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Sub-optimal adherence to doxycycline and treatment outcomes among men with non-gonococcal urethritis: a prospective cohort study

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Abstract

Objective—Doxycycline, one of two recommended therapies for non-gonococcal urethritis (NGU), consists of a seven-day course of therapy (100mg BID). Since suboptimal adherence may contribute to poor treatment outcomes, we examined the association between self-reported imperfect adherence to doxycycline and clinical and microbiologic failure among men with NGU.

Methods—Men aged ≥16 years with NGU attending a Seattle, WA sexually transmitted diseases clinic were enrolled in a double-blind, parallel-group superiority trial from January 2007 to July 2011. Men were randomized to active doxycycline/placebo azithromycin or placebo doxycycline/active azithromycin. Imperfect adherence was defined as missing ≥1 dose in 7 days. Urine was tested for *Chlamydia trachomatis* (CT), *Mycoplasma genitalium* (MG), and *Ureaplasma urealyticum*-biovar2 (UU-2) using nucleic acid amplification tests. Clinical failure (symptoms and ≥5 PMNs/HPF or discharge) and microbiologic failure (positive tests for CT, MG, and/or UU-2) were determined after 3-weeks.

Results—184 men with NGU were randomized to active doxycycline and provided data on adherence. Baseline prevalence of CT, MG, and UU-2 was 26%, 13%, and 27%, respectively.

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CONTRIBUTORS

Authors contributed to the manuscript (MS) in the following manner. Clinical trial concept and design: LEM, PAT, MRG. Conduct of clinical trial: LEM, CWG, MSL. Study design: LEM, CMK. Analysis and interpretation of data: CMK, LEM, DVC, CWG. Drafting of the MS: CMK. Critical revision of the MS: CMK, LEM, DVC, CWG, MSL, PAT, MRG, JMS. Statistical analysis of the MS: CMK.

COMPETING INTERESTS

The authors have no competing interests to report.

28% of men reported imperfect adherence and this was associated with microbiologic failure among men with CT (aRR=9.33; 95% CI=1.00–89.2) and UU-2 (aRR=3.08; 95% CI=1.31–7.26) but not MG. Imperfect adherence was not significantly associated with clinical failure overall or for any specific pathogens, but it was more common among imperfectly adherent men with CT (aRR=2.63; 0.93–7.41, p=0.07).

Conclusions—Adherence may be important for microbiologic cure of select pathogens. Factors other than adherence should be considered for CT-negative men with persistent NGU.

Keywords

Chlamydia infection; adherence; doxycycline; *Ureaplasma urealyticum*-biovar2; urethritis

INTRODUCTION

Standard therapy for men with nongonoccocal urethritis (NGU) and women with cervicitis consists of either seven days of doxycycline (100mg twice daily) or a single 1g dose of azithromycin[1]. Both therapies are considered equally efficacious in the treatment of chlamydial infections[2], which are responsible for nearly a quarter of urethritis and cervicitis cases. However, clinical cure rates appear to be declining over time[3–5] and the standard treatment regimens have been less effective against emerging etiologies of NGU[4–7]. The reason for these declining clinical cure rates is unknown, but treatment failure, reinfection, and poor adherence to therapy likely all contribute to some extent. Although adherence is of less relevance for azithromycin since it is typically given as directly observed therapy, it may play a role in the lower cure rates observed with the use of doxycycline.

Despite the presumed importance of adherence to doxycycline for clinical outcomes, adherence to antibiotic therapy for bacterial sexually transmitted diseases (STDs) is little studied. The few investigations that have examined the effectiveness of doxycycline against NGU have reported a wide range (25% to 100%) of adherence estimates[4, 6, 8–11]. Therefore, the extent to which adherence contributes to clinical outcomes among doxycycline-treated patients with NGU remains unclear.

In a secondary analysis of data from a randomized, controlled trial of men with NGU, we examined the association between doxycycline adherence and treatment outcomes. We hypothesized that men who were imperfectly adherent to the doxycycline regimen would demonstrate higher clinical and microbiologic failure compared to adherent men.

