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FEMALE GENITAL TRACT INFECTIONS (J SOBEL, SECTION EDITOR)

Management of Resistant Trichomoniasis

Cynthia Alessio[1] · Paul Nyirjesy[1]

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Abstract

Purpose of Review *Trichomonas vaginalis* is the most prevalent sexually transmitted parasite in the USA; resistant infection is emerging. New drug therapies and dosing regimens of standard therapies are being studied to treat resistant infection.

Recent Findings Diagnosis of trichomoniasis has become more sensitive, specific, and widely available with the advent of nucleic acid amplification tests (NAATs). Women with resistant trichomoniasis should be treated with high-dose regimens of metronidazole or tinidazole. Alternative treatment options have been described, and there has been some success particularly with high-dose tinidazole/intravaginal paromomycin cream combination, intravaginal boric acid, and intravaginal metronidazole/miconazole.

Summary Resistant trichomoniasis is a growing public health concern with implications for long-term health consequences. More data are needed to further evaluate mechanisms by which resistance occurs as well as promising therapies for those affected.

Keywords *Trichomonas vaginalis* · Trichomoniasis · Metronidazole · Tinidazole · Resistant trichomoniasis · Metronidazole resistance

Introduction

Affecting an estimated 3.7 million men and women, trichomoniasis is the most prevalent nonviral sexually transmitted infection (STI) in the USA [1]. It is more prevalent than chlamydia, gonorrhea, and syphilis combined [2]. Health disparities related to the epidemiology of the infection are prominent. Unlike most STIs, prevalence increases with age; an estimated 11% of infections occur among women over 40 years of age. Prevalence is also high among non-Hispanic black women, incarcerated individuals, women infected with HIV, STI clinic patients, and drug users [1]. Similar to bacterial vaginosis, trichomoniasis has been associated with long-term sequelae including pelvic inflammatory disease, which can impact future fertility, as well as contribute to poor pregnancy outcome and increased transmission of HIV [3]. Since the 1950s, the mainstay of therapy has been the nitroimidazoles, a drug class demonstrating high cure rates against *T. vaginalis.* However, persistent and recurrent infections are becoming a greater concern as the incidence of treatment failure due to resistant infection rises.

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✉ Paul Nyirjesy
pn35@drexel.edu

Cynthia Alessio
cynthia.alessio@gmail.com

[1] Department of Obstetrics and Gynecology, Drexel University College of Medicine, 245 N. 15th St. MS 495, Philadelphia, PA 19102, USA

Clinical Presentation

T. vaginalis preferentially infects the urethra of men and women as well as the vagina and endocervix of women. It is unclear if the rectal or oral cavity can be a reservoir, as few studies have evaluated these sites [1]. Approximately 50 to 60% of infections in women are asymptomatic [4]. The most common symptom is vaginal discharge, which is usually frothy and yellowish-gray or green in color and often associated with a pH > 4.5. Other symptoms include dyspareunia, dysuria, lower abdominal pain, and vulvovaginal irritation [5]. Physical findings may include vulvovaginal erythema, discharge, and rarely, punctate hemorrhages of the vaginal mucosa or cervix, termed colpitis macularis or "strawberry cervix." Common symptoms in men include urethral discharge,

pruritis, dysuria, urinary frequency, and lower abdominal pain [6]. It can also cause epididymitis, prostatitis, and decreased sperm motility [2].

Screening

There are currently no guidelines for the optimal frequency of screening asymptomatic patients for *T. vaginalis*. The CDC recommends testing symptomatic women with vaginal discharge, as well as women who are at high risk for contracting an STI. Local or regional prevalence may be taken into account. Regarding HIV-infected women, screening is recommended at least annually due to high prevalence and increased risk of PID. There is also an increased risk of transmitting HIV with a concomitant trichomoniasis infection and potential for decreased viral load and shedding with treatment. Screening in pregnancy is at the discretion of the provider, as routine screening is currently not recommended [1].

Diagnosis

Trichomoniasis can most commonly be diagnosed using microscopic evaluation of vaginal secretions via saline microscopy. Microscopy can be performed at point of care for low cost, but the sensitivity of this method is poor, ranging between 51 and 65%. It detects motile organisms only when present in vaginal secretions in high concentrations. Furthermore, the sample must be evaluated immediately, within 30 min of obtaining it [1, 7]. Prior to the development of molecular testing, culture was considered the gold standard for diagnosis of *T. vaginalis*. Sensitivity for culture is around 75–96% with a specificity of up to 100% [1]. Traditionally, our impression has been that culture was a relatively underutilized testing modality because many providers did not have culture medium available when needed. A further limitation of culture is that sensitivity may be less than 40% in men [3]. Although a Pap smear can also detect *T. vaginalis*, its sensitivity is similar to saline microscopy; the positive predictive value may be as low as 61.7%, and false positives can occur up to 31% of the time [7–9].

