GENITAL PROTOZOAL INFECTIONS

CHI Formulary Indication Review

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Council of Health Insurance

INDICATION UPDATE

ADDENDUM – December 2023

To the CHI Original Genital Protozoal Infections - Issued May 2020

Contents

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Abbreviations

AAFP	American Academy of Family Physicians
BCG	Bacillus Calmette-Guérin
BID	Twice a Day
BV	Bacterial Vaginosis
CADTH	Canadian Agency for Drugs and Technologies in Health
CDC	Centers for Disease Control and Prevention
CHI	Council of Health Insurance
CPG	Clinical Practice Guideline
EMA	European Medicines Agency
EPT	Expedited Partner Therapy
FDA	Food and Drug Administration
GI	Gastrointestinal

GV	Gentian Violet
HAS	Haute Autorité de Santé (French: High Authority of Health)
HIV	Human Immunodeficiency Virus
HTA	Health Technology Assessment
IDF	Insurance Drug Formulary
IQWIG	Institute for Quality and Efficiency in Health Care (German: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)
MMWR	Morbidity and Mortality Weekly Report
MTZ	Metronidazole
N/A	Not Applicable or Not Available
NAAT	Nucleic Acid Amplification Test
NICE	National Institute for Health and Care Excellence
PBAC	Pharmaceutical Benefits Advisory Committee
PE	Prescribing Edit
PO	Per Os (Orally)
SFDA	Saudi Food and Drug Authority
STAT	Immediately or Urgently
STBBI	Sexually Transmitted and Blood-Borne Infections
STD	Sexually Transmitted Disease
STI	Sexually Transmitted Infection
TDZ	Tinidazole
USA	United States of America
WHO	World Health Organization

Executive Summary

Protozoan infections are parasitic diseases caused by protozoa. The most common genital protozoa infection is **trichomoniasis**. The latter is caused by the parasite *Trichomonas vaginalis*, transmitted via intercourse, and can be treatable. The parasite targets the lower genital tract, affecting the vulva, vagina, cervix, and urethra in women, while in men, it infects the urethra. Importantly, transmission of the infection can take place even in the absence of symptoms[1].

Symptoms include itching, irritation of the genitals, dysuria, dyspareunia, and fishy discharge, however, most patients are asymptomatic upon presentation. Trichomoniasis can lead to complications such as premature birth, increase the risk of cervical or prostate cancer, and getting or spreading other sexually transmitted infections[1]. Regardless of present or absent of symptoms, treatment of *T. vaginalis* is indicated due to limited side effects of therapy, high cure rate, positive impact on

the prevalence of *T. vaginalis* carriage in the population and reduces transmission of the parasite.

The Centers for Disease Control and Prevention (CDC) in the United States estimates that there were over two million cases of trichomoniasis infections in 2018. However, only around 30% developed symptoms. The prevalence of infection is higher in women compared to men. Older women are more susceptible to the infection than their younger counterparts[1]. The average annual incidence of trichomoniasis per 100,000 population for Saudis and non-Saudis, respectively, was 9.4 and 10.4[2].

Trichomoniasis has been estimated to cost the United States almost $24 million in direct medical costs annually[3]. The mainstay treatment of trichomoniasis is the use of specific medications. Additionally, it's important for both sexual partners to be treated simultaneously to prevent reinfection[1].

CHI issued Genital Protozoal Infections clinical guidance after thorough review of renowned international and national clinical guidelines in May 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations.

This report functions as an addendum to the prior CHI Genital Protozoal Infections clinical guidance and seeks to offer guidance for the effective management of Trichomoniasis. It provides an **update on the Genital Protozoal Infections Guidelines** for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

Main triggers for the update are summarized, being **the issuance of updated versions of previously reviewed guidelines** namely Trichomoniasis Treatment Guidelines Up-To Date November **2023**, and the CDC Sexually Transmitted Infections Treatment Guidelines, **2021**. Moreover, **new guidelines are added to the report** such as the WHO Guidelines for the management of symptomatic sexually transmitted infections June **2021**, the Canadian STI-associated syndromes guide: Vaginitis **2023**, the Australian STI Management Guidelines for use in Primary Care **2021**, the Royal Children's Hospital Melbourne Sexually transmitted infections (STIs) **2022**, the AAFP **2018** Vaginitis: Diagnosis and Treatment, and the Melbourne Sexual Health Centre Trichomonas vaginalis treatment guidelines **2021.**

After carefully examining clinical guidelines and reviewing the SFDA drug list, it is important to note that it is recommended to add **Secnidazole and Metronidazole Gel** on the CHI formulary. Additionally, there have been **no withdrawals** for the treatment of Genital Protozoal Infections, however, there have been **updates** regarding certain previously mentioned drugs in terms of drug information and prescribing edits since May 2020.

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in the therapeutic management of Trichomoniasis.

