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Updates in *Trichomonas* Treatment including Persistent Infection and 5-Nitroimidazole Hypersensitivity

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Abstract

Purpose of the review: The purpose of this review is to update information on treatment of *T. vaginalis*. *Trichomonas vaginalis* is estimated to be the most common treatable sexually transmitted infection (STI) in the world and is associated with poor birth outcomes, cervical cancer, sperm motility and morphology issues, and HIV acquisition and transmission.

Recent findings: The efficacy of the recommended 2 gram oral single-dose metronidazole (MTZ) for the treatment of *T. vaginalis* in women has recently been challenged. Two recent multi-centered randomized trials and a meta-analysis have demonstrated that the 7-day dose of MTZ 500 mg twice daily was nearly two times more efficacious at clearing infection compared to the 2 gram dose. Partner treatment is also essential, since up to 70% of male sexual partners can be infected and rescreening of treated women at 3-months is also recommended given the high repeat infection rates. Future studies should examine the importance of treating asymptomatic *T. vaginalis*, best treatment for men, the influence of the microbiome on treatment efficacy, and different formulations of intra-vaginal treatments for hypersensitivity.

Summary: 7 day 500 mg twice daily MTZ should be used as the first line treatment for *T. vaginalis* infected women.

Keywords

Trichomonas vaginalis; persistence; hypersensitivity; treatment; treatment failure

Introduction

T. vaginalis is estimated to be the most common non-viral sexually transmitted infection (STI) worldwide among women.(1). Globally, the estimated prevalence of *T. vaginalis* in women aged 15-49 is 5.3% (higher than estimates of chlamydia, gonorrhea, and syphilis)

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Conflicts of Interest

Christina A. Muzny, MD, MSPH is a consultant for Lupin Pharmaceuticals, BioFire Diagnostics, and Cepheid. She has also received honoraria from Roche Diagnostics and Becton Dickinson. Olivia T. Van Gerwen, MD, MPH and Patricia Kissinger, Ph.D declare no conflicts of interest.

and 0.6% in men (higher than estimates of syphilis). The large discrepancy in prevalence rates between sexes could be due to less testing in men or possibly spontaneous resolution of *T. vaginalis* in men, which has been found to occur in 36-69% of cases.(2, 3) The global incidence of trichomonas is 156 million cases per year; higher than that of chlamydia, gonorrhea, and syphilis.(1) Recent U.S. national prevalence data have found *T. vaginalis* to be present in 1.8% of women aged 18-59 years and 0.5% of men, with a significant racial disparity in African Americans.(4) Prevalence of *T. vaginalis* among pregnant women varies geographically and with the presence of HIV co-infection, ranging from 16%-53% in the U.S.,(5-7) 17-20% in Africa (8-10), and 0.8% in Asia (11). In addition, a recent African study found a trichomonas incidence during pregnancy of 9.2 per 100 person years, higher than that of gonorrhea and HIV.(12) Yet, despite the high global and national burden of disease, trichomoniasis is not reportable and there are no established screening, surveillance, or control programs for women or men in the U.S or elsewhere.(13)

T. vaginalis is associated with adverse birth outcomes such as preterm birth, premature rupture of membranes, and small for gestational age infants.(14) It has also been linked to cervical cancer in women(15) and impaired sperm quality in men (16) as well as increased risk of acquisition and transmission of HIV and other STIs.(14, 17)

For over three decades, single-dose (2 grams) metronidazole (MTZ) has been the recommended treatment for *T. vaginalis* in women and men in the U.S.(18) Single-dose (2 grams) tinidazole (TDZ) is an additional recommended treatment regimen which has better absorption and fewer gastrointestinal effects than MTZ. However, it is significantly more expensive.(19) Multi-dose MTZ (500 mg twice daily for 7 days) is currently listed as an alternative therapy.(18) Single-dose MTZ is well-accepted by patients and providers alike and can be given as directly observed therapy (DOT). However, several recent studies in women have found this dose to be less effective than the multi-dose regimen.(20-22) Here we provide a discussion of our current opinions regarding the optimal treatment of trichomoniasis in women, briefly mentioning treatment options currently under investigation. We then discuss the lack of rigorous data on the optimal treatment of *T. vaginalis*-infected men. Following this, we provide our recommendations for the treatment of persistent *T. vaginalis* infection and as well as treatment in the setting of severe hypersensitivity reactions to 5-nitroimidazole medications (i.e. MTZ and TDZ), two scenarios which are becoming increasingly more common in our clinical practice. We end by proposing next steps for future studies in this line of research.

