

Tetracyclines for Treatment of Tularemia: A Case Series

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Tetracyclines for tularemia have been associated with higher failure rates. There were 48 cases of tularemia at the University of Missouri between 1988 and 2015. We retrospectively analyzed 17 patients with tularemia who were successfully treated with tetracyclines, and 9 of these patients also underwent aspiration or incision and drainage.

Keywords. relapse; tetracyclines; treatment failure; tularemia.

Tularemia is a zoonotic disease caused by the bacterium *Francisella tularensis*. In the United States, approximately 100–300 cases of tularemia are reported to the Centers for Disease Control and Prevention (CDC) annually, and most reported cases occurred in Missouri, Kansas, Arkansas, and Oklahoma over the last decade [1]. With a low infectious dose 50 of 10–25 organisms, *F tularensis* is a very infectious pathogen [2], which raises fears of its potential use as biological weapon [3]. Two subspecies of *F tularensis* cause tularemia in the United States: *F tularensis* subspecies *tularensis* (type A) and *F tularensis* subspecies *holarctica* (type B). Type A strains are more virulent than type B strains, and recent molecular studies have shown that genotype A1b may be significantly more virulent than A1a, A2, or type B strains [4].

Our current knowledge regarding treatment of tularemia is derived from case reports or case series. Treatment options include streptomycin, gentamicin, tetracyclines, and fluoroquinolones [1, 2]. Streptomycin has been considered the drug of choice for tularemia since Foshay and Pasternack [5] reported efficacy in 7 patients in 1946. However, streptomycin is difficult to obtain, and due to a shortage at the time, Enderlin et al

[6] gathered data about the efficacy of alternative agents for the treatment of tularemia in 1994. In that review, the cure rate for tetracycline was 88% (44 of 50) and the relapse rate was 12% (6 of 50). Three of the 6 patients who relapsed after treatment with tetracycline received less than 7 days of therapy, which, in addition to experiments in humans confirming a relationship between relapse and bacteriostatic action of tetracycline [7], led to recommendations by the CDC to prescribe tetracyclines for at least 14 days [1]. Likewise, the World Health Organization (WHO) recommends prescribing doxycycline for at least 15 days [2]. In a recent review of cases in Missouri, 13 patients were treated for at least 14 days with doxycycline alone or in combination with inappropriate antibiotics, and 2 (15%) of those patients had treatment failures [8]. We performed a retrospective analysis of the treatment of tularemia, based on our good experience with tetracyclines [9].

METHODS

We conducted a retrospective review of patients diagnosed with tularemia at the University of Missouri between May 1988 and June 2015. The Institutional Review Board of the University of Missouri approved this study. Patients with tularemia were identified through review of discharge diagnosis (*International Classification of Diseases, Ninth Revision* codes), the infection control department database (which included serology-based and culture-based diagnoses), and the microbiology laboratory database. Diagnosis of tularemia was based on WHO guidelines [2]. Patients with the diagnosis of presumptive tularemia (suggestive clinical symptoms and a clinical sample positive for tularemia by antigen or deoxyribonucleic acid detection or a single positive serology) and confirmed tularemia (culture-positive or paired serum specimens with a 4-fold difference in titer) who were treated with tetracyclines (tetracycline or doxycycline) were identified and included in the study. Determination of subspecies by culture or molecular testing was not done or was not available. Exclusion criteria included use of a non-tetracycline antibiotic active against tularemia, concomitant infection that could confound the determination of cure or relapse, and age below 8 years. Relevant clinical data included age, gender, type of tularemia (ulceroglandular, glandular, typhoidal, oculoglandular, oropharyngeal, pneumonic), month and/or year of presentation, means of diagnosis, need for admission to intensive care unit, prior antibiotic therapy, delay before initiation of tetracycline therapy, duration of tetracycline therapy, necessity for aspiration or incision and drainage, and outcome.

Cure was defined as resolution of all symptoms (eg, fever, lymphadenopathy, ulcer, conjunctivitis, respiratory symptoms)

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after completion of therapy. If aspiration or incision and drainage were required after initiation of tetracycline therapy, treatment was considered successful if patients were continued on tetracycline therapy after the procedure and met the definition of cure after treatment. Relapse was defined as recurrence of symptoms after resolution and completion of the initial course of tetracyclines. Follow-up information on cure and relapse was obtained from the chart or a telephone contact with patient or guardian; the timing of this follow up ranged from 1 year after the episode to several years later.