Below is a table summarizing the major changes based on the different Trichomoniasis treatment guidelines used to issue this report:

Table 1. General Recommendations for the Management of Trichomoniasis

Management of Trichomoniasis		
General Recommendations	**Level of Evidence/ Grade of Recommendation**	**Reference**
The decision to treat trichomoniasis empirically or to wait for test results should reflect the: • Severity of the clinical condition • Probability of infection • Person's risk factors for a sexually transmitted or blood-borne infection (STBBI) • Person's willingness to abstain from sex and to return for test results or follow-up	Not graded	Canadian Vaginitis Guidelines 2023[4]
The 5-nitroimidazole drugs (metronidazole, tinidazole, and secnidazole) are the only class of drugs that provide curative therapy of trichomoniasis. Choice of agent is generally determined by availability, preference for single-day therapy, and cost.	Not graded	Up to date November 2023[5]
• Recommended Regimen for Trichomoniasis Among Women: Metronidazole 500 mg orally 2 times/day for 7 days • Recommended Regimen for Trichomoniasis Among Men: Metronidazole 2 g orally in a single dose	Not graded	CDC Guidelines 2021[6]
• Nonpregnant women's Treatment: An oral suspension is also available with unique dosing (metronidazole oral suspension 250 mg [2.5 mL] orally three times daily for seven days). • Males' treatment: If the oral suspension is	Not graded	Up to date November 2023[5]

preferred to tablets or capsules, the dosing is: metronidazole oral suspension 2 g (20 mL), either as a single oral dose or in two divided oral doses of 1 g (10 mL) each, given on the same day		
• Abstinence from sexual activity – After completion of therapy (single- or multi-dose), the patient and their sex partners should abstain from intercourse until all partners have completed antibiotic therapy and symptoms have resolved (whichever is later)	Not graded	Australian Guidelines 2021[7]
• Reinfection by sex partner is common: It is recommended to repeat treatment of the patient, and all sex partners, with the originally selected treatment regimen. • Sexual partners should be notified, tested, and treated for trichomonas. Partners should be treated with metronidazole 2 g PO as a single dose.	Not graded	Canadian Vaginitis Guidelines 2023[4] Melbourne Guidelines 2021[8]
Single dose secnidazole is the only oral treatment option for both trichomoniasis and bacterial vaginosis (BV).	Not graded	Up to date November 2023[5]
Recurrent or persistent trichomoniasis: ○ If a male patient has persistent T. vaginalis after a single 2-g dose of metronidazole and has been re-exposed to an untreated partner, he should be retreated with a single 2-g dose of metronidazole. If he has not been re-exposed, he should be administered a course of metronidazole 500 mg 2 times/ day for 7 days. • If a woman has treatment failure after the 7-day regimen of high-dose oral metronidazole or tinidazole, two additional treatment options have been determined to have successful results: The first is high-dose oral tinidazole 2 g daily +/- intravaginal tinidazole 500 mg 2 times/day for 14 days. If this regimen fails, high-dose oral tinidazole (1	Not graded	CDC Guidelines 2021[6] AAFP Guidelines 2018[9]

g 3 times/day) plus intravaginal paromomycin (4 g of 6.25% intravaginal paromomycin cream nightly) for 14 days should be considered. • Clinical improvement has been reported with intravaginal boric acid but not with nitazoxanide. • If a man has persistent trichomonas infection despite multi-dose treatment: Metronidazole 2 g orally once daily for seven days (total dose 14 g) is advised. • Consultation with an infectious disease specialist is recommended.		
Metronidazole-resistant infection: • High-dose oral tinidazole –Choice of treatment is based on availability of the drugs below: • Tinidazole only – Oral tinidazole 2 g daily for 14 days plus vaginal tinidazole 500 mg twice a day for 14 days (total drug dose 42 g) • Tinidazole plus vaginal boric acid – Tinidazole, 1 g orally three time a day for 14 days plus vaginal boric acid, 600 mg, twice daily for 28 days successfully treated a female patient with confirmed T. vaginalis infection resistant to both metronidazole and tinidazole. Boric acid should never be given orally as it can cause death. • Tinidazole plus vaginal paromomycin – Tinidazole 1 g orally three times a day plus vaginal paromomycin 6.25% given as 4 g intravaginally at night (ie, 250 mg of drug per dose), both for a total of 14 days, has been reported in one patient. • Secnidazole might also me an option, further studies are needed.	Not graded	Up to date November 2023[5]
Allergy to 5-nitroimidazole drugs: o Desensitization to metronidazole o Secnidazole might be an option for a person	Not graded	CDC Guidelines 2021[6]

