Standard Treatment Regimens for Nongonococcal Urethritis Have Similar but Declining Cure Rates: A Randomized Controlled Trial

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Background. Azithromycin or doxycycline is recommended for nongonococcal urethritis (NGU); recent evidence suggests their efficacy has declined. We compared azithromycin and doxycycline in men with NGU, hypothesizing that azithromycin was more effective than doxycycline.

Methods. From January 2007 to July 2011, English-speaking males ≥16 years, attending a sexually transmitted diseases clinic in Seattle, Washington, with NGU (visible urethral discharge or ≥5 polymorphonuclear leukocytes per high-power field [PMNs/HPF]) were eligible for this double-blind, parallel-group superiority trial. Participants received active azithromycin (1 g) + placebo doxycycline or active doxycycline (100 mg twice daily for 7 days) + placebo azithromycin. Urine was tested for Chlamydia trachomatis (CT), Mycoplasma genitalium (MG), Ureaplasma urealyticum biovar 2 (UU-2), and Trichomonas vaginalis (TV) using nucleic acid amplification tests. Clinical cure (<5 PMNs/HPF with or without urethral symptoms and absence of discharge) and microbiologic cure (negative tests for CT, MG, and/or UU-2) were determined after 3 weeks.

Results. Of 606 men, 304 were randomized to azithromycin and 302 to doxycycline; CT, MG, TV, and UU-2 were detected in 24%, 13%, 2%, and 23%, respectively. In modified intent-to-treat analyses, 172 of 216 (80%; 95% confidence interval [CI], 74%–85%) receiving azithromycin and 157 of 206 (76%; 95% CI, 70%–82%) receiving doxycycline experienced clinical cure (P = .40). In pathogen-specific analyses, clinical cure did not differ by arm, nor did microbiologic cure differ for CT (86% vs 90%, P = .56), MG (40% vs 30%, P = .41), or UU-2 (75% vs 70%, P = .50). No unexpected adverse events occurred.

Conclusions. Clinical and microbiologic cure rates for NGU were somewhat low and there was no significant difference between azithromycin and doxycycline. Mycoplasma genitalium treatment failure was extremely common.

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Keywords. urethritis; treatment; Mycoplasma genitalium; Chlamydia trachomatis; randomized trial.
cases (16%–26%) [4–6]. Although NGU rarely results in serious sequelae in men, persistent or recurrent urethritis is common [7], and many female sex partners are at risk for complications [8]. Effective treatment of NGU, therefore, is a key component of male and female reproductive health.

The Centers for Disease Control and Prevention (CDC) treatment guidelines recommend azithromycin or doxycycline for NGU [9]. In the mid-1990s a randomized trial found the 2 treatments to be comparably effective against NGU caused by C. trachomatis and undifferentiated Ureaplasm species [10], and single-dose azithromycin became the preferred therapy in many settings. It has also been consistently more effective than doxycycline against M. genitalium [11]. However, a recent multicenter trial found that azithromycin was significantly less effective than doxycycline in eradicating C. trachomatis [12], and reports of azithromycin resistance in M. genitalium have been increasing [13].

We conducted a double-blind randomized trial testing the efficacy of azithromycin versus doxycycline against NGU, with a focus on M. genitalium and U. urealyticum biovar 2. We hypothesized that azithromycin would be more effective than doxycycline.

METHODS

Design

This was a single-center, double-blind, parallel-group superiority trial. Men with NGU were enrolled by a single study clinician (M.S.L.) and assigned to the intervention or control group using 1:1 randomization.

Setting and Participants

English-speaking males aged ≥16 years, attending the Public Health–Seattle & King County STD clinic in Seattle, Washington, possessing valid contact information were eligible. Men with visible urethral discharge on examination or ≥5 polymorphonuclear leukocytes per high-power field (PMNs/HPF) on a Gram-stained slide of urethral exudates were included. Men who had received antibiotics in the past month or had allergies to study drugs were excluded.

Men with urethral symptoms or signs were referred to the study clinician who assessed eligibility and obtained informed consent. Participants completed a brief computer-assisted self-interview and underwent a routine STD exam during which 2 urethral swab samples were obtained. The first was used for Gram staining and quantitation of PMNs if not done before referral; the second was stored for future testing. Men also provided 25 mL of first-void urine for nucleic acid amplification tests (NAATs) and culture. After examination, men were given a treatment packet and a symptom/coital log to collect daily information on completion of therapy, symptoms, medication side effects, and sexual activity, and were scheduled to return in 3 weeks.

Randomization and Intervention

Randomization and blinding were managed by the Harborview Medical Center Investigational Drug Service (HMC IDS), using Excel to generate the random sequence in blocks of 10. HMC IDS prepared sequentially numbered treatment packets in sealed opaque envelopes; treatment arm was assigned when the clinician gave the patient the next numbered packet in the sequence. All patients, clinicians, and study staff were blinded to treatment assignment until the end of the trial.

