SUPPLEMENT ARTICLE

# *Mycoplasma genitalium*: Should We Treat and How?

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***Mycoplasma genitalium*** **is associated with acute and chronic urethritis in men. Existing data on infection in women are limited and inconsistent but suggest that *M. genitalium* is associated with urethritis, cervicitis, pelvic inflammatory disease, and possibly female infertility. Data are inconclusive regarding the role of *M. genitalium* in adverse pregnancy outcomes and ectopic pregnancy. Available data suggest that azithromycin is superior to doxycycline in treating *M. genitalium* infection. However, azithromycin-resistant infections have been reported in 3 continents, and the proportion of azithromycin-resistant *M. genitalium* infection is unknown. Moxifloxacin is the only drug that currently seems to uniformly eradicate *M. genitalium*. Detection of *M. genitalium* is hampered by the absence of a commercially available diagnostic test. Persons with persistent pelvic inflammatory disease or clinically significant persistent urethritis or cervicitis should be tested for *M. genitalium*, if possible. Infected persons who have not previously received azithromycin should receive that drug. Persons in whom azithromycin therapy fails should be treated with moxifloxicin.**

Identified in 1980 [1], *Mycoplasma genitalium* is a bacterium of the Mollicutes class that colonizes the male and female reproductive tract. It is well-known as the smallest of any free-living cell and, given the small size of its genome (580 kb), was one of the first bacteria to be fully sequenced [2] and the first genome to be chemically synthesized [3]. Epidemiologic studies of this somewhat novel bacterium's role in disease processes have been conducted since the early 1990s, subsequent to the development of nucleic acid amplification tests [4, 5], and a number of studies have evaluated associations with male and female reproductive tract disease syndromes. Increasing evidence regarding the role of *M. genitalium* as a sexually transmitted disease (STD) raises questions about the clinical management of STD syndromes in general and of *M. genitalium* infection in particular. Primary among these questions is under what circumstances should clinicians treat for *M. genitalium*, and what pharmacologic therapy is most effective? Because there is currently no commercially available assay for *M. genitalium*, we were particularly interested in how data on the role of *M. genitalium* infection in STD syndromes should inform empirical treatment recommendations.

Against this background, we examined 6 specific questions, with the goal of informing and potentially revising the United States Centers for Disease Control and Prevention (CDC) STD Treatment Guidelines. These questions are as follows: (1) Does *M. genitalium* cause significant morbidity in adult men and women? (2) Is 1 of the 2 recommended treatment regimens for male urethritis, azithromycin (1 gram) and doxycycline (100 milligrams twice daily for 7 days), superior to the other in the treatment of *M. genitalium* infection? (3) Is a longer course of azithromycin superior to a single 1-gram dose of azithromycin in the treatment of *M. genitalium* infection? (4) Which, if any, quinolones are effective in the treatment of *M. genitalium* infection? (5) What is the preferred therapy for *M. genitalium* infection? and (6) Should the therapy for STD syndromes, such as nongonococcal urethritis (NGU),

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persistent NGU, cervicitis, or pelvic inflammatory disease (PID), be altered in recognition of the potential role played by *M. genitalium*? To address these questions, we evaluated the evidence in the published literature and sought expert opinion.

## METHODS

We searched the English-language literature using PubMed and the MeSH search term *Mycoplasma genitalium* for articles published through 15 August 2011. After excluding reports on the development of laboratory assays, studies on genomics, and editorials, a total of 112 studies evaluating disease associations, treatment outcomes, and antimicrobial susceptibility were reviewed. Data in tables summarizing these studies were directly abstracted from the article when available and were calculated from data presented when not directly available. Significance testing and calculation of unadjusted odds ratios was done using EpiInfo, version 6 (CDC).

## RESULTS

### Significant Morbidity in Men and Women Caused by *M. genitalium*

To address the question of whether *M. genitalium* causes significant morbidity among adults, we reviewed studies evaluating its association with urethritis in men, lower and upper genital tract disease syndromes in women, infertility, and adverse pregnancy outcomes. Special attention was paid to the amount and consistency of the evidence.

#### *Male Urethritis*

We identified 34 studies published during 1993–2011 that enrolled >10 men with NGU and used polymerase chain reaction (PCR) analysis to evaluate the role of *M. genitalium* as a cause of acute urethritis in men (Supplementary Table 1; online only). Twenty-eight of the 34 studies enrolled populations from high-income countries (United States, Europe, Japan, Australia, New Zealand, Hong Kong, or Russia) [6–33]; 4 additional studies enrolled men from lower-income countries (sub-Saharan Africa [34–37], Central Africa [38], and China [39]). The 28 studies in high-income countries included a total of 5650 men with acute NGU (range, 36–2406 men). Across all studies, 955 (13%) of the 7123 men with NGU tested positive for *M. genitalium* (median, 15%; range, 5%–42%). The median prevalence of *M. genitalium* infection among men with nonchlamydial NGU in 11 studies for which data were available was 25% (range, 10%–38%) [11, 15, 18, 19, 21, 23, 25, 29, 30, 34, 36].

Pooling study results, the proportion of NGU cases associated with *M. genitalium* was similar in studies that defined NGU only by the presence of signs or symptoms (16%) and in studies that defined NGU by both signs or symptoms and ≥5 polymorphonuclear (PMN) leukocytes on Gram stain (17%), although Gram stain criteria were not uniform across studies. However, all 4 studies that used >1 criterion to define NGU found that the prevalence of *M. genitalium* infection was higher when the syndrome was defined both by the presence of symptoms or signs and by the finding of ≥5 PMN leukocytes per high-power field than when only symptoms or Gram stain findings were used to define the syndrome [12, 20, 33, 40].