with reported metronidazole hypersensitivity. ○ The optimal treatment for patients with *T. vaginalis* who are unable to be desensitized has not been systematically investigated and is based on case reports, some of which report using paromomycin or boric acid for treating *T. vaginalis*. ○ Case reports have noted microbiologic and symptomatic cure following long-term treatment with vaginal boric acid, 600 mg intravaginally twice daily, alone or in combination with other agents, for at least 60 days.		
Pregnant women: • Preferably treat symptomatic pregnant patients. If asymptomatic, consult with a sexual health physician. • Ideally, metronidazole should be avoided in the first trimester (metronidazole is category B2 in pregnancy). • If needed, metronidazole 500 mg orally twice daily may be given for seven days. An oral suspension is also available (metronidazole oral suspension 250 mg [2.5 mL] orally three times daily for seven days) Or • Metronidazole 200 mg or 250 mg, orally, 3 times a day for 7 days Or • Metronidazole 2 g PO in a single dose for symptom relief Other guidelines recommend metronidazole gel 0.75%, one full applicator (5 grams) intravaginally, twice a day for 7 days. Additionally, it is recommended to avoid oral tinidazole or secnidazole, especially in the first trimester due to lack of safety data rather than because of established harm.	-	Canadian Vaginitis Guidelines 2023[4] Australian Guidelines 2021[7] AAFP Guidelines 2018[9] Melbourne Guidelines 2021[8] WHO Guidelines 2021[10]

Breastfeeding: • Clinicians sometimes advise deferring breastfeeding for 12–24 hours after maternal treatment with metronidazole. Avoid high doses in breastfeeding. • Breastfeeding should be deferred for 72 hours after a single 2-g oral dose of tinidazole. • Secnidazole – Given the long half-life of the drug (approximately 17 hours), the manufacturer advises avoiding giving milk to the infant for 96 hours after a single dose.	Not graded	Australian Guidelines 2021[7]
HIV Infection – • Male patients receive the same treatment and retesting approaches regardless of HIV infection status. Treatment with metronidazole 2 g in a single oral dose is advised; • Immunosuppression — immunosuppressed patients are treated with metronidazole 500 mg orally daily for seven days.	Not graded	Up to date November 2023[5]

At the end of the report, a **key recommendation synthesis section** is added highlighting the latest updates in **Genital Protozoal Infections clinical and therapeutic management.** Additionally, **appendices** are provided for treatment algorithms and further information on the topic.

Section 1.0 Summary of Reviewed Clinical Guidelines & Evidence

This section is divided into two parts: the first includes recommendations from **updated versions of guidelines** mentioned in the previous CHI Genital Protozoal Infections report, while the second includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

This section contains the **updated versions** of the guidelines mentioned in the May 2020 CHI Genital Protozoal Infections Report and the corresponding recommendations:

Table 2. Guidelines Requiring Revision

Guidelines Requiring Revision	
Old Versions	**Updated versions**
1.1.1. Trichomoniasis Treatment Guidelines **Up-To-Date Mar 24, 2020**	Trichomoniasis Treatment Guidelines **Up-To-Date November 2023**
1.1.2. **Centers of Disease Control** and Prevention of America Treatment Guidelines of Trichomoniasis **2015**	**CDC** Sexually Transmitted Infections Treatment Guidelines, **2021**

1.1.1 Trichomoniasis Treatment Guidelines Up-To-Date (November 2023)

*Please refer to **section 1.1** of the previous Genital Protozoal Infections CHI report.*

UpToDate authors and editors thoroughly examine the existing clinical evidence and optimal clinical approaches to deliver a comprehensive overview of a particular subject. Although not commonly used as a clinical guideline, the information was extensively covered in the prior CHI report, making it pertinent to incorporate the updated version of the "Trichomoniasis Treatment," last revised in November 2023.

The recommendations were not accompanied by a grading scheme, and are presented below[5]:

- The 5-nitroimidazole drugs (**metronidazole**, **tinidazole**, and **secnidazole**) are the only class of drugs that provide curative therapy of trichomoniasis. Choice of agent is generally determined by availability, preference for single-day therapy, and cost.
- Single-dose therapy for male patients is generally preferred because of ease of single dosing, although efficacy may be lower than that of multi-dose metronidazole therapy. However, trial data are limited. In a trial including 325 males comparing a single 2 g oral dose of metronidazole and metronidazole 400 mg three times daily for five days, treatment failure occurred in 43 percent of the single-dose patients and none of the multi-dose patients. Until data from an adequately powered trial are available, both dosing regimens are reasonable and patient preference, usually for single-dose treatment, determines treatment choice. The authors extrapolate this approach to

individuals who have undergone surgical phalloplasty, although the authors are unaware of a reported case of trichomoniasis in a patient with phalloplasty.