The azithromycin group received 1 g of active azithromycin (either 500-mg tablets × 2 or 250-mg tablets × 4), plus 14 placebo doxycycline capsules (100-mg capsules twice daily for 7 days) identical in appearance to the active doxycycline. The doxycycline group received placebo azithromycin tablets identical in appearance to the active drug, plus 14 active doxycycline capsules. Azithromycin tablets (active and placebo) were administered under clinician observation. Patients were instructed to take 1 doxycycline capsule (active or placebo) the evening of their enrollment visit, and 1 each morning and each evening until they were completed.

Follow-up

At the 3-week follow-up visit (allowable window = 2–5 weeks), men underwent examination and specimen collection, turned in their symptom/coital log, and completed a second comput-er-assisted self-interview. Men with M. genitalium or Ureaplasm species at enrollment and recurrent/persistent NGU or a repeat positive test received the alternate regimen (eg, active azithromycin plus placebo doxycycline if they first received active doxycycline and vice versa) and were scheduled for another visit 6 weeks after enrollment (data not shown). Others with recurrent/persistent NGU were unblinded and treated according to clinic standard of care with no further study visits.

Protocol Modifications

All changes to the protocol occurred early in the trial, after institutional review board approval and prior to study unblinding. Initially, the primary outcome was microbiologic cure of M. genitalium and only M. genitalium–positive men were followed. Enrollment began on 1 January 2007. On 4 May 2007 we began asking all men to return for a 3-week follow-up visit and added testing for Ureaplasm species. Eligibility criteria were modified to include human immunodeficiency virus (HIV)–positive individuals (2 May 2008) and explicitly exclude men taking medications contraindicated for the study drugs (2 September 2008). Beginning 10 September 2010, men with M. genitalium who required therapy at follow-up
were offered moxifloxacin (400 mg/day × 7 days) rather than
the alternate regimen, given low M. genitalium cure rates re-
vealed at interim analyses. To facilitate comparisons with
other trials, in modified intent-to-treat (mITT) analyses we
revised the inclusion criteria to “self-reported urethral symp-
toms (dysuria, discharge, itching, tingling) or clinical signs of
visible urethral discharge plus ≥5 PMNs/HPF.”

Outcomes
The primary outcome was clinical cure of NGU after 3 weeks,
deﬁned as <5 PMNs/HPF (with or without urethral symp-
toms) and absence of urethral discharge. We evaluated 7 sec-
ondary outcomes: clinical and microbiologic cure after 3
weeks among men with C. trachomatis, M. genitalium, and
U. urealyticum biovar 2, and clinical cure for idiopathic NGU
(negative for all pathogens). Ureaplasma parvum–positive
men were considered to have idiopathic disease. Microbiologic
cure was deﬁned as a negative NAAT for the baseline infecting
pathogen.

All tests were performed on urine. We used the APTIMA
transcription-mediated ampliﬁcation assay for C. trachomatis
and Neisseria gonorrhoeae and analyte-speciﬁc reagents on the
same platform for Trichomonas vaginalis (GenProbe, Inc, San
Diego, California). Mycoplasma genitalium was assessed by
in-house polymerase chain reaction (PCR) [14]; Ureaplasma
species were detected in broth urine culture followed by
species-speciﬁc PCR [6, 15].

Statistical Methods
The sample size was estimated for the original primary
outcome of microbiologic cure of M. genitalium. Assuming
α = .05 and failure rates of 8% for azithromycin and 33% for
doxycycline [16, 17], a total of 45 M. genitalium–positive men
per arm would provide 85% power to detect a difference of 25
percentage points. We assumed 12% prevalence of M. genital-
um and 20% loss to follow-up, requiring 900 men with
NGU.

One interim assessment was performed after half of the
target sample of M. genitalium–positive men (n = 45) had
been enrolled and completed all 3 scheduled visits (data
accrued 2 January 2007–30 October 2009). Using the O’Brien-
Fleming stopping rule [18], the level of signiﬁcance was
0.0052. Upon review, the data safety and monitoring board
noted that interim differences in treatment were too small to
observe a signiﬁcant difference and expressed concern over
low cure rates for M. genitalium. They advised 1 additional
year of recruitment to further investigate apparent high rates of
antimicrobial resistance.

An intent-to-treat (ITT) analysis included all randomized
men. An mITT analysis excluded men who did not meet the
revised mITT inclusion criteria and/or did not return for
follow-up. We used Pearson χ² test (2-sided P value) to iden-
tify statistically signiﬁcant differences in treatment outcomes,
calculating exact binomial conﬁdence intervals.

Assuming that men whose symptoms persisted would be
more likely to return, participants who were lost to follow-up
were considered clinically cured in ITT analyses. Men who re-
turned earlier than 2 weeks before their scheduled visit were
classiﬁed as “always” cured. The data safety and monitoring board
recommended stopping the alternate regimen, given low
mITT cure rates after interim assessment. The mITT analysis ex-
cluded 123 men who did not return for follow-up and 61
men who did not meet revised inclusion criteria (13 had <5
PMNs, 8 had no discharge or symptoms). Among the
304 men randomized to azithromycin, 245 (81%) returned for
follow-up, of whom 29 (12%) did not return according to
protocol. The mITT population consisted of 206 men randomized
to doxycycline and 216 men randomized to azithromycin.