METHODS

Study Design and Population

Details of the study design, population, and data collection methods have been previously described[5]. Briefly, from January 2007 to July 2011, men presenting at a Seattle, WA STD clinic were recruited for participation in a treatment trial for NGU. Eligible participants had NGU, defined as visible urethral discharge or ≥5 polymorphonuclear leukocytes (PMNs) per high-powered field (HPF), were ≥16 years of age, and reported no antibiotic use in the

previous month. Men were randomized 1:1 to receive one of two pre-packaged treatments: (1) doxycycline, 100 mg administered orally twice daily for 7 days and azithromycin placebo, single dose (two or four tablets formulated to look identical to 1g azithromycin), administered orally; or (2) azithromycin, 1g as a single dose (two 500mg or four 250mg tablets), administered orally and doxycycline placebo administered orally twice daily for 7 days (14 capsules formulated to look identical to the active doxycycline capsules). Clinical and sexual history data collected at enrollment were obtained by a single study clinician (M.S.L.). A computer assisted self-interview (CASI) collected additional demographic and behavioral data, and a standardized log was used to collect information on medication side effects including diarrhea, nausea, vomiting, and rash, as well as sexual activity, condom use, and adherence to study medication.

All microbiologic tests were performed on urine. We used the APTIMA TMA assay to detect *Chlamydia trachomatis* (GenProbe, Inc., San Diego, CA). *Mycoplasma genitalium* was assessed by in-house PCR[12] and *Ureaplasma urealyticum*-biovar 2 was detected in broth urine culture followed by species-specific PCR[13, 14]. Men were considered to have idiopathic NGU if they were negative for *C. trachomatis, M. genitalium, U. urealyticum*-biovar 2 and *T. vaginalis* (*Ureaplasma parvum*-positive men were considered idiopathic).

Men returned to the clinic three weeks post-enrollment (allowable window = 2–5 weeks) for a clinical exam and completion of a follow-up CASI to obtain medication adherence and behavioral information. Clinical failure was defined as self-reported urethral symptoms (dysuria, discharge, itching, tingling) and ≥5 PMNs/HPF or clinical signs of visible urethral discharge. Microbiologic failure was defined as a positive nucleic acid amplification test (NAAT) for the baseline infecting pathogen. Analyses were restricted to men who were randomized to doxycycline, met a restricted definition of NGU at enrollment (self-reported urethral symptoms or clinical signs of visible urethral discharge PLUS ≥5 PMNs/HPF), returned for the follow-up visit, and completed both adherence measures (described below).

Adherence classification

Two methods were used to capture self-reported doxycycline adherence: a paper standardized log and a CASI completed at follow-up. The purpose of the log was to encourage adherence to doxycycline and improve accurate reporting on the CASI. All men were asked to record the dates and times (morning and evening) that they took the doxycycline/doxycycline placebo on the standardized log. The study clinician pre-populated the log with the dates pertaining to the period between enrollment and the follow-up visit; dates outside of the appropriate window (i.e., 7 days after enrollment) were grayed out to encourage dosing within the correct window. Men were instructed to return the log at the follow-up visit. Those who did not return the log at follow-up were given a stamped, addressed envelope and asked to return it via postal mail. The CASI administered to participants during the follow-up visit asked the following two yes/no questions: “Did you take all of the pills you were given at, or since, your last study visit” and “Did you take the pills exactly according to the dosage instructions (1 pill in the morning and 1 pill at night)?”

Using reports from both the log and CASI, we generated a composite adherence measure to classify men as adherent if they reported taking two pills per day for seven days on the log

and responded in the affirmative to the two adherence questions on the CASI. Men were classified as non-adherent if they reported imperfect adherence on either the log, CASI, or both methods. Using this definition, men who missed at least one dose within 7 days were classified as non-adherent.

We created our adherence measure in this way for several reasons. First, work in the field of adherence to antiretroviral therapy for HIV infection suggests that combining adherence measures may better predict clinical outcomes[15]. Second, ceiling effects[16], wherein the vast majority of individuals report being adherent, are often present in self-reported adherence measurement. This high reporting of adherence often reflects the respondents' desire to provide the 'correct' response, and may not be accurate. Third, due to the high specificity of self-reported adherence measures (i.e., a patient's report of non-adherence is usually reliable)[17], we hypothesized that a report of non-adherence on either method indicated that the individual was truly non-adherent.

Statistical Analysis

Pearson's chi-square tests were used to compare the demographic and clinical characteristics of adherent versus non-adherent men. We used Poisson regression models with a log link and robust standard errors[18] to estimate the relative risk of clinical and microbiologic failure at follow-up associated with self-reported imperfect adherence, for NGU in aggregate and by infecting pathogen at enrollment. Models were adjusted for self-reported unprotected sex between visits and results are reported as adjusted relative risks (RR) with 95% confidence intervals (CI). Because only 3% of participants were missing data for the adjustment variable (unprotected sex between visits), multivariate analyses only included participants with no missing data (i.e., complete-case analysis). Analyses were performed using Stata statistical software (Version 12.1; StataCorp, College Station, TX). All tests were performed at a significance level (α) of 0.05. Study procedures and analyses were approved by the University of Washington Human Subjects Division.

