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Review Article

Therapeutic strategies carried out in cases of a metronidazole-resistant *Trichomonas vaginalis* infection: a literature review

Esquemas terapêuticos realizados em casos de infecção por Trichomonas vaginalis resistentes a metronidazol: uma revisão bibliográfica

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ABSTRACT

Trichomoniasis is the most prevalent non-viral sexually transmitted infection worldwide, caused by Trichomonasvaginalis. This parasitic infection primarily affects women, who may experience clinical manifestations such as leukorrhea, unpleasant vaginal odor, vulvar itching, and a strawberry cervix. While metronidazole is the drug of choice for treating this infection, strains of *T. vaginalis* resistant to this medication have been increasingly reported globally. In this context, the objective of this study was to conduct a literature review of reported case studies involving alternative therapeutic regimens used for metronidazole-resistant *T. vaginalis* strains, published up to the year 2019.The databases used were PubMed and the Scientific Electronic Library Online (SCIELO). Scientific articles that were fully available online and provided detailed information on alternative treatment approaches for metronidazole-resistant *T. vaginalis* infections were included. Systematic reviews, master's dissertations, and doctoral theses published up to 2019 were excluded. Results: A comprehensive analysis of 16 scientific articles was conducted, yielding 23 clinical cases. Regarding therapeutic regimens, tinidazole was the most commonly used drug for cases of metronidazole-resistant strains, followed by paromomycin and iodopovidone. No standardized therapeutic guidelines were observed among healthcare professionals in cases of metronidazole-resistant *T. vaginalis* infections based on the analyzed reports.

RESUMO

A tricomoníase é a infecção sexualmente transmissível não viral mais prevalente no mundo causada por Trichomonas vaginalis. Essa parasitose acomete, principalmente, mulheres que podem apresentar manifestações clínicas como leucorreia, odor vaginal desagradável, prurido vulvar e cérvice com aspecto de morango. O metronidazol é o fármaco de escolha para o tratamento dessa infecção, no entanto, cepas de T. vaginalis com resistência a este medicamento têm sido cada vez mais relatadas no mundo. Nesse contexto, este estudo teve como objetivo realizar uma revisão bibliográfica dos relatos de caso com esquemas terapêuticos alternativos utilizados em casos de cepas de T. vaginalis resistentes ao

metronidazol publicados até o ano de 2019. As bases de dados utilizadas foram o Pubmed e Scientific Eletronic Library Online (SCIELO). Incluiu-se artigos científicos que estavam completamente disponíveis on-line e que dispunham de informações detalhadas acerca do tratamento alternativo utilizado para os casos de infecções por T. vaginalis resistentes a metronidazol. Foram descartadas revisões sistemáticas, dissertações de mestrado e teses de doutorado publicadas até 2019. Além disso, foi realizada a leitura completa e análise de 16 artigos científicos. Dentre eles, foram recuperados 23 casos clínicos. Em relação aos esquemas terapêuticos, o tinididazol foi o fármaco mais utilizado nos casos de cepas resistentes a metronidazol, seguido de paromicina e iodopovidona. Por outro lado, não foi observada uma padronização das condutas terapêuticas a serem seguidas pelos profissionais da saúde em casos de infecções por T. vaginalis resistentes a metronidazol nos relatos analisados.

INTRODUCTION

Taxonomy and Morphology

Trichomonas vaginalis (*T. vaginalis*) is a protozoan responsible for a sexually transmitted infection known as trichomoniasis[1]. This organism belongs to the clade Metamonada and is classified within the supergroup Excavata and the group Parabasalia[2].

The main evolutionary form of this protozoan is the trophozoite, whose morphology is influenced by physicochemical factors[1]. Thus, in axenic culture, *T. vaginalis* exhibits a piriform or oval shape, while on the vaginal epithelium, it assumes an amoeboid form[3, 4]. It is important to note that, under unfavorable growth conditions, *T. vaginalis* can round up and internalize its flagella. This process gives rise to forms known as pseudocysts[3-5].

These organisms have a length that can vary from 7 to 30 μm[6]. The protozoan *T. vaginalis* consists of four flagella and an undulating membrane that, together with the flagella, provide motility to the parasite[7]. Inside the parasitic cell, there is an axostyle, a hyaline and slender structure composed of rod-shaped microtubules that provide support to the eukaryote and are thought to be responsible for anchoring the parasite to the vaginal epithelial cells[1, 5]. Additionally, this protozoan contains an ellipsoidal nucleus located in its anterior region, surrounded by a porous nuclear envelope. Furthermore, it possesses dense granules, the hydrogenosomes, which exhibit hydrolase and lysosomal activity[6].

This parasite is a facultative anaerobe and thrives in pH levels ranging from 5.0 to 7.5 and temperatures between 20°C and 40°C. Regarding its nutrition, it uses glucose, maltose, and galactose as food sources and is also capable of storing glycogen[8]. In cases of nutrient scarcity, trophozoites have the ability to metabolize amino acids. These mechanisms are crucial because the vaginal environment undergoes constant variations in pH, hormones, and nutrient availability[9].

The absorption of food particles occurs through pseudopodia, a structure also associated with the attachment of the protozoan to solid surfaces. Pseudopodia are primarily observed in the amoeboid form of *T. vaginalis*, which explains why the parasite assumes this form when in contact with the vaginal epithelium[10].

Biological Cycle

Trichomoniasis is transmitted through contact during sexual intercourse with an already infected partner. It is noteworthy that men rarely exhibit clinical manifestations of *T. vaginalis* infections, and the protozoan can survive for more than a week under the prepuce, which facilitates its transmission to other individuals. Regarding other modes of transmission, trichomoniasis can occur through the sharing of fomites or during the passage of the newborn through the birth canal in cases of maternal infection[11].

In its life cycle, the protozoan initially colonizes the vagina in women and the urethra and/

or prostate in men, primarily. The protozoan multiplies through binary fission, producing two trophozoites from a single parasitic cell. In contact with the vaginal epithelium, *T. vaginalis* moves using its flagella, which aids in its feeding and attachment to the site[5].

Pathogenesis and Clinical Manifestations

The vaginal microbiota is essential for maintaining the optimal pH of the vagina, which serves to prevent the growth of opportunistic microorganisms such as fungi and bacteria[9, 12]. In this context, there is a group of bacteria known as Döderlein bacilli (*Lactobacillus* spp.), which produce hydrogen peroxide and lactic acid[9]. These bacterial metabolic products react with glycogen naturally produced by the vaginal wall cells, maintaining an optimal local pH between 4.0 and 4.5. When the pH becomes alkaline, there is a progressive increase in anaerobic bacteria and a reduction in Döderlein bacilli[13].

Regarding trichomoniasis, the etiological agent *T. vaginalis* is an opportunistic microorganism that requires a pH above 5 to successfully establish itself in the vagina or urethra. To achieve this, the parasite releases amino acids that degrade into alkaline amines, increasing the vaginal pH. Consequently, there is an inhibition of the vaginal microbiota bacilli and the maintenance of an elevated local pH, which facilitates the colonization of the parasite in the genital region[1, 9, 14].

The pathogenic effects of trichomoniasis occur only after the protozoan adheres to the host cells. The main virulence factors associated with the parasite's cytotoxicity and adherence are adhesins, cysteine proteinases, integrins, cell-detaching factor (CDF), and glycosidases[15–17]. However, the possibility of pathogenicity in the absence of cytoadherence should also be considered, as products released by *T. vaginalis*, such as glycosidases and CDF in culture media, have shown high toxicity rates to epithelial cells[18].

