Off-Label Drug Uses

Ciprofloxacin: Tularemia (Adults)

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This *Hospital Pharmacy* feature is extracted from *Off-Label Drug Facts*, a publication available from Wolters Kluwer Health. *Off-Label Drug Facts* is a practitioner-oriented resource for information about specific drug uses that are unapproved by the US Food and Drug Administration. This new guide to the literature enables the health care professional or clinician to quickly identify published studies on off-label uses and determine if a specific use is rational in a patient care scenario. References direct the reader to the full literature for more comprehensive information before patient care decisions are made. Direct questions or comments regarding *Off-Label Drug Uses* to jgeneral@ku.edu.

BACKGROUND

Tularemia is caused by *Francisella tularensis*, an aerobic, gram-negative coccobacillus that can produce infection in a host after the introduction of as few as 10 organisms. Various small mammals in North America and Eurasia are hosts to the bacterium, which is spread to humans through insect bites, handling infected animal tissues or fluid, or exposure to contaminated water, food, soil, or air. Person-to-person transmission of tularemia has not been documented. Depending on the point of entry into the body and whether the disease has disseminated, tularemia can present as a glandular, ulceroglandular, oculoglandular, oropharyngeal, pneumonic, typhoidal, or septic form. Before the advent of antibiotics, mortality from severe infections was as high as 60%. Because it is so highly infectious, tularemia was identified as early as the 1930s as a potential biological weapon.¹⁻³

PATIENT POPULATION

Adults with mild to moderate tularemia or tularemia exposure.

DOSAGE AND DURATION

Contained casualty management: 400 mg intravenously (IV) twice daily for 10 days. Can switch to oral administration when clinically indicated.¹

Mass casualty management or postexposure prophylaxis: 500 or 750 mg orally twice daily for 14

days.¹⁻³ At least 14 days of therapy is recommended in oral regimens.^{1,3}

RESULTS

Data from retrospective studies⁴ and case reports/series⁵⁻⁷ demonstrate varied results with the use of ciprofloxacin in the management of tularemia. Guidelines created by the Infectious Diseases Society of America (IDSA), Working Group on Civilian Biodefense, and the European Commission's Task Force on Biological and Chemical Agent Threats (BICHAT) recommend ciprofloxacin as an alternative in the management of mild to moderate tularemia infection. In scenarios of mass casualty management and postexposure prophylaxis, the Working Group on Civilian Biodefense considers oral ciprofloxacin and doxycycline as drugs of choice.

Guidelines

Infectious Diseases Society of America

The IDSA issued guidelines on the diagnosis and management of skin and soft tissue infections, including ulceroglandular or glandular tularemia. The guidelines note that no prospective controlled or randomized trials have been performed for therapy of tularemia, and all recommendations are based on limited noncontrolled data. For severe cases, streptomycin or gentamicin is recommended. For mild to

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moderate infection, oral tetracycline or doxycycline is recommended. Oral levofloxacin or ciprofloxacin are considered alternate choices for mild to moderate illness in adults based on limited case report data. At least a 14-day course is recommended for all oral antibiotic regimens.³

Working Group on Civilian Biodefense

Consensus-based treatment guidelines from the Working Group on Civilian Biodefense on tularemia as a biological weapon distinguish between contained casualty situations (individual medical management of patients) and mass casualty situations. The drug of choice for the treatment of tularemia in contained casualty situations is streptomycin with gentamicin as an alternative therapy; both are to be continued for 10 days. Ciprofloxacin, doxycycline, and chloramphenicol are recommended as acceptable alternatives; however, doxycycline and chloramphenicol are noted to have higher failure and relapse rates and required longer durations of therapy (14-21 days). Ciprofloxacin is characterized as a promising candidate for the treatment of tularemia and should be initiated at a dosage of 400 mg IV twice daily and continued for 10 days. The guidelines recommend that parenteral antibiotics, including ciprofloxacin, be switched to the oral route when clinically indicated.

In mass casualty situations, oral ciprofloxacin and doxycycline are drugs of choice. Oral ciprofloxacin is also identified as the best alternative to gentamicin for the treatment of pregnant women in the mass casualty setting. The recommended adult ciprofloxacin dosage is 500 mg orally twice daily. The duration of oral therapy is 14 days.

Ciprofloxacin and doxycycline are also recommended as the drugs of choice for prophylactic therapy of exposed persons after release of a biological weapon containing *F. tularensis* and prophylactic therapy of laboratory personnel at high risk of infection, such as after exposure through spills, needlesticks, and centrifuge accidents. The recommended dosage is ciprofloxacin 500 mg orally twice daily for 14 days. The guidelines note that postexposure prophylaxis is not indicated for close contacts between tularemia-infected persons because person-to-person transmission does not appear to occur.¹

The European Commission's Task Force on Biological and Chemical Agent Threats

The BICHAT guidelines on the management of tularemia and bioterrorism-related tularemia also recommend a 10-day course of streptomycin or gentamicin

as first-line treatment of tularemia. Ciprofloxacin, levofloxacin, or ofloxacin (14-day courses) are specified as alternative regimens. Doxycycline (21 days) is recommended as third-line treatment. The authors stated that dual antibiotic therapy should be considered for severe cases. First-line postexposure prophylaxis is oral therapy for 14 days with ciprofloxacin, levofloxacin, or ofloxacin. Doxycycline is considered second-line treatment for postexposure prophylaxis.²

Noncontrolled Trials

In a retrospective review of 190 cases of probable or confirmed tularemia reported to the Missouri Department of Health and Senior Services (MDHSS), detailed medical information was available for 121 of the cases. Of the patients with data available, 65% were male and the median age was 37 years (range, 6 months to 92 years). Of patients with documented exposure history ($n = 81$), at least 50% reported a tick bite. Other exposures included cat bites, mowing grass, handling animal tissue, and exposure to agricultural products (eg, aerosols, dust). Median onset of symptoms was available for 16 patients and was 3 days (range, 1-9 days). More than half of the patients (58%; $n = 70$) were hospitalized with a median duration of 4 days (range, 1-27 days). Glandular and oculoglandular disease occurred in younger patients and pneumonic and typhoidal cases occurred in older patients. Of 109 patients, 51 received an aminoglycoside, 53 received tetracyclines, and 45 received fluoroquinolones; some patients received dual therapy. Of the 10 patients who received ciprofloxacin for at least 10 days, either alone or in combination with ineffective antibiotics, 9 had a successful outcome. Of the 121 cases reviewed, 120 patients recovered.⁴

Case Reports/Case Series

In case reports/series of tularemia, successful management with ciprofloxacin has occurred.^{5,6} Variability among the cases makes it difficult to conclude predictive factors for successful outcome.

SAFETY

This is a limited safety profile. Refer to package labeling for complete prescribing information (eg, Warnings/Precautions, Adverse Reactions, Drug Interactions).

In the clinical experience reported to date, ciprofloxacin was well tolerated. Fluoroquinolone resistance has been raised as a potential issue in the management of tularemia.^{7,8}

Therapy Considerations

Data from retrospective studies and case reports/series demonstrate varied results with the use of ciprofloxacin in the management of tularemia. Guidelines created by IDSA, Working Group on Civilian Biodefense, and BICHAT recommend ciprofloxacin as an alternative in the management of mild to moderate tularemia infection. In scenarios of mass casualty management and postexposure prophylaxis, the Working Group on Civilian Biodefense considers oral ciprofloxacin and doxycycline as drugs of choice.

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