RESULTS

A total of 48 patients with diagnosis of tularemia were identified in the study period. After excluding (1) 20 patients who received non-tetracycline antibiotics active against tularemia (most of them treated with gentamicin alone, ciprofloxacin

alone, gentamicin/ciprofloxacin combination, or tetracycline combined with either gentamicin or ciprofloxacin, and 1 patient treated sequentially with chloramphenicol, streptomycin, and gentamicin), (2) 1 patient with a concomitant infection (*Staphylococcus aureus* bacteremia), and (3) 10 patients younger than 8 years of age, 17 patients were included in the study (Table 1). Tularemia was confirmed in 3 cases and 14 cases were presumptive. The median age was 42 years. The majority of the patients were male (52.9%). Most of the patients were diagnosed in April–October (88%). Seven patients (41%) had the glandular type, 6 patients (35%) had the ulceroglandular type, 3 patients (17.6%) had the typhoidal type, and 1 patient (6%) had the oculoglandular type. Several patients were hospitalized, but none of the patients required admission to the intensive care unit. Most of these patients (11 of 17, 65%) had received ineffective antibiotic therapy before presentation, commonly a β -lactam. An average of

Table 1. Characteristics of Patients With Tularemia Treated With Tetracyclines

Patient	Age	Sex	Year/Month of Diagnosis	Type of Tularemia	Diagnosis	Prior Antibiotic Therapy	Delay Before Tetracycline Therapy	Tetracycline Used/Duration of Therapy	Surgical Procedure ^a	Outcome
1	62	F	1988/November	Ulceroglandular	Single serology	Cephalexin, ceftriaxone	28 days	Tetracycline/10 days	Aspiration	Cure/no relapse
2	8	M	1991/June	Ulceroglandular	Single serology	Cephalexin, erythromycin	14 days	Doxycycline/21 days	Aspiration	Cure/no relapse
3	66	F	1994/August	Glandular	Single serology	None	Unknown	Doxycycline/28 days	Incision and drainage ^b	Cure/no relapse
4	76	F	1995/August	Ulceroglandular	Single serology	Clarithromycin, amoxicillin/clavulanic acid	28 days	Doxycycline/28 days	Incision and drainage	Cure/no relapse
5	42	M	1995/August	Glandular	Single serology	Unknown	21 days	Doxycycline/21 days	None	Cure/no relapse
6	37	M	1996/May	Ulceroglandular	Culture	Cloxacillin	10 days	Doxycycline/42 days	Aspiration ^c	Cure/no relapse
7	36	F	2000/May	Glandular	Culture	Cephalexin, clindamycin	21 days	Doxycycline/21 days	Incision and drainage ^d	Cure/no relapse
8	9	F	2001/May	Glandular	Single serology	Amoxicillin, cephalexin	28 days	Doxycycline/21 days	Aspiration	Cure/no relapse
9	46	M	2002/June	Typhoidal	Single serology	Amoxicillin/clavulanic acid	21 days	Doxycycline/14 days	None	Cure/no relapse
10	77	F	2002/July	Ulceroglandular	Single serology	None	56 days	Doxycycline/14 days	None	Cure/no relapse
11	91	F	2010/April	Oculoglandular	Culture	Vancomycin, ceftriaxone, metronidazole	7 days	Doxycycline/10 days	None	Cure/no relapse
12	19	M	2011/October	Glandular	Single serology	None	42 days	Doxycycline/14 days	Aspiration	Cure/no relapse
13	32	M	2012/August	Typhoidal	Single serology	None	Unknown	Doxycycline/21 days	None	Cure/no relapse
14	31	M	2012/August	Typhoidal	Single serology	None	Unknown	Doxycycline/21 days	None	Cure/no relapse
15	44	F	2013/January	Glandular	Single serology	Azithromycin	84 days	Doxycycline/14 days	None	Cure/no relapse
16	72	M	2014/October	Ulceroglandular	Single serology	Cephalexin, ceftriaxone, TMP-SMX	7 days	Doxycycline/21 days	Incision and drainage	Cure/no relapse
17	11	M	2015/August	Glandular	Single serology	Amoxicillin/clavulanic acid, cephalexin	10 days	Doxycycline/14 days	None	Cure/no relapse

Abbreviations: F, female; M, male; SMX, sulfamethoxazole; TMP, trimethoprim.