Twenty-two of 28 studies compared the presence of *M. genitalium* in men with urethritis with the prevalence of infection in an asymptomatic control group. All found that *M. genitalium* was more common in men with NGU than in men without urethritis, and this difference was significant in 16 (73%) of 22 studies, with odds ratios ranging from 2.2 to 20.3 (Figure 1). Additional evidence supporting a causal role for *M. genitalium* in male urethritis includes studies demonstrating that the organism can cause urethritis in primate models [41–43], evidence of a dose-response relationship between *M. genitalium* bacterial load as measured by quantitative PCR and signs and symptoms of urethritis [23, 44, 45], and

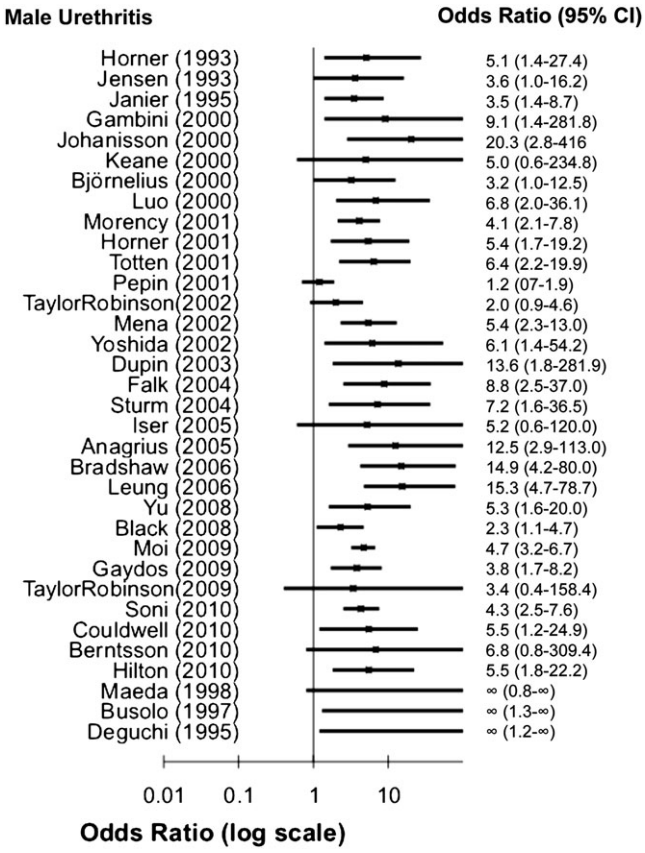


**Figure 1.** Odds ratios and 95% confidence intervals for studies of the association between *Mycoplasma genitalium* assessed by polymerase chain reaction (PCR) and nongonococcal urethritis (NGU).

studies associating successful eradication of *M. genitalium* with the clinical resolution of urethritis and microbiologic persistence with clinical treatment failure [23, 46–50]. On the basis of the consistent epidemiologic evidence associating the presence of the organism with the clinical syndrome of NGU, experimental animal model data, and both observational and experimental clinical data associating microbiologic and clinical treatment failures in humans, we conclude that *M. genitalium* can cause acute urethritis.

***Persistent or Chronic Urethritis in Men***

Eight studies have shown either a significant association or a trend toward such an association between microbiologic treatment failure for acute *M. genitalium* urethritis and clinically persistent or recurrent urethritis [12, 20, 40–45] (Table 1). Four additional studies have assessed the prevalence of *M. genitalium* infection among men presenting with persistent or recurrent urethritis, reporting that 19%–41% of men with the syndrome are infected with *M. genitalium* [16, 51–53]. Three studies included comparison groups of men without chronic urethritis; in 1, *M. genitalium* was not detected in any control subjects (resulting in an undefined odds ratio) [16], 1 found a statistically significant association [51], and 1 found no association [52]. On the basis of treatment studies associating the microbiologic persistence of *M. genitalium* with persistent symptoms of urethritis and evidence of urethral inflammation and studies associating *M. genitalium* with the clinical syndrome of persistent or recurrent urethritis, we conclude that *M. genitalium* can cause persistent or recurrent urethritis.

**Table 1. Summary of Studies Presenting Data on the Proportion of Men With or Without Microbiologic Eradication of *Mycoplasma genitalium* Who Experienced Clinical Cure**

| Study | Proportion, % | | *P* |
|---|---|---|---|
| | Clinical cure but microbiologic failure | Both clinical and microbiologic cure | |
| Dupin et al [20] | 25 | 100 | .03 |
| Maeda et al [40] | | | |
| 7 days | 86 | 100 | .43 |
| 8–28 days | 29 | — | — |
| Gambini et al [12] | 0 | 100 | <.0001 |
| Bradshaw et al [41] | 0 | 100 | <.0001 |
| Stamm et al [42] | 0 | 100 | — |
| Bradshaw et al [43] | 17[a] | 91[a] | <.0001 |
| Björnelius et al [44] | 29 | 77 | <.0001 |
| Mena et al [45] | | | |
| <21 days | 11 | 20 | .39 |
| >21 days[b] | 14 | 77 | .001 |

[a] Numbers are not presented separately for men and women, because differences were the same in both groups.

[b] Only a minority of persons had follow-up testing at >21 days.

***Cervicitis***

Fourteen studies conducted in the United States, Europe, Japan, West Africa, and Australia evaluated the relationship between *M. genitalium* and cervicitis [23, 46–50, 54–61]. Study populations ranged in size from 57 to 7676 women, and all but 1 [50] used nucleic acid amplification tests (primarily PCR) to detect *M. genitalium*. Nearly all studies used different definitions of cervicitis, but most incorporated some objective measure of inflammation, such as number of cervical PMN leukocytes or clinical assessment of signs of cervicitis (eg, cervical mucopus, discharge, edema, and erythema). Taken together, the results of these studies are somewhat conflicting, with 8 (57%) of 14 reporting a significant association [23, 47, 54–58, 61] and 6 (43%) of 14 reporting no association [46, 48–50, 59, 60]. In general, the studies that used only clinical diagnoses of cervicitis were less likely to show an association with *M. genitalium* [49, 50], whereas all studies that defined cervicitis as ≥30 PMN leukocytes per high-power field reported higher prevalence of *M. genitalium* infection among women with cervicitis than among control subjects [23, 48, 54, 55, 57, 60, 61]; however, in 1 case, this was not statistically significant [48]. Statistically significant odds ratios for the association between *M. genitalium* and cervicitis ranged from 1.2 to 5.7 but were rarely adjusted for other factors. We conclude that existing evidence provides some support for the hypothesis that *M. genitalium* may cause cervicitis but is conflicting. Supporting evidence comes from the observation that the vast majority of studies using an objective assessment of cervical inflammation reported a significant association between *M. genitalium* and cervicitis. Nevertheless, the magnitude of this association is highly variable in studies conducted to date, and nearly half of the studies report no association.