The adhesion capacity of the protozoan is influenced by the availability of iron. During menstruation, there is an exacerbation in the production of adhesins, as the protozoan takes advantage of the iron from the increased blood flow in the region[19]. It is important to highlight that the expression of adhesins on the parasite's surface alternates with that of a highly immunogenic protein known as P270, whose function has been associated with an immune evasion mechanism[1, 15, 19–21]. Furthermore, iron also acts as a modulator of cysteine proteinases, which exhibit cytotoxic and hemolytic activity and degrade antibodies such as IgG, IgM, IgA, and the C3 component of complement, which are deposited on the organism's surface[1, 18].

It is worth noting that other cellular components can also be observed in the biological material of individuals with trichomoniasis, such as an increased number of polymorphonuclear leukocytes in secretions[17, 20].

Given the physiopathogenic mechanisms triggered by *T. vaginalis*, individuals infected with this protozoan can exhibit a wide range of clinical manifestations, varying from asymptomatic presentations to severe inflammation[4, 7, 8]. In cases of vaginitis, the main symptom is leukorrhea, characterized as a yellow, abundant, frothy, and mucopurulent discharge that occurs in about 20% of cases. Symptoms also include an unpleasant vaginal odor and vulvar pruritus[22]. Additionally, edema and erythema in the vagina and cervix may be observed, along with the hallmark of trichomoniasis, colpitis macularis, known as the "strawberry cervix" appearance. It is important to note that many women report experiencing abdominal pain, which may indicate an infectious condition in the upper urogenital tract. In men, this protozoan infection primarily manifests asymptomatically. However, there are reports of patients with abundant purulent urethritis[23].

As a sexually transmitted infection, trichomoniasis can facilitate the transmission of the Human Immunodeficiency Virus (HIV) between individuals. In this context, HIV-positive men infected with the parasite show high concentrations of the virus in their semen compared to HIV-negative men[24, 25].

Epidemiology

Trichomonas vaginalis is the etiological agent of the most prevalent non-viral sexually transmitted infection (STI) in the world, with approximately 156 million cases reported annually[26,

[27]. The prevalence of this parasitic infection is not influenced by climate or seasonal variability. However, factors such as age, sexual activity, number of sexual partners, associated STIs, and phase of the menstrual cycle can affect the frequency of this protozoan infection[8, 10].

Trichomoniasis primarily affects women aged 28 to 40 years, particularly those who are socially marginalized and of low income, making it more clinically and socially relevant in this group[28–30]. It is worth noting that the diagnosis of *T. vaginalis* in virgin or postmenopausal women is less frequent compared to analyses of biological material from women outside these groups[7, 8, 11, 28, 31]. Among men, the prevalence of this infection is still poorly understood, as it is predominantly asymptomatic in this group[32].

It is also important to note that the prevalence of trichomoniasis is underestimated in Brazil, primarily due to incorrect and inadequate diagnoses as well as the high number of asymptomatic individuals. In 2013, approximately 4.3 million cases of *Trichomonas vaginalis* were reported in Brazil, a figure that may be related to a lack of or infrequent use of condoms. Regarding cases of coinfections, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, Human Papillomavirus (HPV), genital herpes, and HIV are the most commonly detected pathogens[1, 5, 7, 27].

Prophylaxis

Prophylactic measures are essential for controlling trichomoniasis, reducing the occurrence of new cases and recurrences in treated individuals. Furthermore, it is crucial to implement public policy measures in the field of health education aimed at the preventive control of *Trichomonas vaginalis* in the population[33].

In this context, it is fundamental for the population to have access to sexual education to understand the modes of transmission, prevention, and progression of this parasitic infection. Additionally, a multidisciplinary approach involving trained professionals in health and human sciences is important to empower individuals and enable them to actively combat this infection by reflecting on and taking action regarding partner choices and sexual behavior. Thus, the use of condoms and the maintenance of good hygiene practices are essential to reduce the likelihood of contact with the parasitic agent[29, 30].

Patients should be advised on the importance of refraining from sharing bathing items and intimate clothing, avoiding the use of public toilets, exercising caution with douching, and avoiding excessive use of soap in the genital area, as this can alter vaginal pH, reduce the local microbiota, and create an environment conducive to parasitic colonization[34].

Other prophylactic measures against trichomoniasis include regular check-ups and early diagnosis. In cases where one partner is confirmed to be infected, it is imperative to ensure proper treatment for both the patient and their sexual partner, even if asymptomatic. Additionally, abstinence from sexual contact during treatment should be emphasized to prevent reinfection[35].

Treatment

The primary medication used to treat *T. vaginalis* infection is metronidazole; however, its derivatives, such as tinidazole, are also widely used[11, 36]. Currently, the Centers for Disease Control and Prevention (CDC) recommends administering 500 mg of metronidazole twice daily for seven days or a single 2 g oral dose. It is crucial that both the patient and their partner undergo treatment, regardless of whether the partner exhibits symptoms[37].

Metronidazole has selective toxicity, acting only on anaerobic organisms[38]. Furthermore, it is considered a prodrug, requiring metabolic activation in the hydrogenosomes of *Trichomonas vaginalis*[39]. For this activation to occur, an electron transfer from ferredoxin to the drug is necessary, which takes place via the activity of the protozoan enzyme pyruvate oxidoreductase. The exact pharmacological mechanism of metronidazole is not fully understood, but it is believed to modify the DNA structure and cell membrane proteins of the parasite[39, 40].
In general, during the administration of this drug for trichomoniasis treatment, adverse effects of metronidazole are rarely severe and are directly related to high doses of the medication. Clinical manifestations already described include head-

ache, nausea, tinnitus, dizziness, seizures, cerebellar ataxia, and urticaria[11, 41].

In pregnant women, the use of metronidazole is recommended only after the first trimester of pregnancy, as the drug can cross the placenta and is classified as Category C, which includes medications that may have toxic or teratogenic effects on embryos. Therefore, after the first trimester and during breastfeeding, a single 2 g dose of metronidazole is indicated, or in cases of resistance and persistent symptoms, 400 mg every 12 hours for seven days is recommended[42–44].

The cure rates for trichomoniasis with metronidazole are high; however, treatment failures can occur due to reinfection, non-adherence to therapy, or resistance of *Trichomonas vaginalis* to the drug. In cases of parasitic resistance, treatment may involve higher doses of metronidazole, which can lead to toxicity, treatment abandonment, or the chronicization of the parasitic infection[45].

The mechanisms behind parasite resistance to metronidazole are not fully understood. Researchers suggest this phenomenon may be due to low serum zinc levels, poor absorption and distribution of the drug in the genital region, or inactivation of the medication by bacteria in the individual's vaginal microbiota[46]. Resistance is confirmed when *T. vaginalis* strains fail to respond to two consecutive courses of metronidazole. It is estimated that about 4% to 10% of trichomoniasis cases are caused by metronidazole-resistant strains. Regarding other therapeutic agents, tinidazole-resistant strains have been reported at rates below 1% of infections.