^aInitial procedures done before initiation of tetracycline or doxycycline therapy.

^bRequired repeat incision and drainage on day 14 of doxycycline.

^cRequired repeat aspiration on day 14 of doxycycline.

^dRequired aspiration on day 7 of doxycycline and incision and drainage on day 14 of doxycycline.

27 days had elapsed from the onset of symptoms to the first dose of a tetracycline. Median duration of oral tetracycline therapy was 21 days (range, 10–42 days). Except for 1 patient who was treated with 1 gram of tetracycline every 6 hours in 1988, the other 16 patients received 100 mg of doxycycline twice a day. Nine patients underwent either needle aspiration or incision and drainage of abscessed lymph nodes before initiation of tetracycline or doxycycline therapy. Three of those patients required a repeat aspiration or surgical drainage while on doxycycline therapy: the first patient required incision and drainage on day 14 of doxycycline and received 14 additional days of doxycycline after the procedure; the second patient required aspiration on day 14 of doxycycline and received 4 additional weeks of doxycycline after the procedure; the third patient required needle aspiration on day 7 of doxycycline, underwent incision and drainage on day 14 of doxycycline, and received 1 additional week of doxycycline after the procedure. All 17 patients were cured with no relapses.

DISCUSSION

Streptomycin and tetracyclines are the antibiotics approved by the US Food and Drug Administration (FDA) for treating tularemia. The CDC [1] and WHO [2] recommend aminoglycosides (streptomycin if available or gentamicin) for severe tularemia and tetracyclines or fluoroquinolones for less severe cases. Aminoglycosides are given parenterally and can be ototoxic and nephrotoxic. Tetracyclines and fluoroquinolones have a better toxicity profile and can be given orally. If tetracyclines are used, both guidelines recommend at least 14–15 days of therapy to reduce the risk of relapse due to their bacteriostatic nature. Fluoroquinolones are not FDA approved for treatment of tularemia, but several studies have shown bactericidal activity in vitro and in animal models [10, 11], and good efficacy in humans [8, 12–14], as well as lower therapeutic failure rates when compared with doxycycline [12, 14].

In our study, all of the patients were cured, and none relapsed after treatment with tetracycline or doxycycline. Except for 1 patient who received tetracycline in 1988, all patients received doxycycline, which, in general, has replaced tetracycline due to pharmacokinetic reasons [2]. More importantly, 9 patients (53%) underwent aspiration or incision and drainage of abscessed lymph nodes before initiation of therapy, and 3 patients required repeat procedure while on doxycycline. Doxycycline therapy was not changed after the repeat procedures in these 3 patients, but it was extended for an additional 1 to 4 weeks. The median duration of 21 days was longer than the minimum recommended; 7 of the 9 patients (78%) who required any surgical procedure received at least 21 days of therapy.

Our experience with tetracyclines contrasts with the relapse rate of 15% reported by Weber et al [8], 42.8% reported by Pérez-Castrillón et al [12], and 49% reported by Meric et al [14]. Pérez-Castrillón et al [12] found an association between therapeutic failure and use of tetracyclines as initial treatment and with the ulceroglandular clinical form of disease. In the study by Meric

et al [14], all the patients had oropharyngeal tularemia, and a treatment delay of more than 2 weeks was associated with therapeutic failure. In our series, the ulceroglandular form represented 35% of the cases, there were no cases of oropharyngeal tularemia, and the average delay before appropriate treatment was 27 days.

The retrospective design of the study and the small number of patients are limitations of this study. In addition, we cannot rule out the possibility of selection bias if tetracyclines were prescribed because the disease severity was judged to be low. Further prospective controlled studies are needed to establish the most efficacious and convenient antibiotic therapy for tularemia, including severe cases. Information about subspecies or subpopulations in each treatment group may also provide valuable insight because different strains have different virulence and effect on outcomes [4].

CONCLUSIONS

In conclusion, therapeutic failure was not observed after treatment of tularemia with tetracyclines along with prompt attention to drainage of abscessed lymph nodes. Duration of therapy of 21 days appears to be effective, particularly if aspiration or incision and drainage procedures are needed.

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Potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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