

SANTA CRUZ COUNTY HEALTH SERVICES AGENCY

Medical Treatment and Response to Suspected Tularemia: Information for Health Care Providers During Biologic Emergencies

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**ALL SUSPECT CASES OF TULAREMIA MUST BE REPORTED IMMEDIATELY TO
SANTA CRUZ COUNTY HEALTH SERVICES AGENCY, DISEASE CONTROL:**

During Business Hours: 831-454-4114

After Hours (Nights, Weekends and Holidays): 831-471-1183

I. KEY SUMMARY POINTS

Epidemiology:

- Highly infectious after aerosolization
- Infectious dose can be as low as 10-15 organisms
- Person-to-person transmission does not occur

Clinical:

- Incubation period is 3-6 days (ranges 1-21 days)
- Aerosolization would most likely result in typhoidal tularemia, with pneumonic involvement
- Typhoidal tularemia is a nonspecific illness, with fever, headache, malaise and non-productive cough (mortality rates can be as high as 30-60%)
- Diagnosis requires high index of suspicion given nonspecific presentation

Laboratory Diagnosis:

- Bacterial cultures should be handled in a Biosafety Level 3 facility; isolation of organism can otherwise put laboratory workers at risk
- Organism is difficult to culture and grows poorly on standard media; cysteine-enriched media is required
- Serology is most commonly used for diagnosis

Patient Isolation:

- Standard precautions. Respiratory isolation not required.

Treatment:

- Streptomycin (7.5 mg/kg IM q 12 hours x 10-14 days) or gentamicin (3-5 mg/kg/day IV or IM qd in 3 divided doses x 10-14 days) are the preferred antibiotics
- Tetracyclines are alternative choices, although they are bacteriostatic and associated with higher relapse rates and must be continued for at least 14 days

Prophylaxis:

- Antibiotic prophylaxis is most effective if begun within 24 hours after exposure to aerosol
- Tetracyclines are recommended for 14 days

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II. Introduction/Epidemiology

Tularemia is a zoonotic disease caused by *Francisella tularensis*, a gram-negative intracellular coccobacillus. *F. tularensis* has several biovars; *F. tularensis* biovar

tularensis is the most common naturally-occurring isolate in the United States. The organism is primarily recovered from lagomorphs (rabbits), rodents and arthropods (ticks and deer flies) in the United States and from water, mosquitoes and aquatic mammals outside the United States. The rabbit is the vertebrate most commonly associated with tularemia in North America. In recent years, the reported incidence of tularemia has declined to less than 200 cases per year in the United States.

Tularemia is acquired under natural conditions by direct inoculation (such as an arthropod bite), animal contact such as skinning or eating infected animals, or via the airborne route. (Domestic cats have occasionally transmitted tularemia by bites or scratches.) *F. tularensis* may survive for prolonged periods in water, mud and animal carcasses; even if frozen *Francisella tularensis* is highly infectious. After aerosolization, 10-50 virulent organisms given by aerosol can cause infection in humans, and as few as 10 organisms can cause infection when administered percutaneously. In the event of a bioterrorist attack, aerosolization would be the most likely route of infection.

Tularemia transmission from patient-to-patient has never been reported, even among patients with tularemia pneumonia. Persons exposed to an aerosol of *Francisella tularensis* do not present a risk for secondary infection of others or for re-aerosolization of the organism.

III. **Significance as a Potential Bioterrorist Agent**

- Weaponized by the United States military during the biologic offensive program in the 1950s-1960s.
- Highly infectious after aerosolization; infectious dose can be as low as 10 to 50 microorganisms if inhaled.
- Aerosolized *F. tularensis* would cause typhoidal tularemia (a nonspecific, febrile illness), with high mortality rates (30-60%) if untreated.

IV. **Clinical Manifestations**

During an act of bioterrorism, release of an aerosol will be the most likely route of transmission with typhoidal tularemia the most likely clinical presentation.

There are several different classification systems for clinical tularemia. The most straightforward classifies tularemia into ulceroglandular (75% of patients) and typhoidal (25% of patients). **Ulceroglandular** disease involves lesions on the skin or mucous membranes (including conjunctiva), lymph nodes larger than 1 cm, or both. In **typhoidal** tularemia, the lymph nodes are usually smaller than 1 cm and no skin or mucous membrane lesions are present--this form is more commonly associated with pneumonia and has a higher mortality rate.

A. *Typhoidal Tularemia* -- An acute, nonspecific febrile illness associated with *F. tularensis* that is **not** associated with prominent lymphadenopathy. Typhoidal tularemia is mainly due to inhalation of infected aerosols. **Most likely form during an act of bioterrorism.**

Incubation period: 3 - 6 days (range 1- 21 days)

Symptoms - prominent symptoms include:

- fever with chills
- headache
- myalgias
- sore throat
- anorexia
- nausea
- vomiting
- diarrhea (can be a major component of illness, generally watery stool not bloody)
- abdominal pain
- cough

Patients may develop a sepsis syndrome with hypotension, adult respiratory distress syndrome, renal failure, disseminated intravascular coagulation and shock.

