Trichomonas vaginalis pharmacological treatment

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Abstract

Trichomoniasis is the most common sexually transmitted protozoan infection, which has been treated for several decades using nitroimidazoles, mainly metronidazole and tinidazole. Both drugs are still recommended and resistance to them has fortunately been a relatively rare phenomenon. Resistant or tolerant cases exist, however, and side effects are also notable. Therefore, novel compounds with different mechanism of action are urgently needed. It is encouraging that several novel and innovative leads have been introduced. They will hopefully help us to develop novel antitrichomonal agents to fight harder against this parasitic disease in the future.

Key words: Trichomonas vaginalis, trichomoniasis, diagnosis, drug, treatment, therapy

Prevalance and symptoms of trichomoniasis

According to the World Health Organization, *Trichomonas vaginalis* infection, trichomoniasis, is considered the most common sexually transmitted, curable protozoan infection worldwide (https://www.who.int/bulletin/volumes/85/4/06-031922/en/). According to one large study with 4057 participants from the U.S., the prevalence of trichomoniasis was 0.5% and 1.8% among males and females, respectively [1]. In another report, *T. vaginalis* had infected over 11% of women aged ≥40 years, and the infection prevalence was found to be associated with the age of patients, their place of residence, ethnicity, socioeconomic status, and number of sex partners [2,3]. The high prevalence in the general population has mostly been reported in the U.S. cohorts. Lower prevalence estimates were found in Britain. From urinary samples of 4386 individuals *T. vaginalis* infection was detected in only seven women and no men, giving a weighted prevalence estimate of only 0.3% [4]. As mentioned above, there may be several confounding factors which could explain the lower infection prevalence reported in that study.

Trichomonas is a motile, protozoan organism with a size comparable to leukocytes [5] (Fig. 1). It has at least four flagella that drive cell locomotion. The infection leads to increased vaginal pH and release of cytotoxic proteins that destroy the epithelial lining.

Diagnosis and treatment of trichomoniasis are challenging since the majority of *T. vaginalis* infections in women are asymptomatic [6], and as untreated, the infection may last for months or years. Trichomoniasis is associated with several adverse consequences, such as preterm birth, delivery of a low-birth weight infant, and infection with a *Human immunodeficiency virus* (HIV) [3].

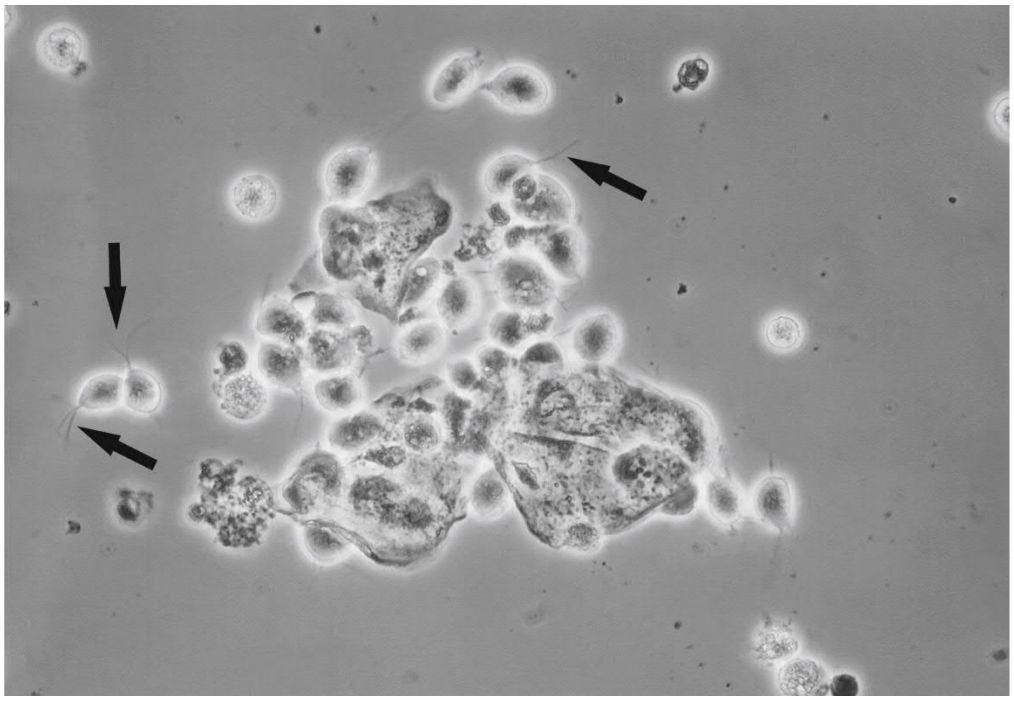

Fig. 1 Wet-mounted vaginal discharge specimen showing several *T. vaginalis* parasites, indicative of trichomoniasis. Some flagella are visible in the parasites (arrows). Courtesy of CDC/ Joe Miller (https://phil.cdc.gov/Details.aspx?pid=14500).