***Female Urethritis***

*M. genitalium* has been detected in 4%–9% of women with urethritis, and 2 of the 3 studies that assessed this reported a significant association, with odds ratios ranging from 2.1 to 2.5 [23, 60] (Figure 2 and Supplementary Table 2; online only). In contrast, one-third of the studies found no significant association [47], although *M. genitalium* was more common among women with than without urethritis. Current evidence suggests that *M. genitalium* may cause female urethritis in addition to male urethritis, but data are too limited to draw definitive conclusions.

***Pelvic Inflammatory Disease***

Nine studies assessed the association between female upper reproductive tract disease and *M. genitalium*. Three studies used serologic testing [62–64], whereas 6 applied PCR to cervical and endometrial [65–69] or urine specimens [70]. All but 3 [64, 66, 70] were hampered by the absence of a comparison group of women without PID, and the evidence overall is somewhat conflicting. Two of the 3 serologic studies found no

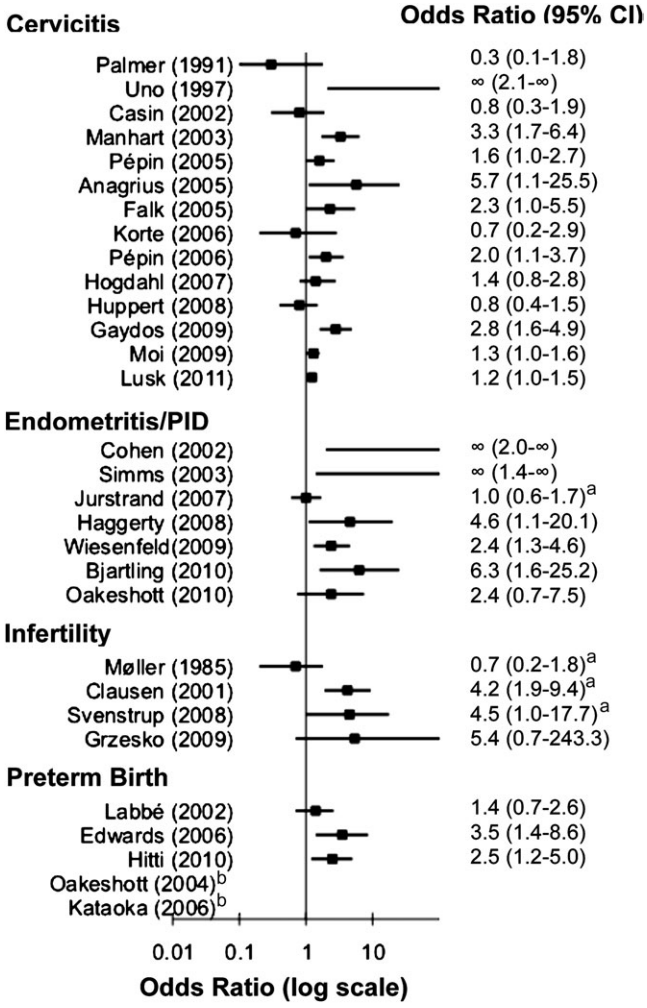


**Figure 2.** Odds ratios and 95% confidence intervals for studies of the association between *Mycoplasma genitalium* (assessed by polymerase chain reaction [PCR], unless otherwise specified) and female reproductive tract disease syndromes. [a]*M. genitalium* assessed by serology [b]RR could not be calculated for Oakeshott (2004 [70]) and Kataoka (2006 [82]); no *M. genitalium* was detected among women with preterm birth.

association with either *M. genitalium* antibody positivity or titer level [63, 64], although 1 showed that 38.7% of women with acute PID and no antibodies to *Chlamydia trachomatis* or *Mycoplasma hominis* experienced a ≥4-fold increase in *M. genitalium* antibody titer between acute and convalescent phase serum samples [62]. However, in the only seroepidemiologic study to include women without clinically diagnosed PID, antibodies to *M. genitalium* were detected in similar proportions of women with PID and healthy pregnant women (17% vs 15%; $P = .48$), although there was a trend toward an association among younger women (age, 15–30 years) [64].

Of the 6 studies using PCR and comparison groups, *M. genitalium* was detected more often in women with endometritis [65, 68, 71] or clinically diagnosed PID [66, 69] than in women without disease, with odds ratios ranging from 4.6 to 6.3. In the only cohort study, the risk of incident clinically diagnosed PID in the Prevention of Pelvic Infection (POPI) trial was higher among young British women with *M. genitalium* at baseline, but this was not statistically significant (relative risk, 2.4; 95% CI 0.74–7.46; $P = .12$), and the overall incidence of *M. genitalium* infection over the course of 1 year was low (0.9%) [70]. *M. genitalium* has been detected in the fallopian tube of a Kenyan woman with mild salpingitis, indicating that it can ascend high into the upper reproductive tract [67], and a causative role for *M. genitalium* in PID is biologically plausible, as indicated by studies in nonhuman primates in which endosalpingitis was induced after inoculation with *M. genitalium* [72].

In summary, existing data provide some support for the hypothesis that *M. genitalium* can cause PID but are conflicting. Supporting data include the observation that *M. genitalium* can be directly detected in the endometrium and fallopian tubes of women with PID and/or salpingitis, epidemiologic associations with endometritis and PID in studies assessing *M. genitalium* by PCR, and animal model studies. However, the frequency with which *M. genitalium*–infected women experience PID remains largely unknown, and serologic data in humans remain conflicting, perhaps partly because of the variety of serologic assays used and concerns about cross-reactivity in some assays between antibody for *M. genitalium* and *Mycoplasma pneumoniae*.

***Infertility***

Four studies—3 conducted in Denmark and 1 in Poland—evaluated whether antibody to *M. genitalium* is more common in women with tubal factor infertility (TFI) than in control groups of fertile women or women with other causes of infertility [73–76]. The 2 highest-quality studies observed a higher prevalence of *M. genitalium* antibody among women with TFI than among women with other causes of infertility, and in both, the association between *M. genitalium* and TFI was independent of a woman's *C. trachomatis* antibody status [74, 75]. One of the other 2 studies found that infertile women were more likely to have antibody to *M. genitalium* than were fertile women, but this finding was not statistically significant and was isolated to infertile women without TFI [76]. Three studies evaluated the association of *M. genitalium* and male infertility [77–79], only 1 of which included a control group [77]. The controlled study, conducted among Danish men attending an infertility clinic, found no association between prevalent *M. genitalium* infection and male infertility assessed by sperm morphology, mobility, or ability to invade mucus substitute material in vitro. Two uncontrolled studies conducted in Tunisia found *M. genitalium* by PCR in 6 (4%) of 120 and 5 (5%) of 104 infertile men defined by sperm quality evaluation according to World Health Organization guidelines. We did not identify any studies involving men that used serologic testing. Thus, existing data provide some support for the hypothesis that

*M. genitalium* can cause female infertility but are inconclusive. Supporting evidence comes from some, but not all, case-control studies that have measured *M. genitalium* exposure with use of serologic testing and from some clinical and animal model studies suggesting that *M. genitalium* can cause PID, which is thought to be a precursor to TFI. In contrast, the limited existing evidence does not support a role for *M. genitalium* as a cause of male infertility.