It is important to note that *T. vaginalis* resistance to metronidazole can be classified as anaerobic or aerobic. In anaerobic resistance, there is a reduction or interruption in the activity of pyruvate, an enzyme crucial for drug activation. In aerobic resistance, there is a disturbance in the removal of oxygen from inside the parasite[46, 47].

The first stage of resistance development, observed at therapeutic drug levels, is aerobic resistance, which results in increased oxygen concentration inside the protozoan and a reduction in anaerobic conditions, which are essential for metronidazole activation[47].

In anaerobic resistance, metronidazole cannot be activated due to disruptions in the activity of the enzyme pyruvate oxidoreductase. However, in such cases, the protozoan strains may respond to prolonged treatment or increased drug doses[46]. This is because the enzyme and ferredoxin are not completely absent. In these scenarios, *T. vaginalis* strains may progress from aerobic resistance to the anaerobic form. It is important to note that various mechanisms contribute to the development of *Trichomonas vaginalis* resistance to metronidazole[46, 47].

In cases of treatment failure due to resistance, increasing the metronidazole dose to 2 g daily for seven days is recommended. High intravenous doses, however, are not advised due to the drug's toxicity, as this administration method has been associated with severe adverse effects such as seizures and encephalopathy[48, 49]. When therapeutic efficacy is not achieved, susceptibility testing for metronidazole and tinidazole should be conducted[50].

Other therapeutic regimens have proven effective and may be considered in cases of metronidazole resistance. These include high doses of tinidazole (2 to 3 g daily for 14 days), which can be combined with intravaginal tinidazole or intravaginal paromomycin[37]. There are also reports of clinical and parasitological cure using alternative treatments such as intravaginal boric acid and nitazoxanide. It is important to emphasize that topical use of intravaginal betadine, clotrimazole, acetic acid, furazolidone, gentian violet, nonoxynol-9, and potassium permanganate is not recommended, as these have demonstrated minimal success rates in the treatment of trichomoniasis[37].

MATERIALS AND METHODS

Databases and Publication Search

The present study constitutes a descriptive systematic review on the alternative treatment performed for cases of *T. vaginalis* infections resistant to metronidazole. This manuscript was translated with the assistance of ChatGPT, an AI language model de-veloped by OpenAI.

The search for publications was carried out during the period from March to April 2020, and the maximum period for retrieving publications in the databases was up to the year 2019. The databases used in the search were PubMed and Scientific Electronic Library Online (SciELO), and the descriptors were "*Trichomonas vaginalis*," "resistance," and "metronidazole."

Inclusion and Exclusion Criteria

During the search for studies in the databases, the titles and abstracts of all the documents found were read for subsequent retrieval and storage of the publications. Thus, scientific articles that were fully available online and provided detailed information about the alternative treatment used for cases of *T. vaginalis* infections resistant to metronidazole were included.

As for the exclusion criteria, studies that addressed the topic but were not fully available, systematic reviews, master's dissertations, and doctoral theses were excluded.

RESULTS AND DISCUSSION

A total of 392 studies were retrieved using the terms "*Trichomonas vaginalis*," "resistance," and "metronidazole." Of these, 371 publications were not included in the study as they did not address any alternative treatments for *T. vaginalis* infections resistant to metronidazole. From the 21 studies retrieved on the topic, a full reading and analysis were conducted on 16 scientific articles, as five authors reported continuing to use metronidazole for the treatment of patients' infections, albeit with different dosages (**Figure 1**). After reviewing the 16 scientific articles, 23 cases of female patients with *T. vaginalis* infections resistant to metronidazole were analyzed. Only clinical cases with complete descriptions in the retrieved articles were included in the analysis.

It was observed that among the retrieved clinical cases, individuals with *T. vaginalis* infections resistant to metronidazole were women aged between 22 and 58 years, with the highest

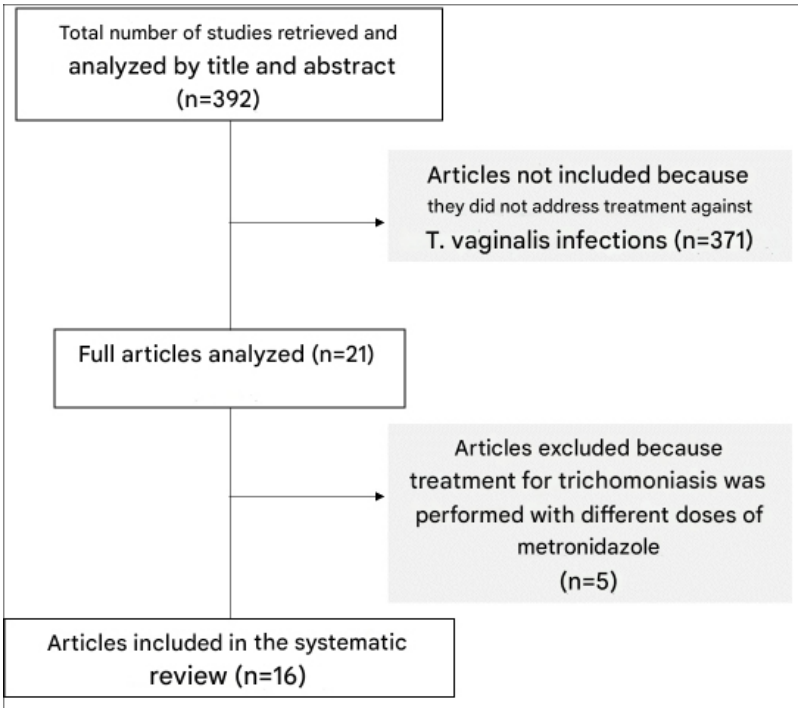

Figure 1. Flowchart of the selection process for articles retrieved and selected for the systematic review on alternative treatments for cases of *Trichomonas vaginalis* resistant to metronidazole.

number of cases reported in the United States (10), followed by England (8) (**Figure 2 and Table 1**).

Regarding therapeutic regimens, tinidazole was the most commonly used drug in cases of metronidazole-resistant strains (19 cases), followed by paromomycin (4) and povidone-iodine (4). In contrast, chloroquine, co-amoxiclav, proguanil, and *Lactobacillus* acidophilus injections were used in two different patients in England. Prochlorperazine, furazolidone, and potassium permanganate were prescribed in three separate cases in the United States, while clotrimazole and estrogen cream were prescribed for one patient in Canada (**Table 1**).

From the analyzed cases, it was noted that five patients experienced adverse effects from treatments involving high doses of metronidazole, paromomycin, furazolidone, tinidazole, and prochlorperazine, either used alone or in combination. The reported clinical manifestations included a wide range of symptoms, primarily involving the genital and tegumentary regions. These symptoms included vulvar pain, genital ulceration, vomiting, nausea, brown-colored urine, severe urticaria, acute respiratory suppression, and vestibular desquamation (**Table 1**)

Table 1. Case reports retrieved up to 2019 of patients with *Trichomonas vaginalis* infections resistant to metronidazole who underwent alternative treatments or treatments combined with this medication.