RESULTS

A total of 606 men with NGU were enrolled in the parent clinical trial. Fifty percent of enrolled men (302 of 606) were randomized to doxycycline of whom 86% (260 of 302) met the revised definition of NGU. Of those, 79% (206 of 260) returned for follow-up. Eighty-nine percent (184 of 206) completed the relevant adherence questions on the standardized log and follow-up CASI and are included in this analysis.

Twenty-eight percent of men (51 of 184) were classified as non-adherent. Of these, 43% (n=22) missed ≥1 dose during the one-week regimen but took it at a later date, and 25% (n=13) missed ≥1 dose completely. Characteristics of the analytic sample and the association with doxycycline adherence are described in Table 1. Fifty-eight percent of men were less than 35 years of age, approximately 60% were white, and one-third reported a history of NGU. Age, race/ethnicity, education, history of NGU and severity of clinical signs were not associated with adherence. A higher proportion of non-adherent men reported experiencing side effects (49.0%) compared to adherent men (35.3%), but the difference was not statistically significant (p=0.09). Of the 25 non-adherent men who reported side effects, only

2 (8%) reported stopping medication because of perceived side effects. Among all non-adherent men, the most frequent reasons for imperfect adherence included forgetting to take medication (12%) and resolution of symptoms (8%). Most men (>70%) indicated an "other" (non-specified) reason for imperfect adherence (data not shown).

Overall, 21% (39 of 184) of men experienced clinical failure at follow-up (Table 2). Among men with *C. trachomatis*, those reporting non-adherence were approximately 2.6 times more likely to experience clinical failure compared to those who were perfectly adherent, although this was of borderline statistical significance (p=0.07). Likelihood of clinical failure at follow-up did not differ significantly between non-adherent and adherent men for any other specific etiology of urethritis, or for NGU overall.

Among men infected with *M. genitalium*, *C. trachomatis*, or *U. urealyticum* biovar-2 at baseline, 69.6% (16 of 23), 6.4% (3 of 47) and 29.2% (14 of 48), respectively, experienced microbiological failure at follow-up. Of these, the prevalence of clinical cure was 38% (6 of 16) among *M. genitalium*-infected men, 67% (2 of 3) among *C. trachomatis*-infected men, and 79% (11 of 14) among *U. urealyticum*-biovar 2-infected men (data not shown).

Adjusting for unprotected sex between visits, microbiologic failure among men with *C. trachomatis* was 9-fold higher among men who were non-adherent compared to those who were adherent (aRR=9.33; 95% CI=1.00–89.2, p=0.05; Table 2). Similarly, among men with *U. urealyticum*-biovar 2 at baseline, those who reported non-adherence were approximately three times as likely to experience microbiologic failure compared to adherent men (aRR=3.08; 95% CI=1.31–7.26, p=0.01). Persistent infection with *M. genitalium* was not significantly associated with adherence.

DISCUSSION

Self-reported non-adherence to doxycycline among these men with NGU was 28% and was significantly associated with an increased likelihood of microbiologic failure among *C. trachomatis* and *U. urealyticum*-biovar 2-infected men. Although men with *C. trachomatis* who reported imperfect adherence were also somewhat more likely to experience clinical failure, non-adherence was not significantly associated with clinical failure overall or that related to *M. genitalium* or U. *urealyticum*-biovar 2.

The proportion of men reporting non-adherence to doxycycline in this trial (28%) is similar to observations from other studies of self-reported adherence[6, 9], but lower than that found in studies using more objective adherence measures, such as Medication Event Monitoring System (MEMS) caps[10, 11]. Consistent with other investigations[9–11, 19], we did not identify any sociodemographic characteristics that were associated with adherence, nor did we identify a main barrier to non-adherence. Although self-reported perfect adherence was somewhat lower among men who reported side effects compared to men who did not report side effects, fewer than 8% of non-adherent men attributed their suboptimal adherence to side effects.