Nucleic acid amplification testing (NAAT) is now available for the detection of *T. vaginalis* with sensitivities higher than those of wet mount and culture. The APTIMA *Trichomonas vaginalis* assay (Hologic Gen-Probe; San Diego, CA) was FDA cleared in 2011 and can detect *T. vaginalis* RNA by transcription-mediated amplification from vaginal and endocervical swabs, thin prep samples, and urine [1, 8]. This assay has a clinical sensitivity of 95.2–100% and a specificity of 95.3–100%. Additionally, this assay can be used with urethral swabs or urine from men. The Cobas Amplicor CT/NG PCR assay (Roche, Indianapolis, Indiana) is FDA cleared for the detection of chlamydia and gonorrhea; however, it can be modified for *T. vaginalis* using vaginal and endocervical swabs, or urine. Sensitivities range from 88 to 97% and specificities from 98 to 99% [1, 10]. The Xpert TV test (Cepheid; Sunnyvale, CA) works by amplifying microbial DNA and provides results in 45 min. Sensitivity is 96–99% and specificity is 99%. Specimens can be obtained from both men and women [11, 12]. Lastly, the BD Max CT/GC/TV (MAX) assay is another NAAT for detection of chlamydia, gonorrhea, and trichomonas. *T. vaginalis* sensitivity was 96.1% for vaginal swabs, 93.4% for endocervical swabs, and 92.9% for female urine samples per a study by Van Der Pol et al. [13]. Specificity across all sample types was > 98.6%. Because *T. vaginalis* commonly occurs in conjunction with other STIs, testing for these three highly common infections simultaneously may potentially lead to better patient management [14].

Other options for testing for trichomoniasis include the OSOM Trichomonas Rapid Test (Sekisui Diagnostics; Framingham, MA), which detects antigens using immunochromatographic capillary flow dipstick technology [1]. Results of this test are ready within 10 min with a sensitivity of 82–95% and specificity of 97–100% [15]. Finally, recent studies have shown that the Affirm VP III (BD Diagnostic Systems, Sparks, MD), a commonly used nucleic acid probe-hybridization test for vaginal infections, has a lower than expected sensitivity of 46% [16]. Furthermore, the OSOM and Affirm VP III tests cannot be used to evaluate specimens from men [1].

Treatment

Standard of Care

Recommended medications for the treatment of trichomoniasis are metronidazole and tinidazole, which are both nitroimidazoles. A one-time 2-g dose of either drug orally has been considered standard therapy and has been recommended by the CDC [1, 15]. Metronidazole has been the mainstay of therapy since 1959. It is easily absorbed into the gastrointestinal tract with > 90% bioavailability. Peak plasma concentrations reach 40 mg/l after a single 2-g oral dose and 8 to 13 mg/l after 500 mg. The ability of metronidazole to exert its killing effect on *T. vaginalis* is concentration dependent under anaerobic conditions at a concentration ranging from 0.1 to > 8 mg/l. The drug is able to reach the necessary plasma concentration in most tissues including the uterus and fallopian tubes. Of interest, studies have suggested that it is not always detectable in vaginal secretions [3]. It is unclear whether insufficient drug concentrations in the vagina play a role in persistent infection and treatment failure.

Cure rates for a single dose of metronidazole is 90–95% and 86–100% for tinidazole [10]. An alternate regimen of metronidazole 500 mg twice daily for 7 days is recommended by the CDC as an alternative first-line regimen. Although single-dose therapy is convenient, especially for patients with compliance issues, evidence has shown that single-dose therapy may not always be sufficient for complete eradication and is more likely to be associated with side effects [2, 3]. Furthermore, a recent meta-analysis by Howe and Kissinger, which showed that treatment failure is 1.87 times more likely with a single-dose regimen of metronidazole as compared with a multidose, raises concerns about the effectiveness of a single 2-g dose of metronidazole [17••], and current evidence suggests that a single 2-g dose should no longer be used to routinely treat trichomoniasis. Metronidazole gel does not reach therapeutic levels in the vagina and is currently not recommended [15].

