Managing Resistant *Trichomonas* Vaginitis

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Vaginal trichomoniasis is a sexually transmitted disease of worldwide importance that is commonly treated with metronidazole. Although surprisingly uncommon, resistance to metronidazole has nevertheless been widely reported. Patients with suspected resistant trichomoniasis should have the diagnosis confirmed either by visualization of motile trichomonads on saline microscopy or by culture. In addition, reinfection from a partner must be ruled out through a careful history. Data regarding treatment of metronidazole-resistant trichomoniasis are mainly limited to case reports or series. Most cases can be treated successfully with increasing doses of oral metronidazole. Other promising options include oral tinidazole and topical paromomycin cream.

Introduction

Vaginal trichomoniasis is a common sexually transmitted disease (STD), with an estimated annual incidence of 170 million cases worldwide [1••] and 3 million in the United States alone [2]. As with other STDs, the prevalence of vaginal trichomoniasis depends largely on the overall level of sexual activity of the group of women being studied, with a range from 5% in family planning clinics to 75% in studies of prostitutes [1••]. Female behavioral factors such as the number of lifetime and recent sexual partners, history of other STDs, and nonuse of barrier or oral contraceptives have been associated with *Trichomonas vaginalis* infection [3]. Asymptomatic men and women probably represent the primary reservoir for this organism.

Trichomoniasis is asymptomatic in up to 25% to 50% of affected women [1••]. When symptomatic, it causes an abnormal purulent, frothy, or bloody discharge, often accompanied by vaginal malodor, pruritus, and dyspareunia. Some affected individuals complain of postcoital bleeding. Other manifestations of trichomoniasis can occur if the infection causes a urinary tract infection, Bartholin's gland infection, or pelvic inflammatory disease [1••]. Physical examination findings include varying degrees of vulvar erythema and excoriations, vaginal erythema and edema, an abnormal discharge, and punctate hemorrhage of the cervix (strawberry cervix). The classic frothy discharge of *T. vaginalis* infection is seen in only 12% of cases, and the strawberry cervix occurs in only 2% [1••]. Relying on history or physical examination alone would therefore miss most patients with trichomoniasis.

Evaluation of a patient with trichomoniasis may reveal a positive whiff or amine test and an elevated pH. In most cases, however, the diagnosis ultimately rests on examination of the saline smear, where live motile trichomonads can be identified. Additional microscopic findings include an increase in leukocytes and a shift away from the normal bacillary flora. However, data show that the wet smear has a sensitivity of 55% to 60% [4,5]. Some clinicians rely on the Pap test for diagnosis, but its sensitivity is similar to that of the wet mount and it carries a false-positive rate of at least 8% [4]. In cases in which the diagnosis remains in question, culture techniques for *T. vaginalis* can detect as few as 300 trichomonads/mL of inoculum [1••]. I consider use of *T. vaginalis* cultures in patients with a history of previously diagnosed trichomoniasis with persistent symptoms or in patients with a high vaginal pH in whom microscopy reveals increased leukocytes and an altered vaginal flora but no trichomonads. One particularly easy way to perform *Trichomonas* cultures is the InPouch TV culture system (Biomed Diagnostics, San Jose, CA), a two-chambered bag system that allows wet-mount microscopic examination through the bag and obviates the need for repeated sampling of the culture to detect positive specimens. Polymerase chain reaction tests for *T. vaginalis* may soon be more widely available and further aid in the detection of this organism.

The only approved medication available in the United States for the treatment of trichomoniasis is metronidazole, which can be given as a single 2-g oral dose or as a 7-day course of 500 mg twice daily, with an expected cure rate of 90% [6••]. Metronidazole enters the cell wall through diffusion, where the nitro group of the drug is reduced anaerobically by pyruvate–ferredoxin oxireductase. The nitro radical-ion intermediates that are thus produced break DNA strands and cause cell death [1••]. Common side effects of metronidazole include anorexia and nausea, a metallic taste, and a disulfiram-like effect if alcohol is ingested. Although case–control studies have failed to reveal an association between birth defects and metronidazole [7], use of this drug is often avoided in the first trimester of pregnancy because it has mutagenic activity in in vitro assay systems; however, current STD treatment guidelines do not impose such a restriction on the single 2-g dose of metronidazole [6••]. It is important to counsel patients to ensure that their partners receive adequate treatment in order to avoid reinfection.

