikely. As symptoms in the exposed would not occur until after complete dispersion of the aerosol, no decontamination is recommended for large areas. Known aerosol releases in smaller areas with visible standing water or wet surfaces should be decontaminated with a two-step process involving spraying with 10% bleach, followed by 70% alcohol ten minutes later. Exposed skin and clothing can be washed thoroughly with soap and water. Corpses can be handled with standard precautions, but aerosol-generating procedures such as bone sawing should be avoided. Contaminated linens should be disinfected via standard hospital protocols.

Post-Exposure Prophylaxis

Prophylactic therapy for tularemia should be provided for 14 days for the following:

- persons who were likely exposed to known intentional release within the last few days (asymptomatic persons who may have been exposed to a covert infectious aerosol from which other cases have been identified should be observed, and started on full treatment antibiotics if a fever or flu-like illness develops within 14 days of probable exposure).
- laboratory workers with a high-risk exposure (spill of culture, centrifuge aerosolization)
- Note: *contacts of cases do not require prophylaxis if not exposed to original aerosol*

Prophylactic regimen:

- **Adults** (including pregnant/lactating women)
  doxycycline 100 mg PO bid or
  ciprofloxacin 500 mg PO bid
- **Children** (benefits of therapy likely outweigh the risks)
  doxycycline 2.2 mg/kg PO bid, up to 100 mg PO bid or
  ciprofloxacin 20 mg/kg PO bid, up to 500 mg PO bid

Vaccination

A safe, live attenuated vaccine offering moderate protection versus pneumonic tularemia has been used in the U.S. since 1959 with very limited availability for laboratory workers at high risk. As tularemia has a relatively short incubation period, and the vaccine has a delayed effect, it is not recommended for post-exposure prophylaxis.

Reporting

Report suspected cases or suspected intentional release of tularemia to your local health department. The local health department is responsible for notifying the state health department, FBI, and local law enforcement. The state health department will notify the CDC.

Disclaimer

Information contained in this fact sheet was current as of October 2001, and was designed for educational purposes only. Medication information should always be researched and verified before initiation of patient treatment.

October 2001

Additional information and references available at www.bioterrorism.slu.edu

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