Pleuropulmonary disease (pneumonic tularemia) is common with pulmonary infiltrates or pleural effusions seen in up to 45% of typhoidal tularemia cases. A patchy, alveolar process is most often seen on chest x-ray. Patients may develop acute respiratory distress syndrome and require mechanical ventilation.

B. *Ulceroglandular Tularemia* -- generally due to inoculation of the organism into the skin or mucous membranes.

Incubation period: 3 - 6 days (range 1 - 21 days)

Symptoms - Local papule develops at the inoculation site, with progression to a pustule then an ulcer within several days. Lymphadenopathy develops in 85% of patients. Nodes are usually tender and 0.5-10 cm in diameter (mean 2 cm). Enlarged nodes may become fluctuant, drain spontaneously or persist for months to years.

A cutaneous ulcer occurs in 60% of cases. Ulcers are usually singular and 0.4-3.0 cm in diameter, with heaped-up borders. Ulcers are almost always accompanied by regional lymphadenopathy.

In addition, the following symptoms may be present (in decreasing order of likelihood of appearance):

- fever (present in 85% of patients)
- chills
- headache
- cough
- myalgia
- chest pain
- vomiting
- arthralgia
- sore throat
- abdominal pain
- diarrhea
- dysuria
- back pain
- stiff neck

Ulceroglandular tularemia can also be complicated by pleuropulmonary disease or pharyngeal involvement. Pharyngeal tularemia (via ingestion of contaminated food, water or droplets) is associated with severe throat pain, exudative pharyngitis and often pharyngeal ulcerations.

V. Laboratory Diagnosis

Routine laboratory work must be done in Biosafety Level 2 facilities. However, handling of bacterial cultures once the organism is identified should be done in Biosafety Level 3 facilities. If tularemia is suspected, please call the Santa Cruz County Public Health Laboratory at 831-454-5445 to arrange for submission of specimens for testing. After hours, please call 831-471-1183.

The diagnosis of tularemia requires a high index of suspicion since the disease often presents with very nonspecific symptoms. The diagnosis can be made by recovery of the organism from blood, ulcers, conjunctival exudates, sputum, pleural fluid, lymph nodes, gastric washings and pharyngeal exudates. Since the organism is difficult to isolate and constitutes a potential danger to laboratory personnel, serologic evidence of infection in a patient with a compatible clinical syndrome is commonly used for diagnosis.

- **Culture**

F. tularensis grows poorly on standard media. It forms small, smooth, opaque colonies when grown on media containing cysteine or other sulfhydryl compounds (e.g., *glucose cysteine blood agar* or *thioglycollate broth*) at 37C. The organism has also been isolated from automated radiometric detection systems if the media is subcultured on chocolate agar. The bacteria grows slowly; some strains may require up to 2-3 weeks to develop visible colonies. **Notify the clinical laboratory in advance of submitting specimens for culture which may contain *F. tularensis*, since isolation of the organism can put laboratory workers at risk for infection.**

- **Serology**

Antibody detection assays include tube agglutination, microagglutination and ELISA. Significant antibody does not appear until the end of the second week of illness, peaks at 4-5 weeks, and can persist for more than a decade. A single titre (by tube agglutination) of > 1:160 is a presumptive positive; a four-fold rise is required for a definitive serologic diagnosis. ELISA and microagglutination tests

may be more sensitive than tube agglutination. Antibodies may cross-react with *Brucella* spp., *Proteus* OX19 and *Yersinia* spp. but dithiothreitol treatment of the serum will eliminate most of these reactions. Serology testing is available through national reference laboratories.

VI. Handling Laboratory Specimens

Tularemia is the third most commonly reported laboratory-associated bacterial infection. Cases have occurred among clinical laboratorians working with bacterial cultures. Laboratory staff handling specimens from persons who are suspected of having tularemia must wear face masks with eye protection, surgical gloves, protective gowns, and shoe covers --- especially when working with pure bacterial cultures. Laboratory tests (*such as serological examinations and staining of impression smears*) can be performed in Biological Safety Level 2 cabinets.

Blood cultures should be maintained in a closed system and clinical isolates from blood or any other site should be handled in Biological Safety Level 3 cabinets.

Every effort should be made to avoid splashing or creating an aerosol. Biosafety Level 3 practices and facilities should be used for inoculation, incubation, centrifugation and harvesting of cell cultures and the manipulation of infected tissues.

Accidental spills of potentially contaminated material should be decontaminated immediately by covering liberally with a disinfectant solution (0.1% sodium hypochlorite or sodium hydroxide (0.1N)). All biohazardous waste should be decontaminated by autoclaving. Contaminated equipment or instruments may be decontaminated with a hypochlorite solution, hydrogen peroxide, peracetic acid, 1% glutaraldehyde solution, formaldehyde, ethylene oxide, copper irradiation, or other O.S.H.A. approved solutions, or by autoclaving or boiling for 10 minutes.