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to doxycycline and 216 men randomized to azithromycin. We
excluded 123 men who did not return for follow-up and 61
men who did not meet the revised inclusion criteria (sympto-
toms or visible discharge plus ≥5 PMNs/HPF). Among the
304 men randomized to azithromycin, 245 (81%) returned for
follow-up, of whom 29 (12%) did not return according to
protocol. The mITT population consisted of 206 men randomized
to doxycycline and 216 men randomized to azithromycin (Figure 1).

RESULTS
From 1 January 2007 through 31 July 2011 (end of funding
period), 1716 men were assessed for eligibility. Of these, 606
met inclusion criteria, agreed to participate, and constituted
the ITT population: 304 men were randomized to active
azithromycin + placebo doxycycline and 302 were randomized
to active doxycycline + placebo azithromycin (Figure 1).

The mITT population consisted of 206 men randomized
to doxycycline and 216 men randomized to azithromycin. We
excluded 123 men who did not return for follow-up and 61
men who did not meet the revised inclusion criteria (sympto-
toms or visible discharge plus ≥5 PMNs/HPF). Among the
304 men randomized to azithromycin, 245 (81%) returned for
follow-up, of whom 29 (12%) did not meet revised inclusion
criteria (21 had <5 PMNs, 8 had no discharge or symptoms). Of
the 302 men randomized to doxycycline, 238 (79%) re-
turned for follow-up, 32 (13%) of whom did not meet revised
inclusion criteria (28 had <5 PMNs, 4 had no discharge or

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symptoms). All 3-week follow-up visits were completed by 31 August 2011.

Characteristics of the 606 men in ITT analyses were similar by study arm (Table 1). Mean age was 33.7 years and the majority was white (55%). Half (53%) presented with symptoms of urethral discharge, 51% complained of dysuria, and 26% reported other urethral symptoms. *Chlamydia trachomatis* and *U. urealyticum* biovar 2 were most commonly detected (23%–24% each), followed by *M. genitalium* (13%). Fifteen men (2.5%) were HIV-positive.

Characteristics of the 422 men in mITT analyses also did not differ by study arm and were similar to the ITT group, although the prevalences of *M. genitalium* and *U. urealyticum* biovar 2 were slightly higher in the mITT group.

Clinical Cure

In mITT analyses (primary outcome), 172 of 216 men (80%; 95% confidence interval [CI], 74%–85%) receiving azithromycin experienced clinical cure versus 157 of 206 (76%; 95% CI, 70%–82%) receiving doxycycline (*P* = .40; Table 2).

Clinical cure occurred less often among the 98 (23%) men who returned early (2–3 weeks) versus after 3–5 weeks (67% vs 81%, *P* = .004), and somewhat less often among HIV-positive men (58% vs 79%, *P* = .15).

In analyses of specific pathogens, there were also no significant differences by arm. Men with *M. genitalium* at baseline experienced the lowest clinical cure rates (63% for azithromycin vs 48% for doxycycline, *P* = .23). Of men with clinical treatment failure, 30% had *M. genitalium*, 26% had *U. urealyticum* biovar 2, 20% had *C. trachomatis*, and 31% had idiopathic disease.

Results were similar in ITT analyses. There were no significant differences in clinical cure rates for all-cause NGU (83% receiving azithromycin vs 82% receiving doxycycline, *P* = .64) or for men with *C. trachomatis*, *M. genitalium*, *U. urealyticum* biovar 2, or idiopathic NGU. In sensitivity analyses, assuming losses to follow-up had experienced clinical failure, clinical cure rates for all-cause NGU were 64% for azithromycin and 61% for doxycycline (*P* = .41; Table 3).

Figure 1. Flow diagram of enrollment and follow-up in the trial. Abbreviations: ITT, intent to treat; mITT, modified intent to treat; PMNs/HPF, polymorphonuclear leukocytes per high-powered field.
Table 1. Characteristics of Study Participants in the Intent-to-Treat and Modified Intent-to-Treat Population at Enrollment, by Randomization Arm