- Secnidazole is a 5-nitroimidazole with a longer half-life (17 to 19 hours) than oral metronidazole (7 to 8 hours) and tinidazole (12 to 13 hours). It is given as a single 2 g oral treatment for trichomoniasis. It is administered as a packet of granules which should be sprinkled onto a standard serving of applesauce, yogurt, or pudding and consumed within 30 minutes. Single-dose secnidazole is the only oral treatment option for both trichomoniasis and bacterial vaginosis (BV) in patients with a vagina.
    - Efficacy – Compared with placebo for treatment of trichomoniasis in females, cure rates of 92 percent were reported at 6- to 12-day follow-up, which is comparable to other 5-nitroimidazole single-dose regimens in this short-term follow-up period.
    - Safety - Gastrointestinal side effects were reported in <5 percent of participants in either arm, which is lower than rates reported with single-dose metronidazole.
    - Data for using secnidazole in males with trichomoniasis are limited. In one trial comparing ornidazole, metronidazole, or secnidazole treatment in 85 men with confirmed trichomoniasis, all three treatment groups tested negative (by microscopic evaluation and culture of discharge) and were asymptomatic at follow-up evaluation.
    - Limitations – there are no head-to-head efficacy comparisons of single-dose secnidazole and the seven-day metronidazole regimen for the treatment of trichomoniasis in females or males.
- The authors still do not believe that patients need to be counseled to avoid alcohol while using metronidazole and extrapolate this approach to tinidazole and secnidazole.

Treatment of non-pregnant women

- Non-pregnant females are preferentially treated with a multi-dose oral metronidazole regimen rather than single-day treatment because multi-dose therapy is associated with improved cure rates at one month.
- Preferred – Metronidazole 500 mg, tablet or capsule, orally twice daily for seven days. The authors prefer this approach because of higher efficacy compared with single-day regimens. An oral suspension is also available with

unique dosing (metronidazole oral suspension 250 mg [2.5 mL] orally three times daily for seven days).

- Alternatives – Alternative treatments vary according to the source guideline (CDC compared with WHO). As direct comparative data are lacking, selection is based on availability and cost.
    - ➔ Single-dose options – Treatment with a single 2 g oral dose of either metronidazole or tinidazole (i.e., four 500 mg tablets) is associated with lower rates of cure compared with metronidazole multi-dose therapy. The authors reserve single-dose therapy for those who are unable to complete a multi-dose treatment course.

      Metronidazole 2 g orally given as a single dose or metronidazole oral suspension 2 g (20 mL), either as a single oral dose or in two divided oral doses of 1 g (10 mL) each, given on the same day.

      OR

      Tinidazole 2 g orally given as a single dose

      OR

      Secnidazole 2 g orally given as a single dose (single dose secnidazole is effective treatment for both trichomoniasis and bacterial vaginosis).
    - ➔ Multi-dose tinidazole – Tinidazole 500 mg orally twice daily for five days is an alternative option listed by WHO. It is not yet known which patient groups may benefit from multi-dose tinidazole compared with single dose for initial treatment. The authors recommend reserving multi-dose tinidazole for patients with persistent infection despite adequate initial treatment and use a higher dose in this setting (tinidazole 2 g daily for seven days)
- Not advised – Vaginal metronidazole gel is not recommended because it does not effectively treat all anatomic reservoirs of infection and should not be used to treat trichomoniasis. However, metronidazole vaginal gel remains on at least one treatment guideline.

Treatment of pregnant women

- Treatment of pregnant persons, **with or without symptoms**, is indicated as *T. vaginalis* infection is common in pregnant persons and has been associated with adverse pregnancy outcomes.
    - Preferred – Metronidazole 500 mg orally twice daily for seven days, regardless of trimester. An oral suspension is also available

(metronidazole oral suspension 250 mg [2.5 mL] orally three times daily for seven days)

The authors believe the available evidence supports the benefits of treatment, including reduced partner and perinatal transmission, and outweighs potential risks, although at least one organization advises waiting until after the first trimester for treatment, if possible

- Alternate regimens – WHO lists the following as alternative treatment options with the notation to avoid metronidazole use in the first trimester of pregnancy if possible. While data directly comparing the treatment options in pregnant persons are lacking, there is no reason to think that pregnancy would make the alternative regimens more effective than multi-dose oral metronidazole.

  Metronidazole 2 g orally in a single dose. An oral suspension is also available (metronidazole oral suspension 2 g [20 mL], either as a single oral dose or in two divided oral doses of 1 g [10 mL] each, given on the same day). While single-day dosing is included as a first-line treatment option in the WHO sexually transmitted infection (STI) treatment guidelines, the authors view it as an alternative for the reasons discussed above. However, both single- and multiple-dose regimens are acceptable as there are no specific data comparing single-dose and multiple-dose regimens in pregnant individuals and there are no reasons to think that efficacy is different in pregnant patients. It is recommended to reserve the single-dose regimen for pregnant individuals who are unable to complete seven days of treatment or prefer single-dose therapy.

  OR

  Metronidazole 200 or 250 mg orally three times daily for seven days. These doses may not be universally available.

- Not advised during pregnancy – In practice, it is recommended to not use metronidazole gel, tinidazole, or secnidazole in pregnant persons.
  - Metronidazole vaginal gel does not effectively treat all anatomic reservoirs of infection and is not advised, although at least one guideline lists metronidazole gel as a third-line treatment option.

- Tinidazole and secnidazole – it is recommended to avoid oral tinidazole or secnidazole, especially in the first trimester, as safety data from human pregnancies are insufficient to make a definitive conclusion regarding teratogenicity and some, but not all, animal data suggest risk.