The common symptoms of *T. vaginalis*-infected women include a copious, yellow-green, frothy, and malodorous vaginal discharge, vulvar irritation, pruritus, dysuria, dyspareunia, and post-coital bleeding [7,8]. Speculum examination may reveal a “strawberry cervix” sign due to punctate hemorrhages of the ectocervix. In addition, erythematous and edematous vaginal walls due to vaginitis may be observed. In men, the infection may present as urethritis, epididymitis, or prostatitis [8]. Trichomoniasis is readily passed between sex partners. In a study of 540 women with trichomoniasis and 261 of their male partners, 71.7% of partners got the infection and 77.3% of them were asymptomatic [9]. An additional challenge is that trichomoniasis sometimes exists with other sexually transmitted diseases, such as HIV, *Chlamydia trachomatis*, and *Neisseria gonorrhoeae* infections [2]. However, the rates of *T. vaginalis*, *C. trachomatis*, and *N. gonorrhoeae* coinfection were low (<1.3%) when studied in the whole population. In a Kenyan cohort, trichomoniasis showed a 1.52 fold increased risk of HIV-1 acquisition [10]. In another large cohort from Uganda and Zimbabwe, statistical analysis indicated an odds ratio 2.74 for HIV in *T. vaginalis*-positive cases [11]. Based on several studies, it can be concluded that *T. vaginalis* infection increases both the

transmission and acquisition of HIV among women, and that successful treatment for trichomoniasis can reduce the transmission of HIV [12].

Diagnosis of trichomoniasis

The clinical features of trichomoniasis are variable and thus not sufficiently sensitive or specific to allow trichomoniasis diagnosis based upon signs or symptoms alone. The laboratory diagnostics are based on several alternative laboratory tests, including the detection of motile trichomonads on the wet preparation of a vaginal swab (wet mount), *T. vaginalis* culture, polymerase chain reaction (PCR) test, transcription-mediated amplification test, and rapid antigen test [13,14]. Pap smear is not recommended as a diagnostic method for trichomoniasis due to its low sensitivity and specificity [7]. The wet mount microscopy is the low cost, classical method which has also shown low sensitivity in the range of 40%–60% [5]. In one study, sensitivities of 50.8%, 75.4%, 82.0%, and 98.4% were reported for wet mount microscopy, culture, rapid antigen test, and transcription-mediated amplification test, respectively [15]. Other studies have further confirmed that rapid antigen testing outperforms both *T vaginalis* culture and wet mount as a diagnostic tool [16,17]. Recently, PCR detection has become the gold standard for diagnosis [18] and can be used with different specimens including both urine and vaginal samples [19]. Tayoun and coworkers introduced a multiplex PCR assay for the simultaneous testing of *T. vaginalis*, *N. gonorrhoeae*, and *C. trachomatis*, which are the three most common sexually transmitted diseases worldwide [19]. They demonstrated that the multiplex assay is rapid, sensitive and highly suitable for clinical laboratories. Point-of-care tests have been developed to facilitate rapid, accurate, and affordable diagnostics especially in emergency departments [20]. In the future, self-testing might become a potential option. Interestingly, >99% of 209 young women aged 14–22 years correctly performed and interpreted their own self-test result using the OSOM Trichomonas Rapid Test (Sekisui Diagnostics, Framingham, MA), with a high correlation with clinicians´ interpretations [21]. Recently, Xiu and coworkers developed a sophisticated 23-plex PCR coupled with matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) assay that can simultaneously detect eleven different agents, including the eight clinically relevant pathogens related to sexually transmitted infections (*T. vaginalis,* HSV-1, HSV-2, *N. gonorrhoeae , C. trachomatis, Treponema pallidum, Mycoplasma genitalium*, and *Haemophilus ducreyi*) and three controversial microorganisms as pathogens (*Mycoplasma hominis, Ureaplasma urealyticum*, and *Ureaplasma parvum*) [22]. They

concluded that, based on its high sensitivity and specificity, the method could serve as a high-throughput screening tool for detecting mixed, sexually transmitted infections.