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ITT Total</th>
<th>ITT Azithromycin (n = 304)</th>
<th>ITT Doxycycline (n = 302)</th>
<th>mITT Total</th>
<th>mITT Azithromycin (n = 216)</th>
<th>mITT Doxycycline (n = 206)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>33.7 (10.0)</td>
<td>34.1 (9.8)</td>
<td>33.3 (10.1)</td>
<td>34.6 (9.5)</td>
<td>33.9 (10.0)</td>
<td>34.3 (9.8)</td>
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<tr>
<td>Race</td>
<td></td>
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<tr>
<td>White</td>
<td>139 (46.0)</td>
<td>159 (52.3)</td>
<td>172 (57.0)</td>
<td>331 (54.6)</td>
<td>112 (53.9)</td>
<td>119 (61.7)</td>
</tr>
<tr>
<td>Black</td>
<td>93 (30.8)</td>
<td>113 (37.2)</td>
<td>93 (30.8)</td>
<td>206 (34.0)</td>
<td>77 (37.0)</td>
<td>59 (30.6)</td>
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<tr>
<td>Other</td>
<td>19 (6.3)</td>
<td>23 (7.6)</td>
<td>19 (6.3)</td>
<td>42 (6.9)</td>
<td>19 (9.1)</td>
<td>15 (7.8)</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>14 (4.6)</td>
<td>9 (3.0)</td>
<td>14 (4.6)</td>
<td>23 (3.8)</td>
<td>6 (2.8)</td>
<td>9 (4.4)</td>
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<tr>
<td>Highest level of education completed</td>
<td></td>
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<tr>
<td>≤ High school/GED</td>
<td>329 (54.6)</td>
<td>130 (42.8)</td>
<td>139 (46.0)</td>
<td>269 (44.4)</td>
<td>91 (42.3)</td>
<td>91 (44.4)</td>
</tr>
<tr>
<td>&gt; High school/GED</td>
<td>233 (45.4)</td>
<td>173 (56.9)</td>
<td>161 (53.3)</td>
<td>334 (55.1)</td>
<td>124 (57.7)</td>
<td>114 (55.6)</td>
</tr>
<tr>
<td>Annual income, $</td>
<td></td>
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<tr>
<td>&lt; 10 000</td>
<td>210 (34.7)</td>
<td>106 (34.9)</td>
<td>104 (34.4)</td>
<td>210 (34.7)</td>
<td>73 (34.8)</td>
<td>69 (34.7)</td>
</tr>
<tr>
<td>10 000–29 999</td>
<td>200 (33.0)</td>
<td>104 (34.2)</td>
<td>96 (31.8)</td>
<td>200 (33.0)</td>
<td>75 (35.7)</td>
<td>67 (33.7)</td>
</tr>
<tr>
<td>≥ 30 000</td>
<td>181 (29.9)</td>
<td>88 (28.9)</td>
<td>93 (30.8)</td>
<td>181 (29.9)</td>
<td>62 (29.5)</td>
<td>63 (31.6)</td>
</tr>
<tr>
<td>Sexual history, past 12 mo</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Heterosexual</td>
<td>401 (66.2)</td>
<td>208 (68.4)</td>
<td>193 (63.9)</td>
<td>142 (65.7)</td>
<td>125 (60.7)</td>
<td>267 (63.3)</td>
</tr>
<tr>
<td>Homosexual</td>
<td>200 (33.0)</td>
<td>81 (26.6)</td>
<td>89 (29.5)</td>
<td>170 (28.1)</td>
<td>62 (28.7)</td>
<td>65 (31.6)</td>
</tr>
<tr>
<td>Bisexual</td>
<td>32 (5.3)</td>
<td>14 (4.6)</td>
<td>18 (6.0)</td>
<td>32 (5.3)</td>
<td>12 (5.6)</td>
<td>15 (7.3)</td>
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<tr>
<td>Not sexually active</td>
<td>3 (0.5)</td>
<td>1 (0.3)</td>
<td>2 (0.7)</td>
<td>3 (0.5)</td>
<td>0 (0.0)</td>
<td>1 (0.5)</td>
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<tr>
<td>HIV status</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Positive</td>
<td>7 (3.6)</td>
<td>2 (0.7)</td>
<td>5 (2.8)</td>
<td>7 (3.6)</td>
<td>12 (3.0)</td>
<td>12 (3.0)</td>
</tr>
<tr>
<td>Negative</td>
<td>243 (85.0)</td>
<td>250 (82.8)</td>
<td>493 (81.4)</td>
<td>175 (85.0)</td>
<td>169 (86.7)</td>
<td>344 (85.8)</td>
</tr>
<tr>
<td>Never tested or unknown</td>
<td>45 (13.2)</td>
<td>40 (13.2)</td>
<td>31 (10.3)</td>
<td>71 (11.7)</td>
<td>26 (12.6)</td>
<td>19 (9.7)</td>
</tr>
<tr>
<td>No. sex partners, past 12 mo, median (IQR)</td>