***Ectopic Pregnancy***

Only 1 study evaluated the potential association of *M. genitalium* with ectopic pregnancy. A case-control study among Swedish women compared the prevalence of *M. genitalium* antibody in women with ectopic pregnancies who received a diagnosis during 1984–1986 with that in a control group of healthy pregnant women tested for rubella in 1988. Antibody to *M. genitalium* was present in similar numbers of women with or without ectopic pregnancy (18% vs 15%; not statistically significant) [64]. *M. genitalium* was marginally associated with ectopic pregnancy in a subgroup of women aged 15–30 years (20% vs 11%; odds ratio, 1.6; 95% confidence interval, .6–4.0). Of note, antibody to *C. trachomatis* was also associated with ectopic pregnancy only among women aged 15–30 years. The very limited existing evidence is insufficient to conclude that *M. genitalium* is associated with ectopic pregnancy.

***Adverse Birth Outcomes***

Five published studies investigated the association of *M. genitalium* with any adverse birth outcome [80–84]. All studies evaluated preterm birth as an outcome. One also evaluated the association of *M. genitalium* with miscarriage [81]. The study end points were relatively uncommon in all 3 studies (1%–4%), with 1 exception [83], limiting their statistical power. Only 3 of the 5 studies tested a control group of women who did not experience adverse birth outcomes [81, 82, 84]. In 2 of the 3 controlled studies, none of the women with preterm birth had *M. genitalium* infection [81, 82]. However, a large case-control study involving pregnant women in Peru found a 2.5-fold increased risk for spontaneous preterm delivery among women positive for *M. genitalium* [84] (adjusted odds ratio, 2.5; 95% confidence interval, 1.20–5.02). In contrast, a case-control study conducted in Guinea-Bissau used PCR analysis to test 1014 women for *M. genitalium* 7 days after delivery and found no association of *M. genitalium* with a combined outcome of still birth, spontaneous abortion, premature birth, or small for gestational age (6.2% vs 6%) or with any of the adverse pregnancy outcomes individually [80]. Therefore, existing evidence is sparse and conflicting regarding a causal role for *M. genitalium* in adverse birth outcomes. On the basis of very limited data, *M. genitalium* does not seem to be common in women who experience preterm births in high-income countries. Data are conflicting in lower-income countries.

## Comparison Between Azithromycin and Doxycycline for Treatment of *M. genitalium* Infection

We identified 7 studies that evaluated microbiologic cure rates achieved with a 7–8-day course of doxycycline [12, 20, 44, 45, 53, 85, 86], 9 that evaluated microbiologic cure rates with azithromycin (1 gram) [12, 41–45, 53, 86, 87], and 4 that evaluated the efficacy of azithromycin (500 milligrams once, followed by 250 milligrams once daily for 4 days) [44, 45, 85, 87] (Table 2). One additional study used a combination of azithromycin doses, and presentation of data did not allow efficacy to be evaluated separately, although all 20 patients were cured [53]. Only 2 randomized trials compared azithromycin with doxycycline [45, 86]. One trial included 78 men with *M. genitalium* urethritis and found that azithromycin was superior to doxycycline (microbiologic cure, 87% vs 45%; $P = .002$) [45]. The other trial included 54 men with *M. genitalium* urethritis and also found that azithromycin was superior to doxycycline (microbiologic cure, 67% vs 31%; $P$ .002), but cure rates for both drugs were substantially lower than those observed in the prior trial [86].

Microbiologic cure rates achieved with doxycycline varied substantially across studies (17%–94%), whereas cure rates achieved with azithromycin (1 g) were higher and more consistent (67%–100%). Pooling data from all studies, doxycycline resulted in microbiologic cures in 88 (42%) of 212 treated men, compared with 371 (80%) of 466 men treated with a 1-gram dose of azithromycin. On the basis of existing published data, we conclude that a 1-gram dose of azithromycin is superior to 7 days of doxycycline in the treatment of *M. genitalium* infection. However, several recent studies have documented treatment failures in men with azithromycin-resistant *M. genitalium* infection [41, 43, 91]. Azithromycin may not be superior to doxycycline in areas that have a high prevalence of azithromycin-resistant *M. genitalium*. Unfortunately, little data currently exist on the epidemiology of azithromycin-resistant *M. genitalium* infection.

## Longer Course Versus Single 1-gram Dose of Azithromycin for Treatment of *M. genitalium* Infection

No randomized trials have compared different azithromycin regimens. However, 2 observational studies have evaluated this issue [44, 87]. One conducted in Norway compared 3 different dosing regimens: 1 g once, 1 g followed by a second 1-gram dose in 5–7 days, and 500 milligrams once followed by 250 milligrams daily for 4 days [87]. Microbiologic cure occurred in 144 (79%) of 189, 20 (74%) of 30, and 72 (78%) of 98 patients given the 3 regimens, respectively. Another study conducted in Sweden compared a 1-gram dose of azithromycin in previously untreated men with 500 milligrams once followed by 250 milligrams daily for 4 days in men in whom doxycycline therapy had first failed [44]. Microbiologic cure occurred in 45 (96%) of 47 men given the extended regimen, compared with 33 (85%)