Trichomonal resistance to metronidazole was reported within 2 years of its introduction, and it has now been reported in many areas of the world. It is estimated that high-level resistance to metronidazole occurs in one in 2000 to 3000 cases [2]. Resistance may be aerobically mediated via decreased transcription of the ferredoxin gene or anaerobically produced by decreased or nonexistent activities of pyruvate–ferredoxin oxireductase and hydrogenase [1••]. Because there are no ongoing surveillance data of vaginal trichomoniasis and clinical and microbiologic response to treatment, accurate data regarding the incidence of metronidazole resistance are sparse. At our chronic vaginitis center (Temple University Vaginitis Referral Center), where approximately 500 new patients are seen annually, metronidazole-resistant trichomoniasis is seen in fewer than 1% of referrals (Unpublished observation). However, in a patient population consisting primarily of women from a largely suburban private-practice referral base, one would expect the incidence of uncomplicated trichomoniasis alone to be relatively low, and our experience may represent an underestimation of the incidence of this problem.

Diagnosis of Metronidazole-Resistant Trichomoniasis

It must be strongly emphasized that attempts at treating metronidazole-resistant trichomoniasis should only be initiated after a proper diagnosis has been achieved. Over 95% of the patients referred to the Temple University Vaginitis Referral Center for persistent trichomoniasis do not have trichomoniasis, by either saline microscopy or culture (Unpublished observation). My experience therefore suggests that the diagnosis should never be taken on faith. As mentioned, judicious use of culture methods can help clear up any uncertainty regarding the diagnosis, and a positive culture will allow for in vitro susceptibility testing of the organism. When a patient presents with persistent vaginal trichomoniasis, it is particularly important to ascertain compliance with prior metronidazole treatment and to exclude potential reinfection by the partner before assuming that true resistance to metronidazole is present.

Trichomonas vaginalis infection does occur in men, where it may cause urethritis or no symptoms [8]. Although infection in most men is believed to be short-lived, prolonged (up to 4 months) asymptomatic carriage has been documented in at least one man [9]. That individual was treated at the end of 4 months, so the duration of potential prolonged carriage in men has not been well established [9]. For these reasons, reinfection is always a possibility, and I have found it helpful to instruct patients to avoid intercourse until they have been cured so that we can focus on the infection without worrying about possible reinfection. Data regarding management of the partner are essentially nonexistent. After counseling him, I usually treat with a 7-day course of metronidazole (500 mg twice daily), expecting that the combination of antibiotic therapy, the natural history of trichomoniasis in most men, and a period of sexual abstinence from the infected partner will result in a cure. To date, in female patients successfully treated for metronidazole-resistant trichomoniasis, I have seen no recurrences attributable to an infected male partner (Personal observation).

Management of Metronidazole-Resistant Trichomoniasis

A prospective study at the Columbus (Ohio) Health Department Clinic gives some insight into management issues [10]. Patients with *T. vaginalis* infection were asked to return following treatment to ascertain their response to therapy. Of the 174 women for whom follow-up was available, 50 were not cured using a single 2-g dose of metronidazole. Twenty-six of these women received the same treatment a second time, 22 (85%) of whom were cured. In the remaining 24 re-treated patients, 20 failed to return for second follow-up, one was inadvertently cured with a larger metronidazole dose, and two were still infected but may have become reinfected. Isolates were tested for in vitro susceptibility to metronidazole. Treatment resistance was more frequent at aerobic minimum lethal concentration (MLC) values higher than 25 µg/mL and anaerobic MLC values higher than 1.6 µg/mL. However, the authors noted that there was a moderate overlap between MLCs for treatment successes and failures except at low and high MLC extremes. Another study comparing in vitro drug susceptibility and doses of metronidazole required for cure in cases of refractory vaginal trichomoniasis also revealed an overlap between in vitro MLCs and in vivo response to therapy [11].

These data suggest that resistance to metronidazole is a clinical diagnosis made on the basis of a patient's lack of response to appropriate therapy. Furthermore, they reveal that metronidazole resistance is often relative, and it may be overcome with increasing doses of the drug. Current Centers for Disease Control and Prevention guidelines for treatment failures recommend 500 mg of metronidazole twice daily for 7 days [6••]. In patients who fail this regimen, increasing doses of metronidazole may successfully effect a cure. In a series of 31 refractory cases of vaginal trichomoniasis treated with a variety of metronidazole regimens [11], most patients were cured with either 2 g daily for 3 to 7 days or 1 g three times a day combined with 500 mg intravaginally daily for 14 days. We generally use the higher dose regimen as firstline therapy in cases of resistance. Although some patients may not be able to tolerate a full 14-day course because of nausea, they may be able to tolerate enough of the treatment to effect a cure. In one case of resistance to high-dose oral metronidazole, Dombrowski *et al.* [12] successfully treated a woman with intravenous metronidazole (2 g every 6 to 8 hours for 3 days). However, metronidazole in higher doses should be

used with caution because it can be associated with seizures, encephalopathy, or peripheral neuropathy. In addition, at least one well-documented failure with intravenous metronidazole has been described [13]. Zinc sulfate douches have also been suggested as a possible adjunctive therapy to metronidazole, but in the series in which this method was evaluated, simultaneous changes in the metronidazole therapy made it difficult to assess the added effects of the zinc sulfate [14].