<td>3 (2–6)</td>
<td>4 (2–6)</td>
<td>3 (2–6)</td>
<td>3 (2–6)</td>
<td>3 (2–6)</td>
<td>3 (2–6)</td>
</tr>
<tr>
<td>Circumcised</td>
<td>162 (26.4)</td>
<td>257 (84.5)</td>
<td>193 (63.9)</td>
<td>401 (66.2)</td>
<td>142 (65.7)</td>
<td>125 (60.7)</td>
</tr>
<tr>
<td>Symptoms at enrollment</td>
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<td>Urethral discharge</td>
<td>323 (53.3)</td>
<td>159 (52.6)</td>
<td>159 (52.6)</td>
<td>323 (53.3)</td>
<td>117 (54.2)</td>
<td>114 (55.3)</td>
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<tr>
<td>Dysuria</td>
<td>310 (51.2)</td>
<td>158 (52.0)</td>
<td>152 (50.3)</td>
<td>310 (51.2)</td>
<td>120 (55.6)</td>
<td>109 (52.9)</td>
</tr>
<tr>
<td>Other urethral symptomsc</td>
<td>160 (26.4)</td>
<td>81 (26.6)</td>
<td>79 (26.2)</td>
<td>160 (26.4)</td>
<td>60 (27.8)</td>
<td>58 (28.2)</td>
</tr>
<tr>
<td>Nonurethral symptomsd</td>
<td>26 (12.0)</td>
<td>44 (14.5)</td>
<td>56 (18.5)</td>
<td>100 (16.5)</td>
<td>26 (12.0)</td>
<td>32 (15.5)</td>
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<tr>
<td>Infecting pathogen</td>
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<tr>
<td>Mycoplasma genitalium</td>
<td>38 (17.6)</td>
<td>45 (14.8)</td>
<td>35 (11.6)</td>
<td>80 (13.2)</td>
<td>38 (17.6)</td>
<td>27 (13.1)</td>
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<tr>
<td>Chlamydia trachomatis</td>
<td>53 (24.5)</td>
<td>76 (25.0)</td>
<td>68 (22.5)</td>
<td>144 (23.8)</td>
<td>53 (24.5)</td>
<td>50 (24.3)</td>
</tr>
<tr>
<td>Trichomonas vaginalis</td>
<td>3 (1.4)</td>
<td>5 (1.6)</td>
<td>6 (2.0)</td>
<td>11 (1.8)</td>
<td>3 (1.4)</td>
<td>5 (2.4)</td>
</tr>
<tr>
<td>Ureaplasma urealyticume</td>
<td>52 (26.0)</td>
<td>65 (21.4)</td>
<td>77 (25.5)</td>
<td>142 (23.4)</td>
<td>52 (26.0)</td>
<td>55 (28.1)</td>
</tr>
<tr>
<td>Ureaplasma parvumf</td>
<td>31 (15.5)</td>
<td>41 (13.5)</td>
<td>40 (13.2)</td>
<td>81 (13.4)</td>
<td>31 (15.5)</td>
<td>29 (14.8)</td>
</tr>
<tr>
<td>Ureaplasma spp unspeciatedg</td>
<td>13 (6.1)</td>
<td>14 (4.6)</td>
<td>8 (2.6)</td>
<td>22 (3.6)</td>
<td>13 (6.1)</td>
<td>8 (3.9)</td>
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<tr>
<td>Idiopathich</td>
<td>85 (41.9)</td>
<td>117 (38.5)</td>
<td>128 (42.4)</td>
<td>245 (40.4)</td>
<td>81 (38.8)</td>
<td>85 (41.9)</td>
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<tr>
<td>No. PMNs/HPF on Gram-stained slide</td>
<td></td>
<td></td>
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<tr>
<td>0–4</td>
<td>0 (0.0)</td>
<td>24 (7.9)</td>
<td>31 (10.3)</td>
<td>55 (9.1)</td>
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<tr>
<td>5–9</td>
<td>48 (22.2)</td>
<td>72 (23.7)</td>
<td>79 (26.1)</td>
<td>151 (24.9)</td>
<td>60 (29.1)</td>
<td>108 (25.6)</td>
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<tr>
<td>≥10</td>
<td>168 (77.8)</td>
<td>208 (68.4)</td>
<td>192 (63.6)</td>
<td>400 (66.0)</td>
<td>168 (77.8)</td>
<td>146 (70.9)</td>
</tr>
<tr>
<td>History of antibiotic use 1–3 mo ago</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>None</td>
<td>177 (81.9)</td>
<td>255 (83.9)</td>
<td>264 (87.4)</td>
<td>519 (85.6)</td>
<td>177 (81.9)</td>
<td>182 (88.3)</td>
</tr>
<tr>
<td>Somei</td>
<td>26 (12.0)</td>
<td>29 (9.5)</td>
<td>16 (5.3)</td>
<td>45 (7.4)</td>
<td>26 (12.0)</td>
<td>12 (5.8)</td>
</tr>
<tr>
<td>Doesn’t know</td>
<td>13 (6.0)</td>
<td>15 (4.9)</td>
<td>13 (4.3)</td>
<td>28 (4.6)</td>
<td>13 (6.0)</td>
<td>8 (3.9)</td>
</tr>
</tbody>
</table>