**Table 2. *Mycoplasma genitalium* and Clinical Treatment**

| Citation | Study design | Study population | Outcome definitions[a] | Treatment regimen | Reported findings |
|---|---|---|---|---|---|
| Horner et al, 1993 [6] | Case series | 98 *M. genitalium*–positive British men with NGU attending STD clinic; aged 19–53 years | Microbiologic failure; follow-up (10–21 days) | Doxycycline (200 milligrams stat plus 100 mg/d × 13 days) | 4/14 (29%) had microbiologic failure |
| Gambini et al, 2000 [12] | Cohort | 52 *M. genitalium*–positive Italian men with NGU attending STD clinic; aged 17–70 years | Microbiologic failure; clinical failure; follow-up (7 days) | Doxycycline (200 mg/d × 7 days) or Azithromycin (1 gram stat)<br>Failures: received alternate treatment regimen | Doxycycline: 2/35 (6%) had clinical and microbiologic failure<br>Azithromycin: 3/17 (18%) had clinical and microbiologic failure<br>Failures: 0/5 (0%) had clinical or microbiologic failure |
| Johannisson et al, 2000 [13] | Case series | 21 *M. genitalium*–positive Swedish men with urethritis (n = 18) and women (n = 3) attending STD clinics; aged 18–60 years | Microbiologic failure; clinical failure; follow-up (3–4 weeks) | Tetracycline (0.5 grams 2×/day × 10 days) | Tetracycline in men: 8/13 (61%) had microbiologic failure; 6/13 (46%) had clinical failure<br>Women: 1/1 (100%) had microbiologic failure |
| Horner et al, 2001 [16] | Cohort | 109 *M. genitalium*–positive British men with NGU attending STD clinic; age range NR | Clinical failure; follow-up (2, 6, 12 weeks) | Doxycycline (200 milligrams stat plus 100 milligrams/days × 13 days) or<br>Erythromycin (500 milligrams 4×/day × 14 days)<br>Persistent urethritis: Erythromycin (500 milligrams 4×/day × 14 days) plus metronidazole (400 milligrams 2×/day × 5 days) | Doxycycline-erythromycin (combined): 7/7 (100%) had clinical failure |
| Maeda et al, 2001 [40] | Cohort | 12 *M. genitalium*–positive Japanese men with NGU attending urology clinic; aged 17–69 years | Microbiologic failure; clinical failure; follow-up (14 days) | Levofloxacin (100 milligrams 3×/day × 14 days) | Levofloxacin: 8/12 (67%) had microbiologic and 1/12 (8%) had clinical failure<br>5/7 (71%) with microbiologic failure but clinical cure had recurrent NGU at 4 weeks |
| Falk et al, 2003 [85] | Cohort | 60 *M. genitalium*–positive Swedish men (n = 34) and women (n = 26) attending STD clinic; age range NR | Microbiologic failure; follow-up (4–5 weeks) | Doxycycline (200 milligrams stat plus 100 milligrams × 8 days) or<br>Lymecycline (300 miligrams 2×/day × 10 days)<br>Asymptomatic *M. genitalium*–positive: azithromycin (500 milligrams stat plus 250 mg/d × 4 days) | Doxycycline-lymecycline (combined): 10/16 men (63%) and 10/14 women (71%) had microbiologic failure<br>Azithromycin: 0/8 men and women (0%) had microbiologic failure |
| Dupin et al, 2003 [20] | Cohort | 9 *M. genitalium*–positive French men with urethritis attending STD clinic; age range NR | Microbiologic failure; clinical failure; follow-up (15–28 days) | Doxycycline (100 mg/d × 7 days) or<br>Minocycline (100 mg/d × 7 days) or<br>Spectinomycin (2 grams) and minocycline (100 mg/d × 7 days) | Doxycycline: 1/1 (100%) had microbiologic and clinical failure<br>Minocycline: 4/7 (57%) had microbiologic and 2/7 (29%) had clinical failure<br>Spectinomycin-minocycline: 0/1 (0%) had microbiologic or clinic failure |
| Bradshaw et al, 2006 [41] | Case series | 34 *M. genitalium*–positive Australian men with NGU attending STD clinic; aged 22–54 years | Microbiologic failure; clinical failure; follow-up (1 month) | Azithromycin (1 gram stat)<br>Failures: Azithromycin (1 gram weekly × 3)<br>Azithromycin failures: moxifloxacin (400 milligrams 2×/days × 10 days) | Azithromycin (stat): 9/32 (28%) had microbiologic failure, and 8/32 (25%) had partial clinical failure and recurrence<br>Azithromycin (weekly): 3/3 (100%) had microbiologic failure<br>Moxifloxacin: 0/9 (0%) had microbiologic failure |