Authors	Year of Publication	Patient gender	Age (years)	Country of Case Occurrence	Main Complaint	History of Therapeutic Regimens Performed in Patients with *T. vaginalis* Infections Resistant to Metronidazole	Adverse Effect(s)	Case Resolution
Kulda et al.[51]	1982	Woman	41	Czech Republic	History of 4 years of recurrent vulvovaginitis due to *T. vaginalis*	1) Five courses of 250 mg oral metronidazole twice daily + 500 mg inserted vaginally daily for 10 days. 2) 1 g oral metronidazole daily. 3) Five 250 mg oral metronidazole tablets daily for 3 days. 4) 150 mg oral tinidazole twice daily for 7 days. 5) Two courses of 500 mg oral metronidazole twice daily for 5 days. 6) 2 g oral metronidazole in a single dose. 7) 1 g oral metronidazole twice daily for 7 days. 8) 1 g oral ornidazole twice daily + 500 mg inserted vaginally once daily for 6 days.	Not reported	Patient clinically asymptomatic and negative after the end of treatment..
Pattman et al.[52]	1989	Woman	22	England	Not reported	1) 400 mg oral metronidazole twice daily for 7 days + 250 mg ampicillin four times daily for 5 days. 2) 300 mg tetracycline twice daily for 2 weeks + 1 g nimorazole every 12 hours for 3 days. 3) 100 mg oral metronidazole twice daily for 3 days + insertion of 100 mg mebendazole tablets at night. 4) 400 mg oral mebendazole three times daily for 14 days.	Not reported	Patient with unchanged symptoms, and **T. vaginalis** trophozoites were detected in vaginal fluid.
Pattman et al.[52]	1989	Woman	50	England	History of four years of recurrent trichomoniasis.	1) 400 mg oral metronidazole twice daily for 7 days + 250 mg ampicillin four times daily for 5 days. 2) 1 g nimorazole every 12 hours for 36 hours + insertion of 200 mg povidone-iodine pessary at night for 7 days. 3) 400 mg oral mebendazole twice daily for 7 days. 4) 400 mg oral mebendazole three times daily for 7 days.	Not reported	Patient did not respond to treatment.
Wong et al.[53]	1990	Woman	36	New Zealand	Foul-smelling white-yellow vaginal discharge.	1) 2 g tinidazole in a single dose. 2) Two regimens of 2 g tinidazole in a single dose. 3) Two regimens of 200 mg metronidazole three times daily for 7 days. 4) 200 mg metronidazole three times daily for 14 days. 5) 200 mg metronidazole three times daily for 10 days. 6) 1 g oral ornidazole in a single dose + 500 mg vaginal pessary. 7) 2 g tinidazole three times at weekly intervals. 8) 2 ml povidone-iodine in douches with a 10% solution twice daily for 4 days. 9) After 14 days, 2 ml povidone-iodine in douches with a 10% solution twice daily for 2 days.	Not reported	Patient clinically asymptomatic and negative six months after the end of treatment.
Watson e Pattman[54]	1996	Woman	39	England	Excessive vaginal discharge.	1) 2 g oral tinidazole in a single dose. 2) 2 g oral metronidazole in a single dose. 3) 200 to 400 mg oral metronidazole three times daily for 7 to 14 days over 4 months.	Not reported	Patient clinically asymptomatic and negative four months after the end of treatment.

						4) Three doses of inactivated **Lactobacillus* acidophilus* strains injected intramuscularly at two-week intervals + 500 mg clotrimazole pessary. 5) Eight weeks after the third injection, acetarsol + two 250 mg vaginal pessaries inserted daily for 10 days.		
Lewis et al.[55]	1997	Woman	48	England	Itching; Thin green frothy vaginal discharge; Vulvovaginitis.	1) 2 g oral metronidazole in a single dose. 2) 2 g oral tinidazole daily for 2 days.	Not reported	Patient clinically asymptomatic and negative seven weeks after the end of treatment.
Lewis et al.[55]	1997	Woman	37	England	Vaginal itching; Profuse creamy discharge.	1) Three weekly courses of 200 mg oral metronidazole three times a day. 2) 400 mg metronidazole twice daily for 7 days. 3) Higher doses of metronidazole + co-amoxiclav + povidone--iodine pessary + tinidazole. 4) 300 mg chloroquine once a week for 7 weeks + 200 mg proguanil daily. 5) 6% nonoxynol-9 pessary for 2 weeks + 300 mg chloroquine once a week for 7 weeks + 200 mg proguanil daily. 6) Nonoxynol-9 pessaries for 1 week each month for 3 months. 7) Nonoxynol-9 pessaries for an additional 4 months.	Not reported	Patient clinically asymptomatic and negative two months after the end of treatment.
Lewis et al.[55]	1997	Woman	44	England	Yellowish creamy discharge; Vaginal itching.	1) 400 mg metronidazole twice daily for 5 days. 2) 2 g oral tinidazole + 500 mg twice daily for 7 days. 3) Nonoxynol-9 pessary for 14 days + maintenance of 1 pessary 3 nights per week. 4) Preparation of 250 mg paromomycin applied every night for 14 days. 5) 2 g tinidazole in a single dose. 6) 14-day course of paromomycin in tablet form. 7) 14-day course of two 250 mg acetarsol pessaries each night.	Vulvar pain due to paromomycin. Ulceration due to paromomycin	Patient clinically asymptomatic and negative six weeks after the end of treatment.
Saurina et al.[56]	1998	Woman	33	United States of America	Erythematous vulvar mucosa; Introital sensitivity; Purulent vaginal discharge.	1) Oral and intravaginal metronidazole for 20 days + oral prochlorperazine. 2) 300 to 400 mg oral furazolidone for 7 days. 3) Vaginal preparation of 100 mg furazolidone in 5 g of 3% nonoxynol-9 three times a day for 7 days. 4) 500 mg oral tinidazole + 500 mg intravaginal tinidazole for 14 days.	Vomiting due to treatment with metronidazole and prochlorperazine. Nausea and brown urine related to the use of oral furazolidone. Nausea due to tinidazole.	Not reported
Nyirjesy et al. [57]	2011	Woman	54	United States of America	Irritation;	1) High doses of metronidazole and tinidazole. 2) Paromomycin cream + 1% gentian violet. 3) 1 g oral tinidazole three times a day + 500 mg twice a day for 14 days. 4) Povidone-iodine vaginal suppositories for 14 days + miconazole/metronidazole/lidocaine pessary for 14 days + potassium permanganate vaginal douche (1:1250) for 14 days. 5) 5 g of a 5% paromomycin intravaginal cream inserted at night + 1 g oral tinidazole three times a day for 14 days. .	Not reported	Patient clinically asymptomatic and negative six months after the end of treatment.