Among men infected with *C. trachomatis* at enrollment, 20% of non-adherent men had *C. trachomatis* detected at follow-up compared to less than 3% of adherent men, resulting in a

nine-fold higher risk of microbiologic failure. This is similar to a study by Bachmann et al. [11], where 25% (3 of 12) of non-adherent patients with *C. trachomatis* experienced microbiologic failure at follow-up. Together, these findings suggest that poor adherence to therapy for chlamydia may play a role in doxycycline treatment failure. Similarly, we noted that non-adherent men with *U. urealyticum*-biovar 2 at enrollment were approximately three times as likely to experience microbiologic failure compared to adherent men. For men with *U. urealyticum*-biovar 2, it is possible that insufficient bacterial eradication may result in persistent urethritis if not re-treated; however this has not been well-studied and is an important area of future research.

Although adherence appeared to significantly affect microbiologic failure of men with *C. trachomatis* and *U. urealyticum*-biovar 2, we only observed a modest increase in microbiologic failure among non-adherent men with *M. genitalium*. This, coupled with the relatively high overall failure rate among men with *M. genitalium* who received doxycycline (70%) suggests that adherence to a doxycycline regimen plays a limited role in the clearance of this pathogen.

Despite the large and significant association we observed between adherence and microbiologic failure for *C. trachomatis*-infected men, the association with clinical cure was smaller and of borderline statistical significance. Furthermore, we did not observe any association between non-adherence and clinical failure overall or among men with *M. genitalium* or *U. urealyticum*-biovar 2. There are a number of possible explanations for this. First, because we employed nucleic acid amplification testing (NAAT), it is possible that men continued to shed residual bacterial DNA in the absence of viable organisms resulting in a positive test, despite resolution of clinical signs and/or symptoms. However, men with *C. trachomatis* in this analysis returned for follow-up an average of 22 days after their initial positive test in accordance with repeat testing guidelines[20], decreasing the probability of detecting non-viable bacteria. Additionally, all PCR testing of *U. urealyticum*-biovar 2 specimens followed growth on culture, thus men with microbiologic failure had viable bacteria present in the urethra, again suggesting detection of non-viable organisms does not explain the conflicting results. Second, the timing of resolution of clinical signs and symptoms may not be correlated with bacterial clearance for some men. In this population, over one-half of men who experienced microbiologic failure at follow-up were considered clinically cured. Thus, adherence to doxycycline may translate to better clinical outcomes in the short-term among men infected with pathogens that may or may not be sensitive to the prescribed doxycycline regimen. Third, given the low frequency of clinical failure (21%) that we observed, it is possible that the full 7-day duration of the doxycycline regimen may not be required to eliminate symptoms. Since the minimum dose of doxycycline that results in clinical and microbiologic cure among men with NGU is currently unknown, it is possible that fewer doses or incomplete regimens are sufficient for clinical but not microbiologic cure. However, this merits further investigation.

This study has several limitations. First, since adherence on both the CASI and daily log were self-reported, they are subject to social desirability and recall bias (relevant to the CASI only), and may be over-estimates of actual adherence[11]. Although our composite adherence measure attempted to correct for this by classifying men as non-adherent if they

reported non-adherence on either the daily log *or* the CASI, the validity of our measure is unknown and there likely remained some residual misclassification. Second, the high proportion of self-reported adherence in this study prohibited us from conducting meaningful additional analyses using alternate definitions of adherence (e.g., taking 80% of doses within 7 days). A different adherence definition may have provided different results. Third, we did not evaluate the "permanence" of clinical failure; therefore the extent to which imperfect adherence portends long-term persistent, symptomatic infection is unknown. Fourth, self-reported adherence via CASI or log was not captured on approximately 10% of men randomized to doxycycline who returned for follow-up and these men may have differed from those who provided complete data. Fifth, medication adherence in a clinical trial is optimized and not likely to reflect adherence in non-research settings. Finally, the relatively small pathogen-specific sample sizes resulted in low statistical power (8%–60%) to detect a difference in failure rates for *M. genitalium*- and *C. trachomatis*-infected men, and low precision of estimated effects.

In this study population, suboptimal adherence to doxycycline was significantly associated with microbiologic failure among men with *C. trachomatis* and *U. urealyticum*-biovar 2. Given that approximately 20% of men were non-adherent, coupled with the relatively high proportion of NGU cases attributed to *C. trachomatis* and possibly to *U. urealyticum*-biovar 2, suboptimal adherence to doxycycline may be an important contributing cause in men with persistent infection. However, the lack of association between clinical cure and adherence among *C. trachomatis*-negative men suggests that declines in the efficacy of doxycycline for clinical outcomes may be the result of factors other than poor adherence. Nonetheless, in regions of the country where the efficacy of azithromycin against *C. trachomatis* may be waning[4] and clinicians may be more inclined to prescribe doxycycline, counseling patients who receive doxycycline on the importance of adherence should be a priority.