*Table 2 continued.*

| Citation | Study design | Study population | Outcome definitions[a] | Treatment regimen | Reported findings |
|---|---|---|---|---|---|
| Wikstrom et al, 2006 [53] | Cohort | 38 *M. genitalium*–positive Swedish men with persistent urethritis (n = 32) and female partners (n = 6) attending STD clinic, initially treated with doxycycline (200 milligrams stat plus 100 mg/d × 8 days); aged 19–47 years | Microbiologic failure; clinical failure; follow-up (3 weeks) | Azithromycin (1 gram stat or 500 milligrams stat plus 250 mg/d × 4 days) or<br>Erythromycin (500 milligrams 2x/d × 10 days)<br>Female partners: azithromycin (1.5 gram × 5 days) | Azithromycin: 0/20 (0%) of men had microbiologic and 2/20 (10%) had clinical failure; 0/4 (0%) women had microbiologic failure; clinical failure NR<br>Erythromycin: 3/5 (60%) of men had microbiologic and 9/11 (82%) had clinical failure |
| Ross et al, 2006 [88] | Randomized double-blind multisite controlled trial | 4 *M. genitalium*–positive European and South African women with PID; age range NR | Microbiologic failure; follow-up (5–24 and 28–42 days) | Moxifloxacin (400 mg/d × 14 days) or<br>Ofloxacin (400 milligrams 2×/day) plus metronidazole (500 milligrams 2×/day × 14 days) | Moxifloxacin: 0/3 (0%) had microbiologic failure<br>Ofloxacin-metronidazole: 0/1 (0%) had microbiologic failure |
| Stamm et al, 2007 [42] | Randomized double-blind multisite controlled trial | 42 *M. genitalium*–positive US men with NGU attending STD clinics; aged 18–45 years | Microbiologic failure; clinical failure; follow-up (5 weeks) | Rifalazil (2.5, 12.5, or 25 milligrams stat) or<br>Azithromycin (1 gram stat) | Rifalazil, 2.5 milligrams: 5/5 (100%) had microbiologic and 6/8 (75%) had clinical failure<br>Rifalazil,12.5 milligrams: 7/7 (100%) had microbiologic and 8/8 (100%) had clinical failure<br>Rifalazil, *25* milligrams: 5/5 (100%) had microbiologic and 3/5 (60%) had clinical failure<br>Azithromycin: 1/7 (14%) had microbiologic and clinical failure |
| Haggerty et al, 2008 [68] | Cohort | 88 *M. genitalium*–positive US girls and women with PID attending outpatient clinics; aged 14–37 years | Microbiologic failure; clinical failure; follow-up (30 days) | Inpatient: cefoxitin (2 gram parenterally every 6 hours) plus Doxycycline (100 milligrams 2×/day × 14 days)<br>Outpatient: Cefoxitin (2 gram intramuscular) plus Probenecid (1 gram) plus Doxycycline (100 milligrams 2×/day × 14 days) | Endometrium and/or cervix: 23/56 (41%) had microbiologic failure<br>Endometrium: 14/32 (44%) had microbiologic failure<br>Greater likelihood of clinical failure among women with *M. genitalium* in the endometrium (adjusted relative risk, 4.6; 95% CI 1.1–20.1) |
| Björnelius et al, 2008 [44] | Cohort | 159 *M. genitalium*–positive Norwegian and Swedish men with urethritis (n = 115) and women with cervicitis (n = 44) attending STD clinics; aged 18–61 years | Microbiologic failure; clinical failure; follow-up (20–56 days) | Doxycycline (200 milligrams stat plus 100 milligrams × 8 days) or<br>Azithromycin (1 gram stat)<br>Doxycycline failures: Extended Azithromycin (500 milligrams stat plus 250 milligrams × 4 days);<br>Azithromycin failures: extended doxycycline (100 milligrams 2×/ day× 15 days) | Doxycycline: 63/76 (83%) of men and 17/27 (63%) of women had microbiologic failure; 54/75 (72%) of men had persisting signs and 45/67 (67%) had persisting symptoms, and 15/20 (75%) of women had clinical failure<br>Azithromycin: 6/39 (15%) of men and 2/17 (12%) of women had microbiologic failure; 20/37 (54%) of men and 5/8 (63%) of women had persisting signs; 7/31 (23%) of men and 6/10 (60%) of women had persisting symptoms<br>Extended Azithromycin: 2/47 (4%) of men and 0/6 (0%) of women had microbiologic failure<br>Extended Doxycycline: 1/3 men (33%) and 1/1 woman (100%) had microbiologic failure |

*Table 2 continued.*

| Citation | Study design | Study population | Outcome definitions[a] | Treatment regimen | Reported findings |
|---|---|---|---|---|---|
| Jernberg et al, 2008 [87] | Cohort | 452 *M. genitalium*–positive Norwegian men with NGU (n = 234) and women with cervicitis (n = 218) attending STD clinics; age range NR | Microbiologic failure; follow-up (4–5 weeks) | Azithromycin (1 gram stat) or Azithromycin (1 gram stat plus 1 gram stat 5–7 days after 1st dose) or Ofloxacin (200 milligrams 2×/day × 10 days) or Moxifloxacin (400 milligrams × 7 days) Asymptomatic *M. genitalium*–positive: Azithromycin (500 milligrams plus 250 milligrams × 4 days) | Azithromycin, 1 gram: 39/183 (21%) had microbiologic failure Aazithromycin, 1 gram × *2*: 10/38 (26%) had microbiologic failure Azithromycin for asymptomatic patients: 22/98 (22%) had microbiologic failure Ofloxacin: 5/9 (55%) had microbiologic failure Moxifloxacin: 0/3 (0%) had microbiologic failure |
| Bradshaw et al, 2008 [43] | Cohort | 120 *M. genitalium*–positive Australian men with urethritis (n = 102) and women with cervicitis (n = 18) attending STD clinic; age range NR | Microbiologic failure; follow-up (1 month) | Azithromycin (1 gram stat) Failures: moxifloxacin (400 milligrams × 10 days) | Azithromycin: 19/120 (16%) had microbiologic failure Moxifloxacin: 0/11 (0%) had microbiologic failure |
| Mena et al, 2009 [45] | Randomized trial | 78 *M. genitalium*–positive US men with NGU attending STD clinic; age range NR | Microbiologic failure; clinical failure; follow-up (1st: 10–17 days; 2nd: 31–41 days) | Azithromycin (1 gram stat) or Doxycycline (100 milligrams 2×/day × 7 days) Failures: Extended Azithromycin (500 milligrams stat plus 250 mg/d × 4 days) | Azithromycin: 3/23 (13%) had microbiologic and 6/23 (26%) had clinical failure Doxycycline: 17/31 (55%) had microbiologic and 10/31 (20%) had clinical failure Extended azithromycin: 2/5 (40%) had microbiologic and 1/5 (20%) had clinical failure |
| Schwebke et al, 2011 [86] | Randomized trial (double-blind) | 54 *M. genitalium*–positive US men attending 4 urban STD clinics; aged 16–45 years | Microbiologic failure[b]; follow-up (1st: 15–19 days; 2nd: 35–40 days) | Azithromycin (1 g stat; with or without tinidazole) or Doxycycline (100 milligrams 2×/d × 7 days with or without tinidazole) | Azithromycin: 15/45 (33.3%) had microbiologic failure; clinical failure NR Doxycycline: 27/39 (69.2%) had microbiologic failure; clinical failure NR |
| Takahashi et al, 2011 [89] | Cohort | 4 *M. genitalium*–positive Japanese men attending urology clinics; aged ≥18 years | Microbiologic failure; clinical failure; follow-up (1–3 weeks) | Levofloxacin (500 milligrams × 7 days) | Levofloxacin: 2/5 (40%) had microbiologic and 2/4 (50%) had clinical failure |
| Hamasuna et al, 2011 [90] | Cohort | 18 *M. genitalium*–positive Japanese outpatient men; aged ≥20 years | Microbiologic failure; clinical failure; follow-up (2–3 weeks) | Gatifloxacin (200 milligrams 2×/day × 7 days) | Gatifloxacin: 3/18 (17%) had microbiologic and 0/43 (0%) had clinical failure |

Abbreviations: NGU, nongonococcal urethritis; NR, not reported; PID, pelvic inflammatory disease; STD, sexually transmitted disease.