Nyirjesy et al.[57]	2011	Woman	29	United States of America	*History of 2 years of T. vaginalis infection.*	1) 6 courses of metronidazole, 3 courses of tinidazole (including one 14-day regimen with 3 g orally and 1 g vaginally per day), and zinc supplements. 2) 2% furazolidone cream twice daily for 14 days. 3) 5 g of a 5% paromomycin intravaginal cream for 14 days + 1 g oral tinidazole three times a day for 14 days.	Mild irritation.	Patient clinically asymptomatic and negative four months and two weeks after the end of treatment.
Forbes et al.[58]	2015	Woman	28	England	Intense vaginal discharge; Dyspareunia; Post-coital bleeding.	1) 400 mg metronidazole twice daily for 5 days. 2) Metronidazole for 14 days at standard dosage. 3) 500 mg tinidazole four times daily for 7 days.	Not reported	Patient asymptomatic and negative thirteen weeks after the onset of symptoms.
Byun et al.[59]	2015	Woman	29	South Korea	1 year of persistent infection with foul-smelling vaginal discharge; irritation; dysuria.	1) High doses of metronidazole and tinidazole administered orally and intravenously. 2) 1% zinc sulfate douche twice daily for 14 days + 500 mg oral tinidazole twice daily for twelve days. 3) Zinc sulfate douche for 7 days.	Mild irritation.	Patient clinically asymptomatic and negative three months after the end of treatment.
Butt e Tirmizi[60]	2018	Woman	37	United States of America	Persistent yellow vaginal discharge for two years.	1) 1 g oral metronidazole in a single dose. 2) 2 g oral metronidazole once a day for 14 days. 3) 2 g oral tinidazole daily + 0.75% intravaginal metronidazole daily for 14 days. 4) 2 g oral tinidazole daily + 1% zinc sulfate intravaginally with tinidazole paste daily for 14 days. 5) 2 g oral tinidazole daily + 500 g intravaginal paromomycin daily for 14 days. 6) 600 mg intravaginal boric acid daily for 90 days. 7) 500 g intravenous metronidazole every 8 hours + 600 mg intravaginal boric acid daily for 14 days. 8) 500 g intravenous metronidazole every 8 hours for 7 days + 2 g liquid tinidazole daily + 600 mg intravaginal boric acid daily for 14 days.	Severe vaginal irritation due to the use of paromomycin. Nausea due to tinidazole.	Patient clinically asymptomatic and negative two months after the end of treatment.
Salas et al.[61]	2018	Woman	30	United States of America	Persistent vaginal discharge for two years.	1) 2 g oral metronidazole or tinidazole in a single dose. 2) Regimens of nitromidazole. 3) 500 mg oral metronidazole twice daily for 7 days. 4) 2 g oral tinidazole once daily for 5 days. 5) 500 mg metronidazole + intravaginal application of metronidazole twice daily for 7 days. 6) 2 g oral tinidazole once daily for 5 days. 7) 2 g oral metronidazole once daily for 5 days. 8) 1 g oral tinidazole three times daily for 14 days + 600 mg intravaginal boric acid twice daily for 28 days.	Not reported	Patient clinically asymptomatic and negative.
Henien et al.[62]	2019	Woman	49	United States of America	Infection by *T. vaginalis* for 5 months; treatment performed without success.	1) 6 regimens of oral metronidazole and tinidazole. 2) Regimens of tinidazole from 1 to 7 days daily for 7 days. 3) 1 g oral tinidazole three times a day for 7 days + 4 g of 6.25% paromomycin intravaginal cream for 14 days	Not reported	Patient asymptomatic four months after the end of treatment.

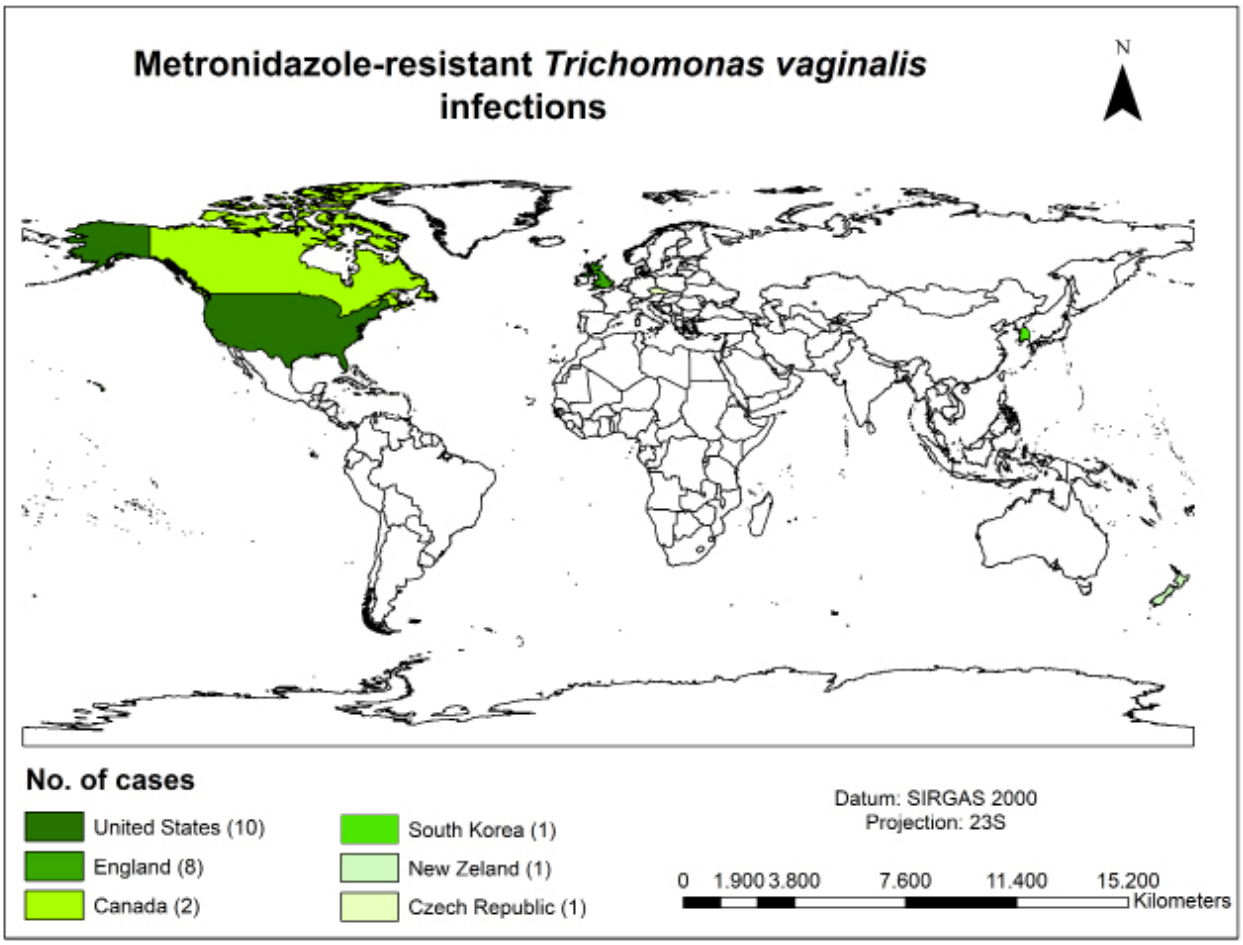

Figure 2. Number of cases retrieved from scientific databases of *Trichomonas vaginalis* infections resistant to metronidazole worldwide up to the year 2019.

Trichomoniasis is one of the most common non-viral sexually transmitted infections in the world, primarily affecting women. Furthermore, this is a protozoan infection that is usually asymptomatic, resulting in minimal significant sequelae for infected individuals in most cases[63, 64]. One factor contributing to this scenario is the high intra-specific variability of *Trichomonas vaginalis* and the effectiveness of metronidazole treatment, which is the first-line drug of choice for healthcare professionals worldwide. However, in recent years, strains of *T. vaginalis* resistant to metronidazole have been reported in different countries around the world[36, 51-62, 65-67].

In this study, it was observed that all recovered cases of metronidazole-resistant *T. vaginalis* occurred in women. This finding may be associated with the observation that the infection is less frequent and tends to be self-limiting in men. In contrast, a different scenario can be observed in women, who may present with symptomatic and persistent cases with clinical manifestations ranging from vaginal itching to severe vaginitis. Additionally, it is important to highlight that trichomoniasis primarily affects women of reproductive age who are sexually active, which facilitates the sexual transmission of this protozoan[26, 68].