Updates in Trichomonas Treatment in Women and Men

Similar to our prior RCT in HIV-infected women with *T. vaginalis* (20) as well as a meta-analysis (21), our recent RCT of 623 HIV-uninfected women with *T. vaginalis* (22) found that women receiving multi-dose MTZ were significantly less likely to be *T. vaginalis* positive at test-of-cure (TOC) than those receiving single-dose (11% vs. 19%, RR 0.55, 95% CI 0.34-0.70; p<0.0001). This finding remained robust in multiple sensitivity analyses (i.e. when a positive *T. vaginalis* culture was used as the outcome at TOC instead of a positive nucleic acid amplification test (NAAT), to remove potential misclassifications that could occur from detection of remnant RNA during NAAT testing). (23) Rates of sexual re-

exposure after *T. vaginalis* treatment were similar in both arms of this study and self-reported MTZ adherence was 96% in the multi-dose group compared to 99% in the single-dose group. In a secondary analysis of these data, (24) women reporting a history of *T. vaginalis* and receiving multi-dose MTZ were significantly less likely to be *T. vaginalis* positive at TOC than those receiving single-dose therapy (11% vs. 24%; $p=0.009$). Similarly, symptomatic women with *T. vaginalis* treated with multi-dose therapy were significantly less likely to be *T. vaginalis* positive at TOC than women receiving single-dose therapy (11% vs. 21%; $p=0.003$). Taken together, these data strongly suggest that multi-dose MTZ should be the recommended *T. vaginalis* treatment regimen in all women moving forward, particularly those with a history of *T. vaginalis* infection and/or are symptomatic.

TDZ has a shorter half-life and less side effects than MTZ (25) but is a class C drug and cannot be used in pregnancy or during lactation. It is also 2-3 times more expensive than MTZ. Despite prior concerns of teratogenicity associated with MTZ use during pregnancy, several meta-analyses support treatment of trichomoniasis with MTZ at all stages in pregnancy, including the first trimester, with cure rates as high as 90%.(26-28) Providers are encouraged to avoid higher dose MTZ regimens in this setting (i.e. doses greater than 400-500 mg twice daily for 7 days).(28)

Several potential effects may be accounting for the superior efficacy of multi-dose MTZ versus single-dose MTZ in women.(29) One potential effect is competition for MTZ by other micro-organisms present in the vaginal microbiota (i.e. *Escherichia coli*, *Enterococcus faecalis*, *Proteus* spp., and *Klebsiella* spp.; aka “sponge organisms”) which are known to absorb MTZ but are unable to reduce it. This process of MTZ inactivation may result in lower drug concentrations at the site of infection below that required to be trichomonocidal to the organism. Treatment success may thus depend upon saturating these organisms through scheduled, successive doses of MTZ (i.e. multi-dose therapy). Another potential effect is inadequate accumulation of active MTZ metabolites (i.e. hydroxyl-metronidazole) during single-dose therapy, potentially decreasing the drug’s therapeutic contribution. Significant accumulation of these active metabolites may occur with repeat dosing in the multi-dose MTZ regimen. Future pharmacokinetic and pharmacodynamic studies with MTZ should be performed to further investigate these potential hypotheses.

While future *T. vaginalis* treatment guidelines may change for women, no head-to-head comparison of single-dose and multi-dose MTZ has been performed in men to inform a change. Current CDC recommendations for *T. vaginalis* treatment in men have largely been extrapolated from studies conducted in women, with single-dose MTZ or TDZ as the recommended regimen.(30) The few studies that have examined treatment outcomes in mostly symptomatic men receiving single-dose MTZ found treatment success rates to be suboptimal from 57.1% (31) to 77.1%.(32) However, these studies were small and did not have a 7 day multi-dose MTZ comparison group. A head-to-head comparison of single-dose versus multi-dose MTZ is thus needed to provide the necessary data to refine treatment recommendations in men. Until this occurs, trichomoniasis treatment will likely be different based on the sex of the patient moving forward. To our knowledge, this is a unique and challenging situation that has never occurred for any STI.

An additional 5-nitroimidazole, secnidazole (SEC), which was recently FDA-approved for treatment of bacterial vaginosis (BV) in women (33, 34), is currently under investigation for treatment of *T. vaginalis*-infected women in a phase 3, multi-center, prospective, randomized, placebo-controlled, delayed treatment, double-blind study (NCT03935217). SEC is given as a single-dose of 2 gram of oral granules which must be taken with unsweetened applesauce, pudding, or yogurt. Its primary advantage is its ability to be taken as a single-dose therapy however, similar to TDZ, it is more expensive than MTZ.(19)

Treatment Regimens for Persistent Infection

Persistent infection with *T. vaginalis* can occur in several circumstances, the most common of which is re-infection from an untreated sexual partner(s). A detailed sexual history should be taken to assess the likelihood of re-infection. Persistent infection may also occur in the setting of inadequate medication adherence (a potential disadvantage of multi-dose therapy) or 5-nitroimidazole drug resistance. *T. vaginalis* resistance to MTZ ranges from 4.3%-9.6%, mostly mild to moderate, and TDZ resistance is <1% (35, 36).