Tinidazole has a mechanism similar to metronidazole but has a longer half-life and can achieve greater serum levels. Because it is about ten times more expensive than metronidazole, most providers use it as second-line therapy for most cases of trichomoniasis [1]. Oral tinidazole has > 90% bioavailability when taken orally and a 2-g dose can produce peak plasma concentrations between 40 and 58 mg/l, far greater than that of metronidazole. In vitro data demonstrate that 60% of *T. vaginalis* isolates had a lower minimum lethal concentration (MLC) for tinidazole compared with that for metronidazole, further enhancing clinical efficacy [3, 18].

Partner Treatment

Because the infection can be readily passed between sex partners, both partners should receive the same treatment. One study showed 72% of male sex partners of women with trichomoniasis were also infected and 77% of them were asymptomatic [3]. Oftentimes, providers advise patients that their partner should be tested and treated. However, sensitive tests for men are not readily available. Providers may consider presumptively treating partners by expedited partner therapy (EPT) and providing prescriptions or medications to the patient for their partner [2]. Optimal timing for a test of cure has not been established for NAAT and testing too soon could detect remnants of nucleic acid from nonviable organisms that have been treated. Per the CDC, the patient can be re-tested as early as 2 weeks following treatment; however, the studies supporting this do not consider sexual exposure or treatment failure. A study by Craig-Kuhn et al. demonstrated that the optimal timing for NAAT re-testing following completion of treatment without sexual re-exposure is 3 weeks for patients who received multidose metronidazole and 4 weeks for those who received single dose. This time frame allows for clearance of the trichomonal nucleic acid and avoids unnecessary re-treatment [19]. A test of cure for all sexually active women should be performed within 3 months, even if the patient is asymptomatic, to ensure that she is cured and to allow for the evaluation of possible re-infection [8, 15].

Alternative Treatments for Nonresistant *T. vaginalis*

Other nitromidazoles such as fexinidazole, secnidazole, and ornidazole are used as antiparasitic agents in other countries, but, with the exception of secnidazole, which is newly available for treatment of bacterial vaginosis, have not been approved in the USA and have not yet been studied for treatment of resistant infection [1]. *Mentha crispa* is a peppermint herbal medication with a similar efficacy as secnidazole in a small randomized trial performed in Brazil [20]. Other topically applied agents, including intravaginal povidone-iodine, clotrimazole, acetic acid, furazolidone, gentian violet, nonoxynol-9, and potassium permanganate, have not been shown to be effective and are not currently recommended by the CDC [15]. There are no reports of these drugs being studied for use in resistant infection [3].

Pathogenesis of Resistant Infection

Resistant trichomoniasis is primarily a clinical diagnosis, where a woman presents with an ongoing infection after taking appropriate treatment. As such, resistant trichomoniasis must be distinguished from reinfection and medication noncompliance. Reinfection may be acquired from a new partner or because the current partner was untreated or inadequately treated, possibly reinfected from another partner. Treatment failure can range from 7 to 10%, but the prevalence of resistant infection is estimated to be about 2–5% [2, 3].

Metronidazole resistance has been clinically defined as failure to cure infection after two courses of treatment [5, 21]. Insufficient absorption of metronidazole or inadequate transport of the drug to the site of infection may play an occasional role in treatment failure [22], but metronidazole resistance of the organism itself seems to be related to alterations in the chemical reaction required for the drug to take effect. Resistance can occur under both aerobic and anaerobic conditions by way of different mechanisms [3]. Nitroimidazoles are prodrugs requiring reductive activation of the nitro group in order to become active. The release of toxic-free radicals such as hydrogen peroxide and nitro radicals allows for metronidazole's trichomonacidal activity [23•]. Decreased oxygen scavenging in the cell leads to higher intracellular oxygen concentration allowing for resistance to occur. Furthermore, expression of flavin reductase 1, an enzyme playing a role in the reduction of the nitro group, has been found to be downregulated in metronidazole-resistant *T. vaginalis*. Correlations have also been found between metronidazole resistance and mutations in the genes for nitroreductase enzymes, which are also essential in this reaction [24].

Treatment of Resistant Infection

In general, treatment of resistant trichomoniasis infections is primarily empirical, and the initial plan as recommended in CDC guidelines is to give higher doses of nitroimidazoles. Patients with suspected resistance should initially be treated with a higher dose of metronidazole of 500 mg twice daily for 7 days [8, 21]. If this treatment fails, high-dose metronidazole or tinidazole should be used (2 g orally for 7 days) [15]. If this latter regimen does not work, tinidazole should be considered the primary nitroimidazole to be used. Tinidazole resistance occurs in only an estimated 1% of cases of vaginal trichomoniasis [21]. Furthermore, tinidazole seems to be more active against isolates that have demonstrated resistance. For subsequent failures, even higher doses of oral tinidazole can be used (2 to 3 g orally for 14 days), in combination with intravaginal tinidazole 500 mg twice daily [15].