[a] Except where otherwise noted, microbiologic failure was defined as detection of DNA by means of polymerase chain reaction in urine, urethral or cervical swab samples, or biopsy specimens at follow-up. Clinical failure was defined as partial clinical response to therapy [12], signs at follow-up [13], signs and/or symptoms at follow-up [16, 44], symptoms at follow-up [20, 40, 53, 90], ≥5 polymorphonuclear (PMN) leukocytes/high-power field (HPF) at follow-up [41, 89], persistent symptoms or ≥5 PMN leukocytes/HPF at follow-up [42], continued endometritis and pelvic pain at follow-up [68], or symptoms and/or discharge at examination plus ≥5 PMN leukocytes/HPF at follow-up [45].

[b] In this study, microbiologic failure was defined as detection of RNA by Transcription Mediated Amplification in urine at follow-up.

of 39 men given the single dose ($P = .11$). Of note, a study of azithromycin-resistant *M. genitalium* (minimum inhibitory concentration, >8 μg/mL) found that, among 9 paired *M. genitalium* strains obtained before and after failed therapy with 1 gram of azithromycin, 7 expressed a resistance mutation only in the isolates obtained following treatment failure [91], suggesting that selective pressure may have resulted in the emergence of resistant organisms. Similar findings were reported from Japan [92–94] and New Zealand [95]. Existing data are insufficient to conclude that one azithromycin regimen is superior to another. However, at least one knowledgeable authority recommends that a 1.5-gram regimen given over the course of 5 days is preferable to a single 1-gram dose because of a possibly diminished risk of resistance associated with a longer course of treatment [96].

### Effectiveness of Quinolones in the Treatment of *M. genitalium* Infection

Clinical and minimum inhibitory concentration data suggest that neither levofloxacin nor ofloxacin, alternative treatment regimens for NGU and cervicitis, are highly active against *M. genitalium*. Likewise, ciprofloxacin is not active against *M. genitalium* [40, 87, 91, 97–109]. Gatifloxacin seemed promising but was removed from the market because of serious adverse effects [110]. Moxifloxacin (400 milligrams for 7 or 10 days) has been used in at least 14 cases in which azithromycin and/or doxycycline treatment failed to eradicate the infection [41, 43, 87, 88], and no cases of clinical or microbiologic treatment failure have been reported. However, no clinical trials have evaluated moxifloxacin as a therapy for *M. genitalium*. Thus, on the basis of very limited observational data, moxifloxacin seems to be superior to both azithromycin and doxycycline for the treatment of diagnosed *M. genitalium* infection. In defining the role of moxifloxicin as a therapy for *M. genitalium*, this apparent superiority must be weighed against the high cost of the drug, the need for relatively prolonged therapy, and the relative paucity of data on the drug for this indication. We conclude that the quinolone class of antibiotics overall is not superior to azithromycin and doxycycline; levofloxacin, ofloxacin, and ciprofloxacin have lower cure rates than azithromycin. Moxifloxacin seems to be superior to other treatments for *M. genitalium*, but this conclusion is based on a small number of cases and the drug has not been tested in clinical trials.

### Preferred Therapy for *M. genitalium* Infection

Based on small numbers of persons, the highest cure rates for *M. genitalium* urethritis seem to occur with moxifloxacin (400 milligrams daily for 7–10 days; cure rates, 100%). Azithromycin regimens, either a 1-gram dose or 500 milligrams once followed by 250 milligrams daily for 4 days, seem to be equivalent, although somewhat less effective than moxifloxacin (azithromycin cure rates range from 67% to 95%). All 3 of these regimens are superior to doxycycline. Treatment of *M. genitalium* urethritis is complicated by the absence of a commercially available assay; thus, in most cases, clinicians will only be able to treat discharge syndromes syndromically. However, in settings with the capacity to test for *M. genitalium*, we conclude that either azithromycin regimen is preferred over doxycycline. Because of the recent concerns about the emergence of azithromycin resistance, all regimens should be followed by clinical evaluation and a test of cure at 3–4 weeks. Azithromycin treatment failures should be treated with moxifloxacin.

### Therapy for Discharge Syndromes and Pelvic Inflammatory Disease and the Potential Role Played by *M. genitalium*

*M. genitalium* seems to be responsible for 15%–20% of cases of NGU. If doxycycline and azithromycin are 50% and 80% effective, respectively, NGU microbiologic treatment failures would occur in an estimated 7.5%–10% and 3%–4.5%, respectively, of men with NGU receiving each drug. (Not all microbiologic treatment failures would lead to clinical failures; thus, this number would be somewhat lower when considering clinical failures.) Whether a difference of this magnitude justifies a change in empirical therapy is uncertain. Consultation with experts on *M. genitalium* undertaken in 2010 led to conflicting recommendations. One expert recommended that azithromycin should be the preferred agent for NGU on the basis of its superiority to doxycycline in the treatment of *M. genitalium* infection, whereas another expressed concern about single-dose azithromycin inducing resistance in *M. genitalium*, recommending that doxycycline should be the preferred therapy for NGU and extended-dose azithromycin should be given to persons with clinical treatment failure. There is little evidence about the clinical efficacy of moxifloxacin in the treatment of other causes of NGU, such as *C. trachomatis* [88], but existing data suggest that it is effective, and in vitro studies indicate that the drug is consistently active with a minimum inhibitory concentration of 0.015μg/ml–1 and a 90% minimum inhibitory concentration of 0.06μg/ml—values that are comparable to or lower than those of levofloxicin [109, 111–114]. We conclude that there is insufficient evidence to recommend any changes to the preferred regimens for NGU in recognition of the role played by *M. genitalium*. However, the alternative regimens should include moxifloxacin (400 milligrams daily for 7 days), and we recommend treatment with moxifloxacin in cases of *M. genitalium* urethritis that do not respond to first-line regimens (over currently specified alternate regimens).

Cross-sectional studies involving men seeking evaluation for persistent or recurrent NGU suggest that *M. genitalium* is responsible for 12%–41% of cases, and numerous clinical studies have documented that failure to eradicate *M. genitalium* is associated with persistent urethritis [12, 20, 40–45]. The 2006 guidelines suggest that men in whom NGU treatment fails

should be evaluated for treatment adherence and reexposure, tested for *Trichomonas vaginalis,* treated for that pathogen, and receive azithromycin (1 g) if they were originally treated with doxycycline. We believe that it is common practice to treat persons in whom azithromycin fails with doxycycline, levofloxacin, or ofloxacin, which are of uncertain efficacy against *M. genitalium*. Because of the strong evidence that *M. genitalium* is associated with NGU in men and that failure to eradicate *M. genitalium* is associated with persistent urethritis, we conclude that men treated with azithromycin who have persistent NGU in the absence of nonadherence or reexposure should receive moxifloxicin (400 milligrams daily for 7) in addition to therapy for *T. vaginalis*.