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In mITT analyses, the microbiologic cure rate was lower than the clinical cure rate and not significantly different by arm, with one exception. In the doxycycline arm, the microbiologic cure rate of *C. trachomatis* was higher than the clinical cure rate (90% vs 76%; *P* = .06; Table 2). Notably, the microbiologic cure rate was extremely low for men with *M. genitalium*: 40% for azithromycin versus 30% for doxycycline (*P* = .41).

### Table 2. Clinical and Microbiologic Cure at Follow-up in the Modified Intent-to-Treat Population, by Infection at Enrollment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Azithromycin (n = 216)</th>
<th>Doxycycline (n = 206)</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>Microbiologic Cure</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Azithromycin (n = 216)</td>
<td>Doxycycline (n = 206)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All participants</td>
<td>79.6 (73.6–84.8)</td>
<td>76.2 (69.8–81.9)</td>
<td>86.3 (73.7–94.3)</td>
<td>90.0 (78.2–96.7)</td>
</tr>
<tr>
<td><em>Chlamydia trachomatis</em></td>
<td>86.8 (74.7–94.5)</td>
<td>76.0 (61.8–86.9)</td>
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</tr>
<tr>
<td><em>Mycoplasma genitalium</em></td>
<td>63.2 (46.0–78.2)</td>
<td>48.1 (28.7–68.1)</td>
<td>39.5 (24.0–56.6)</td>
<td>29.6 (13.8–50.2)</td>
</tr>
<tr>
<td><em>Ureaplasma urealyticum</em></td>
<td>82.7 (69.7–91.8)</td>
<td>72.7 (59.0–83.9)</td>
<td>75.0 (61.1–86.0)</td>
<td>69.1 (55.2–80.9)</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>79.0 (68.5–87.3)</td>
<td>85.7 (76.6–92.5)</td>
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</tr>
</tbody>
</table>

Data are presented as % (95% confidence interval).

**Microbiologic Cure**

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</tr>
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<td>76.0 (61.8–86.9)</td>
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<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Data are presented as % (95% confidence interval).

a Denominator sample size: azithromycin, n = 53 for clinical cure and n = 51 for microbiologic cure; doxycycline, n = 50.

b Denominator sample size: azithromycin, n = 38; doxycycline, n = 27.

c Denominator sample size: azithromycin, n = 52; doxycycline, n = 55.

d Denominator sample size: azithromycin, n = 81; doxycycline, n = 85.
Eradication of specific organisms did not differ between those returning after 2–3 or 3–5 weeks, nor between HIV-positive and HIV-negative men (data not shown).

Intent-to-treat analyses of microbiologic cure were similar to mITT analyses. There was no significant difference between azithromycin and doxycycline for men initially positive for C. trachomatis, M. genitalium, or U. urealyticum biovar 2. In sensitivity analyses, assuming men lost to follow-up had experienced clinical treatment failure, the microbiologic cure rate was substantially lower but still not significantly different by arm (Table 3).

Adjusting for unprotected sex between visits, prevalence ratios comparing azithromycin to doxycycline for clinical and microbiologic cure were similar to unadjusted results (Table 4).

There were no important harms or unintended effects. Expected adverse events (nausea, vomiting, diarrhea, rash) were experienced by 53 men randomized to azithromycin and 56 randomized to doxycycline; nearly all were mild. In the azithromycin arm, 75% of such events were related to the study drug as were 66% in the doxycycline arm. One severe adverse event occurred in the azithromycin group and 3 occurred in the doxycycline group; none were related to study drugs.

DISCUSSION

In this double-blind randomized trial, rates of clinical and microbiologic cure of NGU after CDC-recommended therapy were ≤80%. There were no significant differences in efficacy between azithromycin and doxycycline, and this was true for both clinical and microbiologic cure. Chlamydia trachomatis, U. urealyticum biovar 2, and idiopathic NGU remained relatively sensitive to standard therapies, but M. genitalium was not. The clinical cure rate of M. genitalium-associated NGU, which may account for up to a quarter of cases, was <70% irrespective of the drug used, and the microbiologic cure rate was <40%.

These results were similar to the Stamm et al trial in the mid-1990s [10]. Stamm demonstrated no difference in clinical cure rates after azithromycin or doxycycline treatment (90% and 89%, respectively), but cure rates were 10–15 percentage points higher than ours, as were clearance rates for C. trachomatis (95% for azithromycin; 93% for doxycycline). More recently, Schwebke et al [12] reported significantly lower clearance of C. trachomatis after azithromycin compared to doxycycline (77% vs 95%, P = .01), somewhat lower clinical efficacy of azithromycin for all-cause NGU (69% vs 75%, not significant), and significantly higher efficacy of azithromycin compared to doxycycline for M. genitalium (67% vs 31%, P < .01).