- Teratogenicity — While metronidazole crosses the placenta, it appears to be low risk to the developing fetus. Cross-sectional and cohort studies have not reported teratogenicity or mutagenic effects for single- or multi-dose metronidazole treatment in humans (although studies suggest the drug is mutagenic in bacteria and carcinogenic in mice). There is limited information on the safety of tinidazole or secnidazole in pregnancy and thus the authors do not advise use of these drugs during pregnancy.
- Breastfeeding:
    - Secnidazole – Data on safety of secnidazole use during lactation are lacking. Given the long half-life of the drug (approximately 17 hours), the manufacturer advises avoiding giving milk to the infant for 96 hours after a single dose.

Treatment of male patients

- While other treatment options exist, preferred treatment for male patients with confirmed trichomoniasis include:
    - Preferred – Metronidazole 2 g orally in a single dose. If the oral suspension is preferred to tablets or capsules, the dosing is: metronidazole oral suspension 2 g (20 mL), either as a single oral dose or in two divided oral doses of 1 g (10 mL) each, given on the same day
    - Alternatives:

      Tinidazole 2 g orally in a single dose

      OR

      Secnidazole 2 g orally given as a single dose

      OR

      Metronidazole, 400 or 500 mg, orally twice daily for seven days. Dose selection is based on availability and type of oral formulation; the 500 mg dose of metronidazole is more commonly available. If the oral suspension is preferred, it is given as 250 mg (2.5 mL) orally three times daily for seven days. Although data supporting a longer course of therapy are lacking, this approach is described for individuals with recurrent or persistent infection.

Treatment of sexual partners

- Abstinence from sexual activity – After completion of therapy (single- or multi-dose), the patient and their sex partners should abstain from intercourse until all partners have completed antibiotic therapy and symptoms have resolved. There are no studies on how long trichomonads remain viable after treatment is initiated or completed. counsel patients to abstain from anal intercourse as well because trichomonads have been found in rectal samples and an anal reservoir of organisms could be a source of reinfection.
- Reinfection by sex partner is common:
    - It is recommended to repeat treatment of the patient, and all sex partners, with the originally selected treatment regimen as presented above.
- Persistent infection – Persistent infection can occur despite appropriate treatment of the patient and all sex partners. Once inadequate initial treatment and/or reinfection from a sex partner have been excluded, retreat the index patient and all sex partners as follows:
    - Longer duration of treatment – Individuals with symptom recurrence after single-dose oral metronidazole 2 g should be treated with oral metronidazole 500 mg twice daily for seven days (total dose 7 g)
    - Increased dose and duration of treatment – If the patient has persistent trichomonas infection despite multi-dose treatment, then treat with higher doses of oral tinidazole or metronidazole.

      Females: metronidazole or tinidazole 2 g orally once a day for seven days (total dose 14 g) can be used. This approach can also be effective in patients with low levels of metronidazole resistance, which was noted in 4 percent of 538 T. vaginalis isolates collected from women attending STD clinics in six cities in the United States

      Males: metronidazole 2 g orally once daily for seven days (total dose 14 g) is advised.

Treatment of drug-resistant infection

- If the above treatment regimens fail, and nucleic acid amplification tests (NAAT) confirms persistent trichomonas infection, next steps include in vitro culture and drug susceptibility testing and patient referral to a specialist. One option for culture and drug sensitivity testing is available through the United

States CDC Infectious Disease Laboratories. Metronidazole-resistant T. vaginalis has been documented. Cross resistance to tinidazole is frequent but not inevitable. For secnidazole, trichomoniasis isolates requiring a minimum inhibitory concentration similar to that of metronidazole have been reported. In an in vitro study of trichomonas isolates in South Africa, resistance to metronidazole was more common (11%) than tinidazole (2%) or secnidazole (1%).

- Treatment options for patients with metronidazole-resistant infection include:
    - High-dose tinidazole – Refractory disease has been successfully treated with high-dose oral tinidazole, although the optimal dose, regimen, and combination with other drugs have not been established. Choice of treatment is based on availability of the drugs below.

      Tinidazole only – Oral tinidazole 2 g daily for 14 days plus vaginal tinidazole 500 mg twice a day for 14 days (total drug dose 42 g)

      Tinidazole plus vaginal boric acid – Tinidazole, 1 g orally three time a day for 14 days plus vaginal boric acid, 600 mg, twice daily for 28 days successfully treated a female patient with confirmed T. vaginalis infection resistant to both metronidazole and tinidazole. Boric acid should never be given orally as it can cause death.