VII. Treatment

The treatment of choice for all forms of tularemia except meningitis is streptomycin; gentamicin is an acceptable alternative. For both drugs, dosages must be adjusted for renal insufficiency. **Gentamicin is safe during pregnancy; avoid streptomycin due to its association with irreversible deafness in children exposed in utero.**

(1) **Streptomycin:** Adult dosage is 0.5-1.0 gm (7.5 mg/kg) intramuscularly every 12 hours for 10-14 days. In very sick patients, streptomycin may be give at 15 mg/kg intramuscularly every 12 hours for 10-14 days.

Pediatric dose: 15 mg/kg intramuscularly every 12 hours for 10-14 days.

Alternatives:

(2) **Gentamicin:** 3-5 mg/kg/day intravenously or intramuscularly in three divided doses, with a peak serum level of at least 5 ug/ml desirable. Continue for 10-14 days.

Pediatric dose: 2.5 mg/kg intravenously or intramuscularly every 8 hours for 10-14 days

(3) Tetracycline and chloramphenicol are bacteriostatic and associated with high relapse rates. These agents must be continued for a minimum of 14 days. **Tetracycline:** 2 grams /day IV or orally in four divided doses or **doxycycline** 100 mg IV or orally twice a day for at least 14 days.

Pediatric dose: [Not recommended for children less than 9 years, pregnant or lactating women] If > 45 kg, give adult dosage of doxycycline; if less than 45 kg, give 2.2 mg/kg twice a day. Tetracycline at 30 mg/kg/day orally, to a maximum of 2 grams/day, in four divided doses for at least 14 days.

Chloramphenicol should generally not be used due to the availability of effective alternatives with fewer serious side effects.

(4) Additional agents with favorable in vitro susceptibility tests but limited clinical data on efficacy include: fluroquinolones (except cinoxacin), erythromycin (resistant strains of *F. tularensis* have been identified), and rifampin. Penicillin and cephalosporins are not effective and should not be used to treat tularemia.

Meningitis

A rare complication of tularemia, meningitis requires special attention with regard to therapy as the penetration of streptomycin or gentamicin into the CSF is suboptimal. The treatment of meningeal infection should include combination therapy with chloramphenicol plus streptomycin or possibly a third-generation cephalosporin plus streptomycin (limited data available on efficacy).

VIII. Isolation of Patients

Tularemia is not transmissible from person-to-person. Standard precautions should be followed for all patients -- **respiratory isolation rooms are not required.** Ulcers or wounds in patients with tularemia should be covered and contact isolation maintained as *F. tularensis* can be isolated from such lesions for one month or longer.

IX. Disposal of Infectious Waste

Use of tracking forms, containment, storage, packaging, treatment and disposal methods should be based upon the same rules as all other regulated medical wastes.

X. Autopsy and Handling of Corpses

All postmortem procedures are to be performed using Respiratory Precautions.

Efforts should be made to avoid aerosolization.

- All persons performing or assisting in postmortem procedures must wear mandated P.P.E. (personal protective equipment) as delineated by O.S.H.A. guidelines.
- Instruments should be autoclaved or sterilized with a 10% bleach solution or other solutions approved by O.S.H.A. Surfaces contaminated during postmortem procedures should be decontaminated with an appropriate chemical germicide such as 10% hypochlorite or 5% phenol (carbolic acid).

XI. Management of Exposed Persons

An exposed person is defined as a person who has been exposed to the release of a *Francisella tularensis*-containing aerosol.

- **Post-exposure prophylaxis:** Antibiotic prophylaxis should begin as soon as possible after exposure and is **most effective if begun within 24 hours.** Limited data suggests that tetracyclines may be effective:
Tetracycline 500 mg orally in 4 divided doses for 14 days
Doxycycline 100mg orally twice daily for 14 days

- **Pediatric patients and pregnant women:** Although tetracyclines are not generally recommended for children under age 9 or for pregnant women, the risk of developing tularemia may outweigh these limitations. Fluoroquinolones are a potential alternative for prophylaxis.

Doxycycline:

- If > 45 kg - 100 mg orally every 12 hours
- If ≤ 45 kg - 2.2 mg/kg orally every 12 hours

If antibiotic prophylaxis is not started within 24 hours of exposure, then exposed persons should be instructed to begin a fever watch and seek medical care if temperature exceeds 38.5 °C.

XII. Reporting to the Health Department

Tularemia is a reportable condition in California. Confirmed or suspect tularemia cases must be reported immediately:

During business hours

Santa Cruz County Health Services Agency, Disease Control at 831-454-4114

After business hours

Santa Cruz County Communications at 831-471-1183

XIII. References

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