The currently recommended therapies for cervicitis are azithromycin (single 1-gram dose) or doxycycline (100 milligrams twice daily for 7 days). Although the existing evidence suggests *M. genitalium* may play a role in cases of cervicitis [23, 47, 54–58, 60], it remains somewhat conflicting, and the prevalence of *M. genitalium* infection among women with cervicitis has been variable (ranging from 8% to 27%, with 1 exception [46]). Furthermore, in some settings, *M. genitalium* is significantly more common among women infected with *C. trachomatis* [49, 115], suggesting that the 2 organisms may be found together. The sole study that has directly examined treatment outcomes in *M. genitalium*–infected women with cervicitis showed that 55%–63% of women treated with doxycycline experienced microbiologic or clinical failure, compared with only 12% of women given azithromycin [44], suggesting that azithromycin is more effective against cervicitis associated with *M. genitalium*. Nevertheless, because the causative agent most commonly detected in cases of cervicitis remains *C. trachomatis*, the currently recommended therapies for cervicitis are likely to be adequate in most cases.

We conclude that existing evidence does not support a recommendation to alter the currently recommended therapies for cervicitis in recognition of the potential role played by *M. genitalium*. *M. genitalium* may be considered in cases of cervicitis that persist after treatment with doxycycline or azithromycin. Moxifloxacin should be considered for cases of clinically significant cervicitis that persist after azithromycin or doxycycline therapy in which reexposure to an infected partner or medical nonadherence are unlikely. As with persistent NGU, it is uncertain whether women with persistent cervicitis should first be treated with azithromycin or doxycycline (ie, the drug they did not initially receive) or whether clinicians should immediately use moxifloxicin in women in whom first-line therapy fails. When possible, women with persistent cervicitis should be tested for *M. genitalium* with the decision to treat with moxifloxicin based on the results of diagnostic testing. Because of the multiple causes of female urethritis and the limited amount of data on its association with *M. genitalium*, we do not recommend treatment with moxifloxacin for persistent cases of female urethritis in the absence of a positive diagnostic test result.

The currently recommended therapy for PID consists of cefotetan (2 grams intravenously every 12 hours), cefoxitin (2 grams intramuscularly single dose or intravenously every 6 hours), or ceftriaxone (250 milligrams intramuscularly) plus doxycycline (100 milligrams twice daily for14 days) with probenicid (1 gram) when cefoxitin is delivered intramuscularly. The PID Evaluation and Clinical Health (PEACH) study provides the sole evaluation of the effectiveness of this regimen against *M. genitalium* infection in women with clinically suspected PID; 41% of *M. genitalium*–positive women experienced microbiologic failure, and 44% experienced clinical failure [68], suggesting that the standard regimens are ineffective against *M. genitalium*. Nevertheless, the prevalence of *M. genitalium* infection among women with clinically suspected PID enrolled in the PEACH study was only 6.5%, less than half of the prevalence of *C. trachomatis* (14%) or *N. gonorrhoeae* (15%). Prevalence of *M. genitalium* infection was even lower (3.6%) among women in a multicenter study conducted in Europe and South Africa, whereas prevalences of *C. trachomatis* (42%) and *N. gonorrhoeae* (31.3%) infection were substantially higher [88]. Therefore, we conclude that, in the absence of an etiologic diagnosis for *M. genitalium* infection, the existing evidence does not support a recommendation to change the current therapies for PID. Persistent cases may respond to moxifloxacin (400 milligrams daily for 14 days).

## DISCUSSION

*M. genitalium* is clearly associated with both acute and persistent/chronic urethritis in men, and men with urethritis who receive a diagnosis of *M. genitalium* infection should be treated for the infection. Available observational and randomized trial data have shown that azithromycin is superior to doxycycline in treating *M. genitalium*–associated urethritis, and *M. genitalium* should be suspected in cases of NGU that persist or recur after therapy with doxycycline. Despite the apparent superiority of azithromycin, there are increasing concerns over emerging resistance to this therapeutic agent, and only moxifloxacin has demonstrated 100% cure rates. This apparent high efficacy, however, must be balanced against the very limited amount of data available on treatment with moxifloxacin, the higher cost, and the longer duration of therapy (7–10 days, compared with a single dose for azithromycin).

Whether *M. genitalium* infection is associated with significant morbidity among women and requires therapy is the more pertinent and more difficult question to answer. The data associating cervicitis with *M. genitalium* remain conflicting. More importantly, although some data suggest that *M. genitalium* may

cause PID and the sequelae of that condition (ectopic pregnancy, infertility, and adverse pregnancy outcomes), existing evidence is inconclusive. More definitive studies of the natural history of *M. genitalium* infection in women are required before we can determine that serious reproductive health outcomes occur, in whom they occur, and how often. This final issue—how often *M. genitalium* leads to adverse sequelae—is critical, because future decisions about the importance of screening for the infection will need to be based on cost-effectiveness analyses, and the results of these analyses will depend on the magnitude of the health risks associated with the infection. The POPI trial suggests that *M. genitalium* plays a small role in PID in high-income countries, but this may not be the case in lower-income countries with higher prevalence of *M. genitalium* infection [70].

The question of when to treat for *M. genitalium* is complicated by the lack of a commercially available diagnostic test. Although some laboratories offer *M. genitalium* tests, in the vast majority of settings, clinicians are forced to make decisions about *M. genitalium* treatment based on clinical syndromes without specific diagnostic testing. Because of the prevalence of *M. genitalium* infection among persons with STD syndromes and current evidence on the effectiveness of standard therapies, we believe that currently recommended first-line treatments for NGU, cervicitis, and PID should not be altered on the basis of considerations related to *M. genitalium*. However, moxifloxacin should be considered in persistent or recurrent cases of these syndromes in settings where *M. genitalium* testing is not available. In settings with access to testing, *M. genitalium* infection should be treated with azithromycin, followed by a test of cure. If persistent infection is documented or clinical treatment failure is apparent, patients should receive moxifloxacin therapy.

## Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://www.oxfordjournals.org/our_journals/cid/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

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