      Tinidazole plus vaginal paromomycin – Tinidazole 1 g orally three times a day plus vaginal paromomycin 6.25% given as 4 g intravaginally at night (i.e., 250 mg of drug per dose), both for a total of 14 days, has been reported in one patient. Additional information on vaginal paromomycin is presented in the bullet below.
    - Secnidazole – Data supporting secnidazole treatment of drug-resistant trichomoniasis is limited to one case report. A patient with confirmed metronidazole- and tinidazole-resistant infection was successfully treated with an investigational protocol of secnidazole 2 g orally daily for 14 days combined with boric acid 600 mg suppository vaginally twice daily for 14 days. Four weeks after completing treatment, the patient's symptoms had resolved and test of cure was negative by wet mount, culture, and NAAT.
    - Vaginal paromomycin – Rare patients who do not have a response to 5-nitroimidazoles have been treated with the aminoglycoside paromomycin. Paromomycin 6.25% cream is given as a 4 g intravaginal dose (i.e., 250 mg of drug) daily for two weeks). Dual therapy combining intravaginal paromomycin 6.25% cream, 4 g intravaginally at night, with oral tinidazole, 1 g three times daily, for a total of 14 days, has been reported. Intravaginal paromomycin can cause local side effects (pain,

mucosal ulceration) but these symptoms are self-limited. Applying lubricating jelly to the vaginal tissue prior to vaginal paromomycin application has been reported to reduce ulceration in some patients. Paromomycin is not available commercially in the United States as a cream and must be compounded by a specialty pharmacy. For this reason, it is considered a third-line option when the above regimens have not worked.

- Vaginal boric acid – Successful treatment of drug-resistant trichomoniasis has been reported with vaginal boric acid, alone or combination with other drugs (e.g., secnidazole or clotrimazole).
- Limited data – Case reports have described successful use of nimorazole, ornidazole, niridazole, furazolidone, and hamycin.
- Not advised – Other topical agents that have a limited (<50 percent) cure rate and therefore are not recommended include vaginal povidone-iodine, clotrimazole, acetic acid, furazolidone, gentian violet, nonoxynol-9, and potassium permanganate. A trial of nitazoxanide in three women with difficult to eradicate T. vaginalis reported lack of efficacy.

Allergy to 5-nitroimidazole drugs

- A single case report describes successful treatment with secnidazole in a person with reported metronidazole hypersensitivity.
- Therapy with drugs other than 5-nitroimidazoles is an option, but cure rates have been low (≤ 50%). Case reports have noted microbiologic and symptomatic cure following long-term treatment with vaginal boric acid, 600 mg intravaginally twice daily, alone or in combination with other agents, for at least 60 days.

Coinfections

- HIV Infection, Male – Male patients receive the same treatment and retesting approaches regardless of HIV infection status. Treatment with metronidazole 2 g in a single oral dose is advised; retesting of male patients is not recommended at this time.

- Bacterial vaginosis coinfection – There is a high prevalence of BV in patients with concurrent HIV and T. vaginalis infection and an apparent association between the presence of BV and early failure of single-dose oral metronidazole treatment of trichomoniasis (See Bacterial STDs report)

Special populations

- Immunosuppression — immunosuppressed patients are treated with metronidazole 500 mg orally daily for seven days. As limited data are available to address the wide spectrum of immunosuppression, treatment of these patients is extrapolated from data based on patients with HIV infection.
- Transgender individuals — There is no available data indicating that hormone therapy or surgery should alter trichomoniasis treatment or retesting recommendations. The authors extrapolate from the above data to transgender patients and treat or retest based on the patient's anatomy.

1.1.2 CDC Sexually Transmitted Infections Treatment Guidelines (2021)

*Please refer to **section 1.2** of the previous Genital Protozoal Infections CHI report.*

The recommendations published in the CDC STI Guidelines 2021 were not accompanied by a grading scheme, and are presented below[6]:

Table 3. Recommended and Alternative Regimens (CDC 2021 Guidelines)

	Recommended regimen	Alternative regimen
Men	Metronidazole 2 g orally in a single dose	Tinidazole 2 g orally in a single dose
Women	Metronidazole 500 mg orally 2 times/day for 7 days	

Management of sex partners

- Expedited partner therapy (EPT) might have a role in partner management for trichomoniasis and can be used in states where permissible by law.

- However, no partner management intervention has been demonstrated to be superior in reducing reinfection rates.

Recurrent trichomoniasis

- If a man has persistent *T. vaginalis* after a single 2-g dose of metronidazole and has been re-exposed to an untreated partner, he should be retreated with a single 2-g dose of metronidazole. If he has not been re-exposed, he should be administered a course of metronidazole 500 mg 2 times/day for 7 days.
- If a patient has treatment failure after the 7-day regimen of high-dose oral metronidazole or tinidazole, two additional treatment options have been determined to have successful results for women. The first is high-dose oral tinidazole 2 g daily plus intravaginal tinidazole 500 mg 2 times/day for 14 days. If this regimen fails, high-dose oral tinidazole (1 g 3 times/day) plus intravaginal paromomycin (4 g of 6.25% intravaginal paromomycin cream nightly) for 14 days should be considered.
- Alternative regimens might be effective but have not been systemically evaluated; therefore, consultation with an infectious disease specialist is recommended.
- Clinical improvement has been reported with intravaginal boric acid but not with nitazoxanide.
- The following topically applied agents have minimal success (<50%) and are not recommended:
    - Intravaginal betadine (povidone-iodine)
    - Clotrimazole
    - Acetic acid
    - Furazolidone
    - GV
    - Nonoxynol-9
    - Potassium permanganate
    - No other topical microbicide has been reported to be effective against trichomoniasis.