Pharmacological treatment of trichomoniasis

Patients with trichomoniasis need prompt and effective treatment as soon as the diagnosis has been confirmed. Metronidazole and other nitroimidazoles, including tinidazole, ornidazole, nimorazole, and carnidazole, have been used as effective drugs [23]. Despite their widespread use for decades, resistance has been relatively rare. The treatment guidelines of Centers for Disease Control and Prevention (CDC) clearly state that nitroimidazoles are currently the only class of antimicrobial medications known to be effective against *T. vaginalis* infections (https://www.cdc.gov/std/tg2015/trichomoniasis.htm) [24].

Three different regimens for standard treatment have been presented: 1) a single 2 g dose of metronidazole, 2) a single 2 g dose of tinidazole, and 3) 500 mg metronidazole twice a day for seven days. Benefits of tinidazole include a longer half-life, it reaches higher levels in serum and the genitourinary tract, and it has shown slightly fewer gastrointestinal side effects compared with metronidazole [25,26]. A meta-analysis of 54 randomized or quasi-randomized controlled trials indicated that almost any nitroimidazole drug given as a single dose or over a longer period results in parasitological cure in at least 90% of cases [23]. The oral single dose treatment with a higher dose is associated with more frequent side effects than the longer treatment with a lower dose. Because of the limitations of studies, it was not possible to rank tinidazole superior to metronidazole or *vice versa*. Tinidazole tends to have a longer half-life in the body, and thus it may possess longer duration effect when compared with metronidazole. If metronidazole failed, tinidazole should be the other drug to be used [5].

As special cases, patients with known HIV infection should receive 500 mg metronidazole twice daily for seven days [5]. Treatment seems to be justified also in pregnant women diagnosed with trichomoniasis [5,27,28]. If left untreated, the infection can result in adverse outcomes; especially the rate of preterm delivery is increased. The preferred drug is metronidazole and women should stop breastfeeding during treatment [5].

Nitroimidazole resistance of *T. vaginalis*

Nitroimidazole resistance has emerged as a real threat that may challenge the well-established treatment regimens for trichomoniasis in the future. Graves and coworkers recently conducted a systematic review of the literature on the mechanisms of 5-nitroimidazole resistance [29]. Based on the data from 58 articles, drug resistance is higher to metronidazole (2.2–9.6%) than tinidazole (0–2%).

Graves and colleagues [29] pointed out that the mechanisms for drug resistance may have already existed in 1962, when Robinson described the first case of metronidazole-resistant trichomoniasis [30]. Interestingly, the resistance mechanisms of nitroimidazoles in T. vaginalis are probably different than in some bacteria. In *Trichomonas*, the resistance to 5-nitroimidazoles appears to be more relative than absolute. Graves et al. [29] further pointed out that the failure of clinical treatment may be more of a function of drug tolerance rather than developed drug resistance. One clinical observation supporting this concept is that *T. vaginalis* infections, unresponsive to the currently recommended doses of metronidazole, can often be treated by increasing dosages [31].

Future perspectives

Even though both metronidazole and tinidazole are well-documented and successfully used drugs against *T. vaginalis*, the resistance of the parasite to metronidazole has emerged as a notable issue [32,29]. Side effects are another concern in some patients. Therefore, novel treatment options are highly desired. Recently, Lee and coworkers reviewed several compounds showing some promising results against *T. vaginalis* [33]. The compounds among many others, showing micromolar or even nanomolar IC_{50} values, included such as nitrothiazole and benzothiazole derivatives [34], hybrid conjugates with incorporated β-lactam, triazole and isatin nuclei [35,36], and thiosemicarbazone-derived ruthenium metal complexes [37]. Recently, Supuran´s, De Simone´s, and Parkkila´s groups introduced a novel enzyme, *T. vaginalis* β-carbonic anhydrase (TvaCA1), which can be targeted using several known carbonic anhydrase inhibitors [38,39]. These studies are reviewed in another chapter of this book.

Compliance with Ethical Standards

Conflict of Interest: The author declares that he has no conflict of interest.

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Ethical Approval: This chapter does not contain any studies with human participants or animals performed by the author.

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