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Table 1

Demographic and clinical characteristics associated with self-reported adherence to doxycycline, among men with NGU participating in a clinical trial (N=184)*

	Total N = 184	Adherent N = 133	Non-adherent N = 51	P-value†
Characteristic	**N (%)**	**N (%)**	**N (%)**	
Age				
16–24	34 (18.5)	28 (21.1)	6 (11.8)	
25–34	72 (39.1)	48 (36.1)	24 (47.1)	
35–44	51 (27.7)	37 (27.8)	14 (27.5)	
≥ 45	27 (14.7)	20 (15.0)	7 (13.7)	
Race/Ethnicity				0.93
White, non-Hispanic	109 (59.2)	80 (60.2)	29 (56.9)	
Black, non-Hispanic	51 (27.7)	37 (27.8)	14 (27.5)	
Other, non-Hispanic	15 (8.2)	10 (7.5)	5 (9.8)	
Hispanic	9 (4.9)	6 (4.5)	3 (5.9)	
Education				0.40
≤ High School	75 (41.0)	52 (39.1)	23 (46.0)	
> High School	108 (59.0)	81 (60.9)	27 (54.0)	
History of NGU				0.92
Yes	58 (32.8)	41 (32.5)	17 (33.3)	
No	119 (67.2)	85 (67.5)	34 (66.7)	
NGU etiology at enrollment				
M. genitalium	23 (12.6)	15 (11.4)	8 (15.7)	0.43
C. trachomatis	47 (25.5)	37 (27.8)	10 (19.6)	0.73
U. urealyticum	48 (27.3)	34 (26.6)	14 (29.2)	0.25
Idiopathic	76 (41.3)	54 (40.6)	22 (43.1)	0.76
Urethral discharge at enrollment				0.58
Yes	166 (90.2)	119 (89.5)	47 (92.2)	
No	18 (9.8)	14 (10.5)	4 (7.8)	
Urethral discharge amount				0.18
Small	91 (55.2)	67 (56.8)	24 (51.1)	
Moderate	65 (39.4)	47 (39.8)	18 (38.3)	
Large	9 (5.5)	4 (3.4)	5 (10.6)	
Urethral discharge character				0.12
Clear	67 (42.1)	52 (46.0)	15 (32.6)	
Cloudy	84 (52.8)	54 (47.8)	30 (65.2)	
Purulent	8 (5.0)	7 (6.2)	1 (2.2)	
Side effects‡				0.09
Yes	72 (39.1)	47 (35.3)	25 (49.0)	

	Total N = 184	Adherent N = 133	Non-adherent N = 51	P-value†
Characteristic	**N (%)**	**N (%)**	**N (%)**	
No	112 (60.9)	86 (64.7)	26 (51.0)	

NGU, non-gonococcal urethritis

*Due to missing values, numbers may not sum to column total

†From Pearson's chi-square test

‡Reported on daily log. Includes any report of nausea, vomiting, diarrhea, or rash

Table 2

Clinical and microbiologic failure of non-adherent versus adherent men with NGU participating in a clinical trial, by NGU etiology at enrollment (N=184)

Outcome	Non-adherent no./Total no. (%)*	Adherent no./Total no. (%)*	Adjusted† Relative Risk (95% CI)	P-value‡
Clinical failure				
All participants	13/51 (25.5)	26/133 (19.5)	1.13 (0.60 – 2.11)	0.71
M. genitalium	3/8 (37.5)	7/15 (46.7)	0.69 (0.25 – 1.87)	0.46
C. trachomatis	5/10 (50.0)	6/37 (16.2)	2.63 (0.93 – 7.41)	0.07
U. urealyticum	3/14 (21.4)	8/34 (23.5)	0.87 (0.27 – 2.83)	0.82
Idiopathic	3/22 (13.6)	7/54 (13.0)	0.83 (0.20 – 3.49)	0.80
Microbiologic failure				
M. genitalium	6/8 (75.0)	10/15 (66.7)	1.25 (0.75 – 2.08)	0.39
C. trachomatis	2/10 (20.0)	1/37 (2.7)	9.33 (1.00 – 89.2)	0.05
U. urealyticum	8/14 (57.1)	6/34 (17.6)	3.08 (1.31 – 7.26)	0.01

NGU, non-gonococcal urethritis; CI, confidence interval

* no./Total no. = number of men with failure/total number who reported being adherent or non-adherent, for each row

† Adjusted for unprotected sex between visits. Adherent is the referent category.

‡ From Poisson regression models