In patients who fail metronidazole therapy, a variety of regimens have been evaluated for possible effectiveness. In vitro studies have shown that mebendazole, furazolidone, and rifabutin are the drugs most active against metronidazole-resistant trichomonads [15]. Clinical experience with these medications is either lacking or, in the case of benzimidazole agents [16] and furazolidone (Personal observation), disappointing. Povidone-iodine douches [17] and nonoxynol-9 [18] have each been reported as successful treatment in one case, but failures with both treatments have also been reported [19,20].

Perhaps the best-described nonmetronidazole regimens consist of tinidazole and paromomycin cream. Tinidazole, a 5-nitroimidazole, has a similar structure to that of metronidazole, and one would expect cross-resistance to be common. However, multiple case reports of successful treatment of refractory cases of trichomoniasis have been reported with high-dose tinidazole [13,20,21]. In general, the doses used were 2 g/d or more for 14 days; the patients I have treated with tinidazole have received 1 g orally and 500 mg intravaginally, each given three times daily. Because cross-resistance to some degree is probable, lower doses of tinidazole seem less likely to be beneficial, and we proceed empirically and directly to high-dose therapy to minimize the chance of inducing resistance to tinidazole. The side effects of tinidazole are similar to those of metronidazole, although patients seem to tolerate the gastrointestinal side effects of tinidazole better [20]. Perhaps the greatest difficulty with tinidazole is that it is not readily available in the United States. However, pharmacies that specialize in compounding medications are sometimes able to obtain tinidazole powder and make preparations suitable for patient consumption. The results of managing male partners under these circumstances with tinidazole is largely unknown.

Although it is thought to be very rare, failure to respond to high-dose tinidazole therapy has been reported in at least two cases [22,23••]. In these cases, the remaining option is paromomycin cream. Paromomycin is an aminocyclitol antibiotic whose spectrum includes many protozoa. It was evaluated in the mid-1960s as a possible topical treatment for trichomoniasis but abandoned in favor of metronidazole because of a 63% failure rate with 30-mg vaginal pessaries given three times daily [24]. Recently, a 2- or 3-week course of 6.25% paromomycin cream (4 g/d intravaginally) resulted in a cure in six of nine patients with metronidazole resistance or allergy [23••]. Of the four patients with metronidazole resistance in this study, only one failed treatment. Although she had also failed high-dose tinidazole therapy alone, she was cured with a combination of paromomycin cream and oral tinidazole.

It should be kept in mind that vaginal ulcerations may develop from paromomycin cream. Although they are self-limited and heal completely with prompt discontinuation of treatment, vaginal ulcerations may have a very rapid onset, be quite severe, and cause pain and even in one case urinary retention (Unpublished observation). Patients should be warned of this possible side effect prior to initiating therapy and counseled to stop treatment immediately if they notice any localized side effects. The cause of these ulcers is unclear, although it may be related to local formulation differences.

Metronidazole-Allergic Trichomoniasis

Allergy to metronidazole, manifested by rash, urticaria, and potentially anaphylaxis, is uncommon. For the rare patient with trichomoniasis in the presence of metronidazole allergy, desensitization to metronidazole with either an oral [25] or intravenous [26] protocol may result in successful treatment. Cross-reactivity to tinidazole should theoretically be high; therefore, if tinidazole is used in a patient with metronidazole allergy, it should be given in a setting capable of handling an acute allergic reaction. In patients in whom desensitization is not possible, a course of paromomycin cream may be an effective alternative treatment.

Conclusions

It is fortunate that despite extensive use of metronidazole, vaginal trichomoniasis for the most part remains susceptible to this antibiotic. In cases of clinically documented metronidazole resistance, cultures and in vitro susceptibility testing may be helpful in guiding therapy. Infections usually respond to higher doses of metronidazole, high-dose tinidazole, or possibly paromomycin cream. However, because such cases are encountered infrequently, these recommendations are based for the most part on case series and not randomized studies. Further experience could be obtained through a centralized registry of refractory trichomonal infections to further clarify management issues.

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