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Trichomonas vaginalis: treatment questions and challenges

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"The recognition of pathologies beyond the standard symptoms of infection has led to a greater appreciation of the public health consequences of trichomoniasis…"

Trichomoniasis is the most prevalent non-viral sexually transmitted disease worldwide and affects an estimated 170 million people [1]. The manifestations of infection with *Trichomonas vaginalis*, the causative agent of trichomoniasis, are primarily observed in women, and range from an asymptomatic presentation to copious, malodorous discharge and punctate epithelial lesions, known as strawberry cervix. Men can also present with urethritis, prostatitis and discharge, but the vast majority of *T. vaginalis* infections in men are asymptomatic. In addition to the observable symptoms in women, trichomoniasis has been associated with adverse outcomes in pregnancy, and increased susceptibility to and transmission of HIV-1 and cervical cancer [2,3]. The recognition of pathologies beyond the standard symptoms of infection has led to a greater appreciation of the public health consequences of trichomoniasis and the realization that its previous categorization as merely a nuisance infection, or simply a marker for other sexually transmitted infections, was erroneous [4,5].

Treatment for trichomoniasis has relied almost exclusively on drugs of the 5-nitroimidazole class. In the USA, trichomoniasis is treated with either metronidazole or tinidazole. Tinidazole has better molar efficacy against *T. vaginalis* isolates *in vitro* [6] and has fewer side effects than metronidazole. However, because of the similarities in chemical structure, infections that are highly resistant to metronidazole may also fail to cure after standard treatments with tinidazole.

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Both the action of the 5-nitroimidazoles and the specific mechanism of resistance in *T. vaginalis* isolates to these drugs remain poorly understood. In general, 5-nitroimidazoles enter the parasite by passive diffusion as a prodrug. Activation of the drug occurs within the parasite by redox enzymes involved in ATP production in the hydrogenosome and/or by flavin reductases, such as thioredoxin reductase [7,8]. Reduction of 5-nitroimidazoles produces cytotoxic radical anions that damage DNA and form adducts with critical parasite proteins. Laboratory-derived, drug-resistant isolates have lower intracellular concentrations of activated drug, which has been attributed to lower concentrations of the redox enzymes or coenzymes (e.g., FAD) responsible for drug activation or maintenance in a reduced form [8]. However, it is not clear that the mechanism(s) of resistance in laboratory-induced strains are accurate representations of 5-nitoimidazole insensitivity in clinically resistant infections [9,10]. Genetic analyses of *T. vaginalis* isolates demonstrate resistant isolates clustering within one of two primary subpopulations, suggesting that it will be possible to isolate molecular markers of drug resistance [11] [Conrad M *et al.*, Population genetics of the sexually transmitted pathogen *Trichomonas vaginalis* and evidence for sexual recombination (2012), Manuscript submitted]. Identification of the mechanism of clinical drug resistance is a critical need for better understanding of the epidemiology of resistant infections as well as improving individual case management.

Resistance of *T. vaginalis* to 5-nitroimidazoles is quantitative and not qualitative; thus, infections that fail to cure with standard treatment doses can often be cleared with higher, more prolonged treatment with the same drugs [12]. This is clearly not an ideal strategy for dealing with drug-insensitive infections and may result in selection of more highly resistant strains. Women who repeatedly fail to cure trichomoniasis with 5-nitroimidazoles have few options. Alternative treatments for trichomoniasis utilize compounds that are not absorbed well from the intestinal tract (paromomycin sulfate, furazolidone) or are not ingestible (povidone iodine) and therefore must be administered intravaginally. While these compounds are very effective against trichomonads *in vitro*, intravaginal therapy tends to be less efficacious than systemic treatment in contacting and killing all parasites. Nevertheless, further research into utilization of intravaginal treatments, especially with povidone iodine pessaries, is needed.

Alternate therapies to treat trichomoniasis are also needed for persons allergic to metronidazole and tinidazole. Many individuals with hypersensitivity reactions to these drugs have relatively mild symptoms and can be successfully treated without severe side effects using short-course desensitization protocols [13]. Over the course of a single day, patients are administered metronidazole either orally or intravenously, starting with a very low dose of a few micrograms and gradually ramping up to a curative dose. However, some individuals can respond with an anaphylactic reaction or develop Stevens–Johnson syndrome following a single treatment [14,15]. For these women, the less effective intravaginal treatments are the only option. The situation is further complicated because it is difficult to obtain the intravaginal treatments as they require special formulation. Even 5-nitroimidazole hypersensitive patients for whom the short-course desensitization protocols are indicated may find that the expense of formulating and administering the incremental doses is not covered by their health insurance.