CDC guidelines also discuss the option of in vitro susceptibility testing of resistant isolates [1, 15]. A study by Bosserman and colleagues examined isolates undergoing susceptibility testing from women who had failed at least 2 courses of standard therapy for trichomonas. In vitro, 115 of 175 isolates demonstrated metronidazole resistance. Resistance to tinidazole was similar or lower. Out of the women who received an alternative recommended nitroimidazole treatment based on susceptibility testing, 82% were cured compared with 53% of women who received a lower dose than recommended. Thus, susceptibility testing may be beneficial for management of women with persistent infection [22]. Several in vitro studies have looked at the level of metronidazole resistance; however, more data is needed to determine if there is any relationship to clinical response to treatment [25–27]. Although susceptibility testing may help guide treatment, it is important to remember that metronidazole resistance is ultimately a clinical diagnosis. Susceptibility testing for tinidazole is encouraged but it is not mandatory and the benefits are unclear.

Beyond the nitroimidazoles, compounded vaginal paromomycin is an approach to treatment which has been used with the greatest success in resistant infections. Paromomycin is an aminoglycoside which destroys ribosomal RNA. It is not absorbed by the GI tract and must be used vaginally. Used as solo therapy, paromomycin cream may have a relatively high failure rate. Of further concern, it can cause acute vulvar ulcers, which are self-limited but can be very painful [18]. To mitigate the possibility of ulcers, we routinely recommend that patients apply petrolatum liberally to the vulva and vestibule to protect the area, and that they stop use of the cream immediately if they begin to notice any vulvar or vaginal pain while using it. Management of resistant trichomoniasis was reviewed by Miller and Nyirjesy in 2011, and at the time, the best treatment options for which there was the most published experience were high-dose oral and vaginal tinidazole or high-dose oral tinidazole with paromomycin cream [6]. Table 1 summarizes data about what we consider the best options for treating patients with highly resistant infections.

Since our earlier review, case reports have shown that high-level nitroimidazole-resistant trichomoniasis can be treated successfully with a combination of high-dose oral tinidazole (1 g three times a day) and intravaginal paromomycin cream (6.25%, 5 g vaginally nightly) for 14 days. Two cases of patients with infections resistant to high-dose metronidazole and tindazole were cured with a combination of high-dose oral tinidazole and vaginal paromomycin cream [35]. In a more recent case, we described a patient with a resistant infection who initially, mistakenly, took high-dose oral tinidazole, followed by a course of vaginal paromomycin cream, but was not cured [36••]. She subsequently took the same two medications, but this time in combination, and was successfully cured. This case illustrates the possibility that paromomycin and tinidazole, which have completely different mechanisms of action, may have either an additive or possibly even a synergistic effect. To our knowledge, there has not been a single treatment failure with this combination.

Since our last review, a new option for treating trichomoniasis, boric acid, has been described. Boric acid is an inorganic acid that has long been used for the treatment of vulvovaginal candidiasis, especially for non-*Albicans candida*, as well as more recently an adjunct to treatment for women with recurrent bacterial vaginosis. The usual dose for these vaginal infections is 600-mg capsule administered vaginally every night for a variable amount of time. In vitro studies have suggested activity against *T. vaginalis* by inhibiting its growth across a range of vaginal pHs. Activity appears dose dependent; case reports have demonstrated *T. vaginalis* clearance, particularly in women who have failed metronidazole therapy and in those with a metronidazole allergy. A review of cases reports by Thorley [37••] demonstrated clearance of *T. vaginalis* using boric acid in a variety of intravaginal dosing regimens, ranging from 600 mg every other night up to 600 mg twice daily over the course of 1 to 5 months. In general, across all uses, vaginal boric acid is well tolerated, inexpensive, and widely available. Thus, the possibility that vaginal boric acid may be a useful option for a clinical scenario where the options are limited and, in the case of tinidazole, expensive, is encouraging. However, it should be emphasized that experience with boric acid for trichomoniasis remains very limited.