A number of differences in trial design and analytic strategy may contribute to these differences. First, ours was a single-site trial, whereas the others were multisite studies. Second, we measured clinical and microbiologic cure 3 weeks after treatment (to exclude detection of residual DNA [19–21]), whereas Stamm et al and Schwebke et al assessed men at 2 and 5 weeks after therapy, reporting 2-week clinical cure and cumulative rates for C. trachomatis eradication. Third, the Stamm

---

Table 3. Sensitivity Analysis of Intent-to-Treat Population: Clinical and Microbiologic Cure at Follow-up by Infection at Enrollment and Assumptions About Losses to Follow-up (N = 606)

<table>
<thead>
<tr>
<th></th>
<th>Clinical Cure</th>
<th>Microbiologic Cure</th>
<th>Clinical Cure</th>
<th>Microbiologic Cure</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td>253 (83.2)</td>
<td>247 (81.8)</td>
<td>.64</td>
<td>...</td>
</tr>
<tr>
<td>Chlamydia trachomatis\ a</td>
<td>69 (90.8)</td>
<td>56 (82.4)</td>
<td>.14</td>
<td>67 (90.5)</td>
</tr>
<tr>
<td>Mycoplasma genitalium\ b</td>
<td>30 (66.7)</td>
<td>20 (57.1)</td>
<td>.38</td>
<td>20 (44.4)</td>
</tr>
<tr>
<td>Ureaplasma urealyticum\ c</td>
<td>52 (80.0)</td>
<td>60 (77.9)</td>
<td>.76</td>
<td>49 (75.4)</td>
</tr>
<tr>
<td>Idiopathic\ d</td>
<td>98 (83.8)</td>
<td>113 (88.3)</td>
<td>.31</td>
<td>...</td>
</tr>
</tbody>
</table>

Abbreviations: AZM, azithromycin; DOX, doxycycline; ITT, intent to treat.

* Azithromycin: n = 76 for clinical cure and n = 74 for microbiologic cure; doxycycline: n = 68.
* Azithromycin: n = 45; doxycycline: n = 35.
* Azithromycin: n = 65; doxycycline: n = 77.
* Azithromycin: n = 117; doxycycline: n = 128.
et al trial assessed *C. trachomatis* by culture, whereas both other trials used NAATs. Finally, the Schwebke et al trial classified men who did not return as having clinical and/or microbiologic treatment failure [12] (comparable to our ITT sensitivity analysis), whereas the Stamm et al trial excluded them from analyses [10] (comparable to our mITT analysis). Because our ITT results were highly sensitive to the classification of men lost to follow-up, and true ITT analyses become impractical if the outcome cannot be ascertained when subjects fail to return [22], we believe our mITT results are most relevant.

The efficacy of azithromycin and doxycycline for all-cause and *C. trachomatis*-associated NGU that we observed was somewhat lower than in the mid-1990s [10], but not dramatically so. However, the extremely low efficacy of both drugs against *M. genitalium* is concerning. Whereas previous studies have consistently shown low cure rates for *M. genitalium* after treatment with doxycycline [11, 12, 16, 23], the low cure rates for azithromycin were unexpected. In all previous comparisons, azithromycin was significantly more effective than doxycycline [11, 12, 23]. Our findings suggest that susceptibility of *M. genitalium* to azithromycin is especially low in Seattle, declining over time, or both. Comparing 3 US trials, the microbiologic cure rate of *M. genitalium* following azithromycin declined from 77% in New Orleans (2002–2004) [11], to 67% in the eastern and southern United States (2006–2009) [12], to 40% in our Seattle-based study (2007–2011). Similar time trends occurred in Australia where azithromycin cure rates declined from 84% (2005–2007) to 69% (2007–2009). Pre-treatment specimens from half the Australian participants who failed treatment were susceptible to azithromycin, suggesting that therapy selected for resistant isolates [24] and resistance may increase in areas of high usage. Antimicrobial susceptibility testing of isolates recovered in this trial is ongoing.

These results raise a number of questions about NGU treatment. Their relative consistency with the initial 1990s trial suggests that azithromycin remains an effective therapy for NGU overall, and for *C. trachomatis* specifically, though efficacy may be declining. Nevertheless, the reasons for the lower efficacy of azithromycin in the well-designed Schwebke et al trial merit further investigation. In contrast, these findings, along with other studies of *M. genitalium* and NGU, suggest that treatment guidelines for persistent NGU may require revision. Current guidelines recommend that men originally treated with doxycycline receive azithromycin and metronidazole or tinidazole for *T. vaginalis*. Here, 30% of men with persistent urethritis had *M. genitalium* and neither azithromycin nor doxycycline was particularly effective. There are no commercial assays for *M. genitalium* in the United States and, although a number of correlates of *M. genitalium* have been identified, few differentiate *M. genitalium*-associated NGU from other etiologies [25], making it challenging to identify these infections. Moxifloxacin (400 mg × 7 days) has been highly effective against *M. genitalium* in a number of settings [26–29] and our Seattle STD clinic now treats persistent NGU with moxifloxacin. However, this must be balanced with the potential for moxifloxacin-associated hepatotoxicity.

This double-blind randomized trial was well controlled and used sensitive NAATs to detect pathogens, and losses to follow-up were relatively low. Nevertheless, results may not be entirely generalizable; antimicrobial resistance patterns vary regionally and may differ in other locations. Despite a robust sample size, we had smaller numbers in some subgroup analyses and pathogen-specific estimates may be less stable.