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Thus, there is a clear need for identifying new therapies, preferably oral, that are effective against 5-nitroimidazole-resistant *T. vaginalis* infections and that can be used in patients allergic to this class of drugs. Unfortunately, like new drug development for most parasitic infections, there is little economic impetus to do so as the persons most heavily affected have very limited financial resources. Approximately 85% of trichomoniasis cases occur in developing countries, but even in the USA (and presumably other more industrialized countries), risk of infection is highest in minority populations in the lower socioeconomic tiers [1,16]. A number of novel compounds have demonstrated strong efficacy against *T. vaginalis in vitro* but have not progressed towards further testing because no pharmaceutical companies have selected them for development. In recent years, several companies have very generously donated drugs to treat helminth infections in resource-poor countries; however, it is a much more challenging prospect to develop and fully test a new compound that may never be profitable than to donate drugs that have known safety and efficacy, as well as marketability in nondonation settings.

In light of the difficulties in funding development of novel therapeutics specific for trichomoniasis, two approaches that may augment the armamentarium for treating resistant infections or persons with drug allergies are to identify existing approved drugs that can be used alone or in combination to cure infections or determine if new drugs being developed for other protozoan parasites also have activity against *T. vaginalis*. For the first approach, we recently screened 1024 compounds *in vitro* that are approved for human use by the US FDA or that are in Phase III trials in other studies [Goodhew EB *et al.*, Manuscript in Preparation]. While we found no drugs that worked as well as the 5-nitroimidazoles, there were some that had clear partial efficacy. We are currently evaluating combinations of these drugs *in vitro* to determine if they can enhance the potency of 5-nitroimida-zoles against resistant isolates or provide viable alternatives for treating women with severe allergic reactions. The 'piggyback' approach appears plausible as aromatic diamidines designed for treatment of African trypanosomiasis show good efficacy *in vitro* against both 5-nitroimidazole-susceptible and -resistant strains of *T. vaginalis* [17]. Unfortunately, clinical trials of one of these promising drugs were halted because of toxicity issues [18]. Nevertheless, as additional drugs from this class reach human testing, there is a reasonable expectation that they may also be effective against trichomonads. Other antiprotozoan drugs that kill trichomonads *in vitro* and might have efficacy against *T. vaginalis* infections include nitazoxanide (approved for use against giardiasis and cryptosporidiosis) and miltefosine (approved for treatment of human visceral leishmaniasis). However, nitazoxanide is poorly absorbed from the intestinal tract and therefore may only be an option for intravaginal treatment of trichomoniasis. No attempts at treatment of trichomoniasis using miltefosine have been reported and its teratogenic properties warrant extreme caution for use in women of child-bearing age.

Additional critical questions associated with treatment of trichomoniasis that compel further investigation pertain to persistence of infection following apparent cure, and whether it is important to detect and treat asymptomatic infections. Unlike most curable sexually

transmitted infections, the incidence and prevalence of trichomoniasis is higher in older sexually active women than in younger age groups [19]. The combination of the finding that another significant risk factor for *T. vaginalis* infection is history of previous trichomoniasis [19] with the observation that some women who have been previously infected and treated with apparent cure can again present with infection in the absence of additional sexual activity suggests that treatment of some infections only results in resolution of clinical signs without eradicating the infection [20]. Nucleic acid amplification tests have recently become commercially available and should be employed to systematically evaluate the frequency of symptomatic cure without parasite clearance and the effectiveness of other treatment regimens. The public health significance of asymptomatic infections and infections that persist following treatment needs further investigation. For example, are individuals with persistent or asymptomatic *T. vaginalis* infections a risk for transmitting trichomoniasis to their sex partners? Persons with asymptomatic infections are generally thought to harbor fewer parasites than individuals with clinical trichomoniasis and would therefore be less infectious. However, *T. vaginalis*-positive persons who do not know they are infected and thus do not seek treatment, especially men, may be unknowingly contributing to the spread of infection. Similarly, whether the presence of an asymptomatic infection increases a person's risk of infection with HIV and other sexually transmitted infections, which are clearly associated with symptomatic trichomoniasis, requires investigation. Trichomoniasis is finally gaining the attention it warrants as a public health concern in developing as well as more industrialized countries. Continued research will lead to a better understanding of its health impact and improved strategies for countering its detrimental effects.

Biography

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