Drug allergy, intolerance, and adverse reactions

- The optimal treatment for patients with *T. vaginalis* who are unable to be desensitized has not been systematically investigated and is based on case

reports, some of which report using paromomycin or boric acid for treating *T. vaginalis*.

Breastfeeding and pregnancy

- Although multiple reported case series studies demonstrated no evidence of adverse effects among infants exposed to metronidazole in breast milk, clinicians sometimes advise deferring breastfeeding for 12–24 hours after maternal treatment with metronidazole.
- Maternal treatment with metronidazole (400 mg 3 times/day for 7 days) produced a lower concentration in breast milk and was considered compatible with breastfeeding over longer periods.
- Data from studies involving human subjects are limited regarding tinidazole use during pregnancy; however, animal data indicate this drug poses moderate risk. Thus, tinidazole should be avoided for pregnant women, and breastfeeding should be deferred for 72 hours after a single 2-g oral dose of tinidazole.

1.2 Additional Guidelines

This part includes the added guidelines to the previous CHI Genital Protozoal Infections report, along with their recommendations.

Table 4. List of Additional Guidelines

Additional Guidelines
WHO Guidelines for the management of symptomatic sexually transmitted infections **2021**
Canadian STI-associated syndromes guide: Vaginitis **2023**
Australian STI Management Guidelines for use in Primary Care **2021**
The Royal Children's Hospital Melbourne Sexually transmitted infections (STIs) **2022**
AAFP 2018 Vaginitis: Diagnosis and Treatment
Melbourne Sexual Health Centre Trichomonas vaginalis treatment guidelines **2021**

1.2.1 WHO Guidelines for the Management of Symptomatic Sexually Transmitted Infections (2021)

Table 5 details the recommended regimens for the treatment of trichomoniases recommended by the World Health Organization (WHO)'s guidelines for the management of symptomatic STIs[10]:

Table 5. WHO Recommendations for the Treatment of Trichomoniasis

	Recommended regimen
First-line	Metronidazole 2 grams, orally, in a single dose
	Metronidazole 400 mg or 500 mg, orally, twice daily for 7 days
Effective substitutes	Tinidazole 2 grams orally, single dose
	Tinidazole 500 mg orally, twice daily for 5 days
Pregnancy (metronidazole should, ideally, be avoided in the first trimester)	Metronidazole 200 mg or 250 mg, orally, 3 times a day for 7 days
	Metronidazole gel 0.75%, one full applicator (5 grams) intravaginally, twice a day for 7 days

1.2.2 Canadian STI-Associated Syndromes Guide: Vaginitis (2023)

The public health agency of Canada has published guidelines on sexually transmitted infections, with the ones pertaining to vaginitis being last updated in February 2023. The main recommendations relating to the management of protozoal genital infections are summarized below[4]:

Table 6. Definitions of Levels of Recommendation and Quality of Evidence

Levels of Recommendation	
A	Strongly recommends that clinicians routinely provide the treatment to eligible patients. **Good evidence** that the treatment improves important health outcomes and concludes that benefits substantially outweigh harms.
B	Recommends that clinicians routinely provide the treatment to eligible patients. There is at least **fair evidence** that the treatment improves important health outcomes and concludes that benefits outweigh harms.
C	No recommendation for or against routine provision of the treatment. There is at least **fair evidence** that the treatment can improve health outcomes but concludes that the balance of the benefits and harms is

	too close to justify a general recommendation.
D	Recommends against routinely providing the treatment to asymptomatic patients. There is a t least **fair evidence** that the treatment is **ineffective** or that harms outweigh benefits.
I	**Evidence is insufficient** to recommend for or against routinely providing the treatment. Evidence that the treatment is effective is **lacking, of poor quality or conflicting,** and the balance of benefits and harms cannot be determined.
Quality of Evidence	
Level I	Evidence from at least one properly randomized, controlled trial.
Level II	Evidence from at least one well-designed clinical trial without randomization, from cohort or case-control analytic studies (preferably from more than one center), from multiple time-series studies or from dramatic results in uncontrolled experiments.
Level III	Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

The decision to treat trichomoniasis empirically or to wait for test results should reflect the:

1. Severity of the clinical condition
2. Probability of infection
3. Person's risk factors for a sexually transmitted or blood-borne infection (STBBI)
4. Person's willingness to abstain from sex and to return for test results or follow-up.