In such cases, there is a pressing need for the rapid adoption of effective treatment for trichomoniasis, as this protozoan infection can lead to fertility issues during and after pregnancy, including preterm labor, low birth weight in infants, stillbirth, postpartum endometritis, and neonatal mortality[69]. Thus, the administration

of metronidazole to women appears to be much more frequent than in men, who often receive treatment for *T. vaginalis* infection only when there is confirmation of infection in their partner, rather than through laboratory confirmation of their own infection.

Among the analyzed articles, most cases of *T. vaginalis* resistant to metronidazole occurred in the United States, which may be associated with the high prevalence of the infection in the country—approximately 3.7 million cases in women[26, 63]—and the absence or lack of recovery of published case reports of *T. vaginalis* resistant strains in other countries throughout this research.

Regarding the treatment of trichomoniasis, the drugs currently approved by the Ministry of Health are metronidazole and tinidazole, as well as other 5-nitroimidazoles[70]. In addition to these, other medications in this class can be used, such as secnidazole, imorazole, ornidazole, and azanidazole. It is important to emphasize that infections caused by *T. vaginalis* strains resistant to metronidazole have already been reported in different countries, particularly in regions of North America.

Generally, the mechanisms conferring resistance to the protozoan can vary. These include mutations in genes that encode the enzyme ferredoxin, which is involved in the energy metabolism of *T. vaginalis*, and in the enzyme nitroreductase, responsible for the activation of metronidazole within the parasitic cell and subsequently for inducing cell death[68, 71]. Other reported mechanisms of resistance to metronidazole include: aerobic resistance to metronidazole due to increased oxygen concentration inside the protozoan, resulting from a molecular and enzymatic deficiency in removing this element from within the parasite; anaerobic resistance forms in vitro; expression of carbohydrates on the cell surface; and modulation of extracellular ATP in the interaction between *T. vaginalis*, the host, and metronidazole[22, 68, 71].

Among the drugs reported in the clinical cases analyzed in this study for the treatment of *T. vaginalis* resistant to metronidazole, it was observed that tinidazole was the most recommended. This finding was expected, as this drug has mechanisms of action for destruction and inhibition of DNA synthesis very similar to those of metronidazole, the primary medication for the treatment of trichomoniasis. Furthermore, tinidazole is listed as one of the most recommended medications for the treatment of trichomoniasis in reference manuals for healthcare professionals[37]. Despite this, frequent use of other antibiotics such as paromomycin and povidone-iodine was evidenced. In these cases, it is necessary for the treatment of trichomoniasis to be systemic, since the protozoan can be detected in other areas outside the vagina, such as the urethra and perivaginal glands[22]. Additionally, the use of these antibiotics may be related to the prevention of other STIs and cases of bacterial vaginosis, which are commonly observed in cases of co-infection with trichomoniasis.

Alternative medications, such as chloroquine and proguanil, which are antimalarials, were employed, albeit less frequently. However, these substances do not have proven efficacy against *T. vaginalis* infections. Moreover, injections of *Lactobacillus* acidophilus were also used, typically administered to restore the vaginal microbiota[72]; co-amoxiclav, which is a broad-spectrum antibiotic against both gram-positive and gram-negative microorganisms, whether or not they produce beta-lactamases; furazolidone, which can cause damage to proteins and DNA[73]; the antioxidant potassium permanganate; clotrimazole, an antifungal that inhibits the formation of ergosterol; and estrogen cream for restoring the vaginal epithelium. It is important to highlight that none of the aforementioned drugs, except for metronidazole, tinidazole, and other 5-nitroimidazoles, are recommended for the treatment of trichomoniasis.

From the analyzed clinical cases, it was observed that five patients experienced adverse effects due to the use of high doses of metronidazole, paromomycin, furazolidone, tinidazole, and prochlorperazine, whether used alone or in combination. In this context, there were reports of adverse effects following the use of oral and topical medications, highlighting cases of nausea, vomiting, decreased appetite, fever, and skin problems.

In the case of metronidazole, inflammatory skin reactions were reported, as mentioned in the case of a patient from the United States[36].

In general, in addition to intrinsic factors related to the host, exposure to high doses, prolonged use, combination with other drugs or substances, and improper handling of medications can lead to negative adverse effects in patients. Although no case reports were retrieved in which patients experienced adverse effects following intravenous medication use, formulations of this type offer no advantage over oral drugs[74].

From the analyzed material, it was concluded that cases of *T. vaginalis* resistant to metronidazole occur more frequently in women residing in North American countries, particularly the United States. Furthermore, despite clinical and parasitological cure in a large number of recovered cases, there was no observed standardization of therapeutic approaches to be followed by healthcare professionals in cases of *T. vaginalis* infections resistant to metronidazole in the analyzed reports. In this scenario, it is important to emphasize that some of the main barriers to reducing the global prevalence of *T. vaginalis* are cases of resistance to metronidazole and the lack of systematization of alternative treatments for persistent parasitic infections[46]. Generally, patients with *T. vaginalis* resistant infections are subjected to higher doses of metronidazole, which can trigger increased and even intolerable adverse effects, necessitating treatment interruption. Another issue regarding trichomoniasis is the confirmation of its diagnosis, which is often confused with bacterial or fungal infections of the genitourinary tract due to the great similarity in the clinical manifestations of these infection groups. In this context, antibiotics that are ineffective against *T. vaginalis* are prescribed in most cases[45]. In terms of public health, trichomoniasis, like other sexually transmitted infections, remains strongly associated with the treatment and diagnosis of genital infections. This directly reflects the lack of knowledge and misinformation about these conditions, as well as the low demand for medical care, both among men and women.