If re-infection has been excluded, persistent trichomoniasis has been treated successfully with longer courses or higher doses of the same medications used in standard therapy (i.e. high-dose oral MTZ or TDZ 2 grams orally daily for 7 days).(30) Single-dose 2 gram MTZ or TDZ should be avoided in this circumstance. In the US, If drug resistance is suspected, the isolate may be sent by to the CDC for 5-nitroimidazole drug resistance testing (<https://www.cdc.gov/laboratory/specimen-submission/detail.html?CDCTestCode=CDC-10239>). If a patient fails the 7-day regimen of high-dose oral MTZ or TDZ, two additional treatment options are high-dose oral TDZ 2–3 grams daily (in divided doses) plus intravaginal TDZ 500 mg twice daily for 14 days(37) and high-dose oral TDZ (1 grams three times daily) plus intravaginal paromomycin (4 grams of 6.25% intravaginal paromomycin cream nightly) for 14 days.(38) Intravaginal formulations need to be compounded.

In a recent retrospective cohort study of 542 pregnant women at an academic medical center in Charleston, South Carolina, 44% (143) had evidence of persistent *T. vaginalis* infection upon repeat NAAT testing 21 days or more after treatment. Rates of persistent *T. vaginalis* infection in this cohort were similar among those treated with single-dose MTZ and those treated with multi-dose therapy.(39) The authors of this study suggested that all pregnant women with trichomoniasis should undergo repeat NAAT testing 3 weeks after treatment to ensure cure. Testing before 3 weeks, however, can lead to false positives.(40)

Treatment in the Setting of 5-Nitroimidazole Hypersensitivity

Women with trichomoniasis who report a previous serious adverse reaction to 5-nitroimidazoles (i.e. Ig-E mediated hypersensitivity, generalized fixed drug eruption) present a difficult therapeutic conundrum. MTZ desensitization per a validated protocol with the assistance of an allergy specialist is recommended in these situations.(18, 41-43) While 5-nitroimidazoles are the only antimicrobial class known to be effective against *T. vaginalis*, there is anecdotal evidence for alternative regimens. Given its demonstrated trichomonacidal

activity in vitro,(44) intra-vaginal boric acid (BA) 600mg twice daily for 60 days has been used in this clinical setting with some success.(45)

Intra-vaginal paromomycin has also been used to treat trichomoniasis in 5-nitroimidazole intolerant patients in settings where MTZ desensitization is not possible. One case series from Britain reports successful eradication of *T. vaginalis* 117 days following a 14-day twice daily treatment course of 6.25% paromomycin intravaginal pessaries.(46) However, use of intra-vaginal paromomycin has been associated with vaginal ulceration which may limit its tolerability by some patients but will regress once therapy is stopped.(47) At this time, there is scant evidence to support the routine use of either intra-vaginal BA or paromomycin in the treatment of *T. vaginalis* outside of the setting of 5-nitroimidazole hypersensitivity and the ideal dosing regimens to optimize both tolerability and efficacy are not known.

Conclusion/Next Steps

CDC and WHO are likely to adopt the 7-day 500 mg twice daily treatment as standard of care for women. but the 2-gram treatment is likely to continue to be recommended for men. The discordance in treatment time may lead to unintended transmission. A better understanding of the natural history in men and RCTs in men are needed to determine the best treatment in men. Most treatment studies have been conducted among symptomatic women. More studies are needed to determine the benefit of treating asymptomatic persons. The effectiveness of newer drugs such as SEC, and different configurations of existing drugs, such as pulse dosing, are needed. Given the evidence for the influence of the vaginal microbiome on *T. vaginalis* acquisition and treatment, more research is needed drug combinations that cover *T. vaginalis* and other co-infections. There is also a need for effective and tolerable intra-vaginal medications in the case of hypersensitivity.

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*of special interest

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Key Points

- *T. vaginalis* is associated with poor birth outcomes, cervical cancer and amplified HIV transmission.
- 7-day 500 mg oral MTZ is superior to 2 gram single-dose and should be the preferred treatment.
- While alternative intra-vaginal treatments are available for MTZ hypersensitivities, more options are needed.