Finally, Byun and colleagues reported 8 cases of trichomoniasis, all of which had failed to respond to various nitromidazole dosing regimens, which were treated with 1% zinc sulfate douches with or without oral tinidazole for 14–28 days [5]. All of the patients were described as clinically improved with negative saline microscopy, but the absence of negative cultures or NAATs after treatment greatly limits the

Table 1 Primary options for treating metronidazole-resistant trichomoniasis

Treatment	Formulation	No., treated	No. (%), cured	Adverse effects
Tinidazole [28–30]	500 mg PO BID + 500 mg PV BID × 14 days	24	22 (92%)	GI intolerance
	OR 1 g PO TID + 500 mg PV TID × 14 days	2	2 (100%)	Metallic taste, mild nausea
	400 mg PO TID × 10 days	3	3 (100%)	
	500 mg PO TID × 10 days (and × 7 days)	1	1 (100%)	
	2 g PO state dose			
Paromomycin [29, 31–34]	6.25% cream, 5 g applicator PV daily × 14 days	13	8 (62%)	Vaginal ulceration
	250 mg tablet (Gabboral) PV BID × 14 days (stopped after 10 days)	1	1 (100%)	Vaginal pain and ulcers
	250 mg suspension in unguentum base, PV daily × 7 days (stopped after 2 days)	1	1 (100%)	Vaginal ulceration, resolved with saline soaks
	6.25% cream, 5 g applicator PV daily × 7 days (stopped after 5 days)	1		
Paromomycin/Tinidazole [35, 36••]	1 g tinidazole PO TID + 4 g of 6.25% intravaginal paromomycin cream, 5 g, nightly × 14 days	1	1 (100%)	Mild irritation
	Paromomycin 6.25% cream – 5 g PV daily + tinidazole 1 g PO TID × 14 days	2	2 (100%)	
Boric Acid [37••]	600 mg intravaginal BA BID × 2 months	1	1 (100%)	
	600 mg intravaginal BA + intravaginal clotrimazole alternating nights × 5 months	1	1 (100%)	
	600 mg intravaginal BA BID + intravaginal gentian violet applied once weekly × 1 month	1	1 (100%)	
	600 mg intravaginal BA BID × 60 days	1	1 (100%)	

ability to draw conclusions from this experience. On a separate note, Chacon and colleagues have shown that chlorinated metronidazole, an analog of metronidazole, which produced higher rates of free radicals increasing the efficacy of the drug, may be more effective against *T. vaginalis* in vitro, but clinical experience with this formulation of metronidazole is lacking [23•].

Treatment of Resistant Infection in Partners

To our knowledge, there are very limited data that address how to treat metronidazole-resistant *T. vaginalis* strains in men. In case series of the partners of women with resistant strains, metronidazole 500 mg twice daily for 7 days, used in three partners, was the most commonly used treatment [28–30]. When we have treated women with resistant trichomoniasis, if they are still with their current male partners, we recommend that they take tinidazole 1 g daily for 7 days. To date, none of our patients have returned with a newly acquired *T. vaginalis* infection, but our experience should be considered anecdotal at best.

Metronidazole Hypersensitivity Reactions

There have been instances of adverse reactions to metronidazole including urticaria, pruritis, erythema, anaphylaxis, angioedema, and gastrointestinal distress. Reactions do not always recur with repeated doses. Tinidazole is closely related to metronidazole and data on cross-reactivity is highly limited, though similar adverse reactions have been documented [3, 8]. Thus, metronidazole desensitization should be performed. Oral and intravenous incremental dosing protocols for increasing doses of metronidazole being given over the course of a day have been used to desensitize patients successfully [38]. A study by Helms et al. demonstrated that out of 15 women who received metronidazole desensitization by a published IV or oral regimen, 100% were cured of infection. One woman who received the oral regimen developed a pruritic rash which resolved with steroids and another woman who received the IV regimen developed mild urticaria and pruritis, managed with antihistamines. Of the women with suspected metronidazole allergy who were treated with alternative regimens instead of undergoing desensitization, only about 42% were cured [38]. For patients unable to undergo metronidazole desensitization, it may be reasonable to try tinidazole desensitization. It may also be reasonable to try an alternative regimen such as paromomycin cream, paromomycin cream in combination with high-dose tinidazole, or boric acid. However, there is no data on how well these alternative regimens work in this patient population.

Conclusions

T. vaginalis is a highly prevalent sexually transmitted infection worldwide and the true incidence is likely underestimated due to the fact that it is nonreportable. Fortunately, the

proportion of resistant infection is low but for those affected by it, the burden can be physically and emotionally substantial. The drugs available to treat *T. vaginalis* are highly limited as well as the data supporting alternative regimens for persistent infection. Future studies are needed to further examine the mechanisms by which resistance develops and new treatment regimens that can overcome it. The long-term health consequences associated with persistent infection must also be investigated.

Compliance with Ethical Standards

Conflict of Interest Dr. Alessio has no conflicts of interest to disclose.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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