REFERENCES

1. Vieira PdB, Brandelli CLC, Veríssimo CDM, Tasca T. Mecanismos específicos de patogenicidade de protozoários de mucosa: Entamoeba histolytica, Giardia lamblia e *Trichomonas vaginalis*. Clinical and Biomedical Research. 2012;32(1).
2. Adl SM, Bass D, Lane CE, Lukes J, Schoch CL, Smirnov A, et al. Revisions to the Classification, Nomenclature, and Diversity of Eukaryotes. J Eukaryot Microbiol. 2019;66(1):4-119.
3. Dias-Lopes G, Saboia-Vahia L, Margotti ET, Fernandes NS, Castro CLF, Oliveira FOJ, et al. Morphologic study of the effect of iron on pseudocyst formation in *Trichomonas vaginalis* and its interaction with human epithelial cells. Mem Inst Oswaldo Cruz. 2017;112(10):664-73.
4. Hirt RP. *Trichomonas vaginalis* virulence factors: an integrative overview. Sex Transm Infect. 2013;89(6):439-43.
5. Petrin D, Delgaty K, Bhatt R, Garber G. Clinical and microbiological aspects of *Trichomonas vaginalis*. Clin Microbiol Rev. 1998;11(2):300-17.
6. Cheon SH, Kim SR, Song HO, Ahn MH, Ryu JS. The dimension of *Trichomonas vaginalis* as measured by scanning electron microscopy. Korean J Parasitol. 2013;51(2):243-6.
7. Edwards T, Burke P, Smalley H, Hobbs G. *Trichomonas vaginalis*: Clinical relevance, pathogenicity and diagnosis. Crit Rev Microbiol. 2016;42(3):406-17.
8. Maciel GdP, Tasca T, De Carli GA. Aspectos clínicos, patogênese e diagnóstico de *Trichomonas vaginalis*. Jornal Brasileiro de Patologia e Medicina Laboratorial. 2004;40.
9. Godha K, Tucker KM, Biehl C, Archer DF, Mirkin S. Human vaginal pH and microbiota: an update. Gynecol Endocrinol. 2018;34(6):451-5.
10. Machado ER, Souza LPd. Tricomoníase: assistência de enfermagem na prevenção e controle Ensaios e Ciência: Ciências Biológicas, Agrárias e da Saúde. 2022;16(4):229-43.
11. Kissinger P. *Trichomonas vaginalis*: a review of epidemiologic, clinical and treatment issues. BMC Infect Dis. 2015;15:307.
12. Hammerschlag MR, Alpert S, Onderdonk AB, Thurston P, Drude E, McCormack WM, et al. Anaerobic microflora of the vagina in children. Am J Obstet Gynecol. 1978;131(8):853-6.
13. Sánchez-Hernández JA, Mayta-Baldivieso MJ, J.A. R-T. Alteraciones del pH vaginal asociado a lactobacilos o bacilo de Döderlein. Rev Mex Patol Clin Med Lab. 2012;59(1):56-60.
14. Thoma ME, Gray RH, Kiwanuka N, Aluma S, Wang MC, Sewankambo N, et al. Longitudinal changes in vaginal microbiota composition assessed by gram stain among never sexually active pre- and postmenarcheal adolescents in Rakai, Uganda. J Pediatr Adolesc Gynecol. 2011;24(1):42-7.

15. Alderete JF, Garza GE. Identification and properties of *Trichomonas vaginalis* proteins involved in cytadherence. Infect Immun. 1988;56(1):28-33.
16. Alderete JF, Provenzano D, Lehker MW. Iron mediates *Trichomonas vaginalis* resistance to complement lysis. Microb Pathog. 1995;19(2):93-103.
17. Bhakta SB, Moran JA, Mercer F. Neutrophil interactions with the sexually transmitted parasite *Trichomonas vaginalis*: implications for immunity and pathogenesis. Open Biol. 2020;10(9):200192.
18. Lopez LB, Braga MB, Lopez JO, Arroyo R, Costa e Silva Filho F. Strategies by which some pathogenic trichomonads integrate diverse signals in the decision-making process. An Acad Bras Cienc. 2000;72(2):173-86.
19. Lehker MW, Arroyo R, Alderete JF. The regulation by iron of the synthesis of adhesins and cytoadherence levels in the protozoan *Trichomonas vaginalis*. J Exp Med. 1991;174(2):311-8.
20. Lehker MW, Alderete JF. Biology of trichomonosis. Curr Opin Infect Dis. 2000;13(1):37-45.
21. Ryu JS, Kang JH, Jung SY, Shin MH, Kim JM, Park H, et al. Production of interleukin-8 by human neutrophils stimulated with *Trichomonas vaginalis*. Infect Immun. 2004;72(3):1326-32.
22. Ferracin I, Oliveira RMWd. Corrimento vaginal: causa, diagnóstico e tratamento farmacológico. Infarma - Ciências Farmacêuticas. 2005;17(5/6):82-6.
23. Mercer F, Johnson PJ. *Trichomonas vaginalis*: Pathogenesis, Symbiont Interactions, and Host Cell Immune Responses. Trends Parasitol. 2018;34(8):683-93.
24. Kissinger P, Adamski A. Trichomoniasis and HIV interactions: a review. Sex Transm Infect. 2013;89(6):426-33.
25. Masha SC, Cools P, Sanders EJ, Vaneechoutte M, Crucitti T. *Trichomonas vaginalis* and HIV infection acquisition: a systematic review and meta-analysis. Sex Transm Infect. 2019;95(1):36-42.
26. Rowley J, Vander Hoorn S, Korenromp E, Low N, Unemo M, Abu-Raddad LJ, et al. Chlamydia, gonorrhoea, trichomoniasis and syphilis: global prevalence and incidence estimates, 2016. Bull World Health Organ. 2019;97(8):548-62P.
27. Van Gerwen OT, Opsteen SA, Graves KJ, Muzny CA. Trichomoniasis. Infect Dis Clin North Am. 2023;37(2):245-65.
28. Barbosa MDS, Andrade de Souza IB, Schnaufer E, Silva LFD, Maymone Goncalves CC, Simionatto S, et al. Prevalence and factors associated with *Trichomonas vaginalis* infection in indigenous Brazilian women. PLoS One. 2020;15(10):e0240323.
29. Moura SLO, Silva MAMd, Moreira ACA, Freitas CASL, Pinheiro AKB. Percepção de mulheres quanto à sua vulnerabilidade às Infecções Sexualmente Transmissiveis. Escola Anna Nery. 2021;25.
30. Moura SLO, Silva MAMd, Moreira ACA, Pinheiro AKB. Relações de gênero e poder no contexto das vulnerabilidades de mulheres às infecções sexualmente transmissíveis. Interface - Comunicação, Saúde, Educação. 2022;26.
31. Bhatt R, Abraham M, Petrin D, Garber GE. New concepts in the diagnosis and pathogenesis of *Trichomonas vaginalis*. Can J Infect Dis. 1996;7(5):321-5.
32. Van Gerwen OT, Camino AF, Sharma J, Kissinger PJ, Muzny CA. Epidemiology, Natural History, Diagnosis, and Treatment of *Trichomonas vaginalis* in Men. Clin Infect Dis. 2021;73(6):1119-24.
33. Valleroy T, Garon C, Perroud J, Wagner AL. Public willingness to receive chlamydia, gonorrhea, syphilis, and trichomoniasis vaccines: a scoping review. BMC Health Serv Res. 2023;23(1):1290.
34. Willcox RR. Epidemiological aspects of human trichomoniasis. Br J Vener Dis. 1960;36(3):167-74.
35. Bouchemal K, Bories C, Loiseau PM. Strategies for Prevention and Treatment of *Trichomonas vaginalis* Infections. Clin Microbiol Rev. 2017;30(3):811-25.
36. Goldman LM, Upcroft JA, Workowski K, Rapkin A. Treatment of metronidazole-resistant *Trichomonas vaginalis*. Sex Health. 2009;6(4):345-7.
37. Prevention CfDCa. Trichomoniasis 2024 [cited 2024 November 5]. Available from: https://www.cdc.gov/dpdx/trichomoniasis/index.html.
38. Mendz GL, Megraud F. Is the molecular basis of metronidazole resistance in microaerophilic organisms understood? Trends Microbiol. 2002;10(8):370-5.
39. Benchimol M. The hydrogenosome as a drug target. Curr Pharm Des. 2008;14(9):872-81.
40. Lofmark S, Edlund C, Nord CE. Metronidazole is still the drug of choice for treatment of anaerobic infections. Clin Infect Dis. 2010;50 Suppl 1:S16-23.
41. Hernandez Ceruelos A, Romero-Quezada LC, Ruvalcaba Ledezma JC, Lopez Contreras L. Therapeutic uses of metronidazole and its side effects: an update. Eur Rev Med Pharmacol Sci. 2019;23(1):397-401.
42. Ajiji P, Uzunali A, Ripoche E, Vittaz E, Vial T, Maison P. Investigating the efficacy and safety of metronidazole during pregnancy; A systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol X. 2021;11:100128.
43. Kim TG, Young MR, Goggins ER, Williams RE, HogenEsch E, Workowski KA, et al. *Trichomonas vaginalis* in Pregnancy: Patterns and Predictors of Testing, Infection, and Treatment. Obstet Gynecol. 2020;135(5):1136-44.
44. Nwosu OC, Bloom K. The safety of metronidazole in pregnancy. Health Care Women Int. 2021;42(4-6):726-38.
45. Cudmore SL, Garber GE. Prevention or treatment: the benefits of *Trichomonas vaginalis* vaccine. J Infect Public Health. 2010;3(2):47-53.
46. Cudmore SL, Delgaty KL, Hayward-McClelland SF, Petrin DP, Garber GE. Treatment of infections caused by metronidazole-resistant *Trichomonas vaginalis*. Clin Microbiol Rev. 2004;17(4):783-93, ta-