In this population, azithromycin and doxycycline were similarly effective against NGU, but clinical and microbiologic cure rates showed some decline from the 1990s. The exception was *M. genitalium*, which accounts for 10%–25% of NGU cases and responded poorly to both regimens. The absence of a commercially available assay for *M. genitalium*, along with treatment failure up to 70%, presents substantial challenges for the clinical management of NGU. Development of

---

**Table 4. Prevalence Ratios (Azithromycin Relative to Doxycycline) for Clinical and Microbiologic Cure at 3-Week Follow-up Visit, by Baseline Infecting Organism, Modified Intent-to-Treat Population**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Crude Prevalence Ratio (95% CI)</th>
<th>P Value</th>
<th>Adjusted Prevalence Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical cure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>1.02 (.92–1.14)</td>
<td>.66</td>
<td>1.02 (.92–1.14)</td>
<td>.70</td>
</tr>
<tr>
<td><em>C. trachomatis</em></td>
<td>1.16 (.95–1.41)</td>
<td>.14</td>
<td>1.17 (.95–1.43)</td>
<td>.14</td>
</tr>
<tr>
<td><em>M. genitalium</em></td>
<td>1.20 (.74–1.95)</td>
<td>.73</td>
<td>1.12 (.59–2.13)</td>
<td>.72</td>
</tr>
<tr>
<td><em>U. urealyticum</em></td>
<td>1.10 (.89–1.36)</td>
<td>.37</td>
<td>1.13 (.90–1.40)</td>
<td>.30</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>.89 (.77–1.04)</td>
<td>.12</td>
<td>.89 (.77–1.03)</td>
<td>.52</td>
</tr>
<tr>
<td>Microbiologic cure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>C. trachomatis</em></td>
<td>.96 (.83–1.12)</td>
<td>.62</td>
<td>.97 (.83–1.13)</td>
<td>.68</td>
</tr>
<tr>
<td><em>M. genitalium</em></td>
<td>1.18 (.54–2.57)</td>
<td>.69</td>
<td>1.36 (.64–2.91)</td>
<td>.43</td>
</tr>
<tr>
<td><em>U. urealyticum</em></td>
<td>1.08 (.85–1.38)</td>
<td>.54</td>
<td>1.09 (.86–1.37)</td>
<td>.51</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; C. trachomatis, Chlamydia trachomatis; M. genitalium, Mycoplasma genitalium; U. urealyticum, Ureaplasma urealyticum.

* Prevalence ratios were adjusted for unprotected sex between visits. Unprotected sex was defined as any sexual encounter without a condom. Not having unprotected sex was defined as anyone who did not have sex between visits, or had sex with a condom for each sexual encounter. Twenty participants were missing values for unprotected sex between visits; these participants are not included in the adjusted analysis. Prevalence ratios, 95% CIs, and P values were obtained from multivariate log binomial regression models with robust standard errors, with either clinical cure at visit 2 or microbiologic cure at visit 2 as the outcome.

* Referent group is doxycycline.
commercially available assays, monitoring of *M. genitalium* susceptibility to azithromycin, and new antibiotic regimens for NGU are needed.

### Notes

**Acknowledgments.** The authors would like to thank the men who participated in the trial, as well as the clinicians and staff in the Public Health–Seattle & King County Sexually Transmitted Diseases Clinic (Yolanda Bantolino, Sylvia Berry, Irene King, Eduardo Muñoz, Victory Murphy, Sally Pendras, Sue Szabo, Michael Verdon, Fred Koch, Roxanne Kerani, Barbara Kekeler); study staff (Sarah McDougal, Noa Kay, Dwyn Dither-Schreck); George Kenny, Sabina Astete, Lisa Lowenstein, and Linda Arnesen in the Totten Laboratory; Linda Cles in the UW Chlamydia Laboratory; Gen-Probe, Inc for reagents; Ana-Maria Xet-Mull and Kerani, Barbara Krekeler); study staff (Sarah McDougal, Noa Kay, Dwyn Murphy, Sally Pendras, Sue Szabo, Michael Verdon, Fred Koch, Roxanne Kerani, Barbara Kekeler); and the National Cancer Institute (R25 CA094880 trainee support to placebos). The HMC IDS provided doxycycline, and placebo azithromycin placebo). The HMC IDS provided trichomonad testing at the University of Washington; HMC IDS (Jeffrey Purcell, Bao Chau Vo, Asaad Awan, Kelly Nguyen); and the data safety and monitoring board (Edward W. Hook III, David H. Martin, H. Hunter Handsfield, Sarah Holte). We also thank Carolyn Deal, Elizabeth Rodgers, and Peter W. Flanery at the Division of Microbiology and Infectious Diseases at the National Institutes of Health, and Pfizer, Inc, for supplying study drugs. Finally, we extend special thanks to King K. Holmes for guidance and support.

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**Potential conflicts of interest.** All authors: No reported conflicts. 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.

### References