

## Serendipitous Treatment of Tularemia in Pregnancy

Joyce J. Johnsrud,<sup>1</sup> Carolyn Rebecca Smith,<sup>2</sup> and Robert W. Bradsher<sup>1</sup>

<sup>1</sup>Division of Infectious Diseases, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA, and <sup>2</sup>Boston Mountain Rural Health, Bee Branch, Arkansas, USA

We present a young pregnant woman who developed ulceroglandular tularaemia following a bite wound from a kitten. She grew *Francisella tularensis* from the ulcer. While awaiting bacterial culture results and serology for *Bartonella*, she was treated with azithromycin, with resolution of fever and axillary tenderness. Treatment recommendations for tularemia are either gentamicin or doxycycline, both of which can be perilous to the fetus. A Centers for Disease Control and Prevention report on the macrolide susceptibility of North American isolates of this organism has been underappreciated. The unanticipated result from this patient may give another potential option for treatment of tularemia in pregnancy.

**Keywords.** azithromycin; *Francisella tularensis*; infection in pregnancy; tularemia.

We saw a 26-year-old pregnant woman with culture-positive ulceroglandular tularemia. While 18 weeks pregnant, she developed an ulcer at the site of a puncture bite (Figure 1A) from a 4-month-old rescue kitten. Five days after the bite, she came to clinic with a temperature of 100.5°F and flu-like symptoms. She received amoxicillin but returned 4 days later with a fever of 100.8°F and normal blood pressure, and the puncture site (Figure 1B) had ulcerated, with a small amount of purulent drainage. She had developed severe axillary tenderness on the same side as the bite, although distinct nodes were not described by her nurse practitioner. A culture was obtained from the drainage, and azithromycin was prescribed for possible cat scratch disease; blood cultures were not obtained, and her white blood cell count was 9900. Within 4 days of starting azithromycin, she reported resolution of systemic symptoms and improvement in drainage and axillary tenderness. Bartonella IgM and IgG were negative. Culture from the finger wound grew *Francisella tularensis* at the referral laboratory and was confirmed at the Arkansas State

Health Department lab following the Centers for Disease Control and Prevention (CDC) Emergency Preparedness and Response Laboratory Response Network (LRN) protocol designed to respond to biological threats. Direct immunofluorescence and polymerase chain reaction testing for *F. tularensis* were both positive. Sensitivities to antibiotics for this organism would have required transporting the specimen to the CDC, but the culture had to be destroyed according to the LRN protocol by a date before transportation could be arranged. Four weeks after therapy, she was seen in the infectious disease clinic and was doing well. She reported resolution of her symptoms and signs (Figure 2). She was afebrile, and no lymphadenopathy was present in the epitrochlear or axillary region. Tularemia IgM and IgG antibodies were >100 U/mL. At follow-up 4 months later, she reported successful delivery with no known complications.

Limited data exist on treatment of tularemia in pregnancy [1] and children [2]. Gentamicin and doxycycline, the typical firstline agents used for treatment of tularemia, are potentially dangerous to the 18-week fetus. Levofloxacin is a pregnancy category C agent, indicating that risk cannot be ruled out, making azithromycin, a pregnancy category B agent, an attractive option (Table 1). One case report from France demonstrated successful use of a macrolide in treatment of a pregnant woman with oropharyngeal tularemia caused by *F. tularensis* subspecies *holarctica* (also known as *F. tularensis* type B), the predominant strain in Europe [3]. Two other pregnant women from France with tularemia were reported who had unsuccessful treatment with a macrolide (josamycin and azithromycin) [4]. Macrolides are not traditionally considered for treatment of North American ulceroglandular tularemia, which is most often caused by the more virulent *F. tularensis* subspecies *tularensis* (also known as *F. tularensis* type A). However, *in vitro* studies have demonstrated that *F. tularensis* subsp. *tularensis* is susceptible to azithromycin [5], with notably lower minimal inhibitory concentrations (MICs) than type B strains [6]. Additionally, in a study conducted by the CDC, 169 clinical isolates of North American *F. tularensis*, which included both type A and type B biovars, were all reported to be macrolide-susceptible, with MICs ranging from 0.5 to 4 (personal communication, Dr. Dirk Haslow, Arkansas Department of Health) [7]. This was contrasted against the Russian type B strain, in which the macrolide MIC was much higher, at 256 g/mL. In this pregnant patient, azithromycin was serendipitously effective in treating North American ulceroglandular tularemia.

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Correspondence: Robert W. Bradsher, MD, MACP, FIDSA, Division of Infectious Diseases, University of Arkansas for Medical Sciences, 4301 W Markham St, Mail Slot 639, Little Rock, AR 72205 (bradsherrobertw@uams.edu).

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**Figure 1.** A, Initial ulcer at site of puncture bite. B, Ulcer at day 9.



**Figure 2.** Resolution of ulcer at 4-week follow-up after treatment with azithromycin.

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**Table 1. Common Treatment Regimens in the United States for Tularemia and Treatment-Related Complications in Pregnancy**

Antibiotic	Pregnancy Category	Category Interpretation (From US FDA)	Distribution	Treatment Complications
Gentamicin	Category D	Evidence of risk	Crosses the placenta	Congenital deafness
Doxycycline	Category D	Evidence of risk	Crosses the placenta	Possible discoloration of teeth and enamel hypoplasia
Ciprofloxacin	Category C	Risk cannot be ruled out	Crosses the placenta	Teratogenicity observed in animal models, not observed in limited human studies
Levofloxacin	Category C	Risk cannot be ruled out	Crosses the placenta	Teratogenicity observed in animal models, not observed in limited human studies
Azithromycin	Category B	No evidence of risk in studies	Crosses the placenta	

Abbreviation: FDA, Food and Drug Administration.