ble of contents.
47. Gehrig S, Efferth T. Development of Drug Resistance in *Trichomonas vaginalis* and its Overcoming with Natural Products. The Open Bioactive Compounds Journal. 2009;2.
48. Azad AK, Singh RK, Sinha RI, Sinha KK, Kumar M. Metronidazole induced neurotoxicity: a case report. International Journal of Basic & Clinical Pharmacology. 2023;12(4):594-6.
49. Guglielmo BJ. Metronidazole Neurotoxicity: Suspicions Confirmed. Clin Infect Dis. 2021;72(12):2101-2.
50. Sobel JD, Nyirjesy P, Brown W. Tinidazole therapy for metronidazole-resistant vaginal trichomoniasis. Clin Infect Dis. 2001;33(8):1341-6.
51. Kulda J, Vojtechovska M, Tachezy J, Demes P, Kunzova E. Metronidazole resistance of *Trichomonas vaginalis* as a cause of treatment failure in trichomoniasis--A case report. Br J Vener Dis. 1982;58(6):394-9.
52. Pattman RS, Sprott MS, Kearns AM, Earnshaw M. Failure of mebendazole to cure trichomonal vaginitis resistant to metronidazole: case reports. Genitourin Med. 1989;65(4):274-5.
53. Wong CA, Wilson PD, Chew TA. Povidone-iodine in the treatment of metronidazole-resistant *trichomonas vaginalis*. Aust N Z J Obstet Gynaecol. 1990;30(2):169-71.
54. Watson PG, Pattman RS. Arsenical pessaries in the successful elimination of metronidazole-resistant *Trichomonas vaginalis*. Int J STD AIDS. 1996;7(4):296-7.
55. Lewis DA, Habgood L, White R, Barker KF, Murphy SM. Managing vaginal trichomoniasis resistant to high-dose metronidazole therapy. Int J STD AIDS. 1997;8(12):780-4.
56. Saurina G, DeMeo L, McCormack WM. Cure of metronidazole- and tinidazole-resistant trichomoniasis with use of high-dose oral and intravaginal tinidazole. Clin Infect Dis. 1998;26(5):1238-9.
57. Nyirjesy P, Gilbert J, Mulcahy LJ. Resistant trichomoniasis: successful treatment with combination therapy. Sex Transm Dis. 2011;38(10):962-3.
58. Forbes GL, Drayton R, Forbes GD. A case of metronidazole-resistant *Trichomonas vaginalis* in pregnancy. Int J STD AIDS. 2016;27(10):906-8.
59. Byun JM, Jeong DH, Kim YN, Lee KB, Sung MS, Kim KT. Experience of successful treatment of patients with metronidazole-resistant *Trichomonas vaginalis* with zinc sulfate: A case series. Taiwan J Obstet Gynecol. 2015;54(5):617-20.
60. Butt S, Tirmizi A. Intravenous metronidazole, liquid tinidazole, and intra-vaginal boric acid to cure trichomonas in a patient with gastric bypass surgery. Int J STD AIDS. 2018;29(8):825-7.
61. Salas A, Hamill MM, Tuddenham S. Nitroimidazole Resistance in *Trichomonas vaginalis* Infection: A Teachable Moment. JAMA Intern Med. 2019;179(2):247-8.
62. Henien M, Nyirjesy P, Smith K. Metronidazole-Resistant Trichomoniasis: Beneficial Pharmacodynamic Relationship With High-Dose Oral Tinidazole and Vaginal Paromomycin Combination Therapy. Sex Transm Dis. 2019;46(1):e1-e2.
63. Newman L, Rowley J, Vander Hoorn S, Wijesooriya NS, Unemo M, Low N, et al. Global Estimates of the Prevalence and Incidence of Four Curable Sexually Transmitted Infections in 2012 Based on Systematic Review and Global Reporting. PLoS One. 2015;10(12):e0143304.
64. Patel EU, Gaydos CA, Packman ZR, Quinn TC, Tobian AAR. Prevalence and Correlates of *Trichomonas vaginalis* Infection Among Men and Women in the United States. Clin Infect Dis. 2018;67(2):211-7.
65. Aggarwal A, Shier RM. Recalcitrant *Trichomonas vaginalis* infections successfully treated with vaginal acidification. J Obstet Gynaecol Can. 2008;30(1):55-8.
66. Hager WD. Treatment of metronidazole-resistant *Trichomonas vaginalis* with tinidazole: case reports of three patients. Sex Transm Dis. 2004;31(6):343-5.
67. Mitchell L, Hussey J. *Trichomonas vaginalis*: an unusual presentation. Int J STD AIDS. 2010;21(9):664-5.
68. Graves KJ, Novak J, Secor WE, Kissinger PJ, Schwebke JR, Muzny CA. A systematic review of the literature on mechanisms of 5-nitroimidazole resistance in *Trichomonas vaginalis*. Parasitology. 2020;147(13):1383-91.
69. Cotch MF, Pastorek JG, 2nd, Nugent RP, Hillier SL, Gibbs RS, Martin DH, et al. *Trichomonas vaginalis* associated with low birth weight and preterm delivery. The Vaginal Infections and Prematurity Study Group. Sex Transm Dis. 1997;24(6):353-60.
70. Brasil. Protocolo clínico e diretrizes terapêuticas para atenção integral às pessoas com infecções sexualmente transmissíveis (IST). In: Transmissíveis DdDdCCeIS, editor. Brasília: Ministério da Saúde; 2022. p. 211.
71. Bradic M, Warring SD, Tooley GE, Scheid P, Secor WE, Land KM, et al. Genetic Indicators of Drug Resistance in the Highly Repetitive Genome of *Trichomonas vaginalis*. Genome Biol Evol. 2017;9(6):1658-72.
72. Fraiha H. Bases parasitologicas e farmacologicas da terapeutica da malaria. / Parasitological and pharmacological bases of malaria therapy Rev Fund SESP. 1981;26(1):41-52.
73. Leitsch D. Drug Resistance in the Microaerophilic Parasite Giardia lamblia. Curr Trop Med Rep. 2015;2(3):128-35.
74. Schwebke JR, Barrientes FJ. Prevalence of *Trichomonas vaginalis* isolates with resistance to metronidazole and tinidazole. Antimicrob Agents Chemother. 2006;50(12):4209-10.