Table 7 details the empiric treatment options recommended for trichomoniasis:

Table 7. The Canadian 2023 Recommendations Regarding the Empiric Treatment for Trichomoniasis

	Empiric treatment
Non-pregnant people	Metronidazole 2 g PO in a single dose [A-I] or Metronidazole 500 mg PO BID for 7 days [A-I] Notes: • Efficacy is 82-88% for both regimens; increases to 95% if partner also treated.

	• Intravaginal metronidazole gel is not effective. • Prevalence of metronidazole-resistant T. vaginalis is estimated at 5%; it usually responds to high-dose metronidazole.
Pregnant people	Metronidazole 2 g PO in a single dose for symptom relief [A-I]. Notes: • Metronidazole 500 mg PO BID for 7 days [A-I] is an alternate treatment in pregnancy. • It is not recommended that those who are asymptomatic during pregnancy be treated [D-I]. • It is not known whether treatment will improve pregnancy outcomes.
Sexual partners to be treated with the same empiric treatment regimen.	

1.2.3 Australian STI Management Guidelines for use in Primary Care (2021)

The Australian guidelines on the management of STIs were developed by the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine and endorsed by the Blood Borne Viruses and Sexually Transmitted Infections Standing Committee. The main recommendations on the management of trichomoniasis are summarized below[7]:

- Recommended regimen for an uncomplicated infection:
    - Metronidazole 400 mg PO with food, twice daily for 7 days
- Alternative regimen for an uncomplicated infection:
    - Metronidazole 2 g PO with food, stat
- Treatment advice:
    - Avoid alcohol with metronidazole treatment and for 24 hours thereafter.
    - Advise no sexual contact for 7 days after treatment is commenced, or until the course is completed and symptoms resolved, whichever is later.
- Special considerations – complicated infection:
    - Consider seeking specialist advice before treating any complicated presentation.
    - Pregnancy: Category B2 in pregnancy

    - Breastfeeding: Metronidazole may affect taste of breast milk; avoid high doses in breastfeeding
    - Allergy to principal treatment choice: There is no effective alternative to 5-nitroimidazole compounds. Metronidazole desensitization has been described.
    - HIV patients: Reports indicate single-dose metronidazole is less effective than extended metronidazole.
- Treatment for sex partners:
    - For all sexual partners
    - There is currently insufficient data to provide a definitive period for contact tracing, partner treatment encouraged presumptively.
    - Partners with a penis may test negative for trichomonas as it is more likely to resolve spontaneously in these people.

1.2.4 The Royal Children's Hospital Melbourne Sexually Transmitted Infections (2022)

The clinical practice guidelines on the management of STIs published by the Royal Children's Hospital in Melbourne were endorsed by the Pediatric Improvement Collaborative. The main recommendations on the management of trichomoniasis are summarized below[11]:

- First-line treatment:
    - Metronidazole 2 g PO single dose (> 12 years old)

      OR
    - Metronidazole 10mg/kg (max 400 mg) PO BID for 7 days
- Topical treatment is not advised.
- No sexual contact for 7 days after treatment.
- Current sexual partner should be treated.

1.2.5 American Academy of Family Physicians (AAFP) Recommendations on the Diagnosis and Treatment of Vaginitis (2018)

The main recommendations on protozoal infections published by the AAFP are summarized below[9]:

- Initial regimens recommended:
    - Metronidazole, 2 g orally, single or divided dose on the same day

or

- Tinidazole, 2 g orally, single dose

- Alternative regimens:
  - Metronidazole, 500 mg orally twice daily for seven days
- Pregnancy:
  - Metronidazole, 2 g orally, single dose in any stage of pregnancy
- Recurrence:
  - Differentiate persistent or recurrent infection from reinfection.
  - If metronidazole, 2-g single dose fails:
    - ❖ Trial of metronidazole, 500 mg twice daily for seven days
  - If metronidazole, 500 mg twice daily for seven days fails:
    - ❖ Trial of metronidazole, 2 g daily for seven days
  - If above regimens fail:
    - ❖ Consider susceptibility testing.
- Treatment of sex partners:
  - Concurrent treatment of sex partners is recommended.
  - Advise refraining from intercourse until partners are treated and symptom-free.

1.2.6 Melbourne Sexual Health Centre Trichomonas Vaginalis Treatment Guidelines (2021)

The below non-graded recommendations are published by the Melbourne Sexual Health Centre (MSHC) Trichomonas vaginalis Guidelines 2021[8]:

- The 5-nitroimidazoles, which include metronidazole (MTZ) and tinidazole (TDZ), are the only class of drug known to be effective against Trichomonas vaginalis.
- Table 8 details the guidelines' recommended regimens regarding the management of trichomoniasis:

Table 8. Recommended Regimens for the Management of Trichomoniasis (MSHC 2021)

Condition	Recommended regimen	Comments
Trichomonas in women	Metronidazole 400 mg PO, twice daily for 7days	Recent studies have shown multi-dose metronidazole to be significantly more effective than single dose metronidazole in women, with a cure rate of approximately 95%. Alcohol should be avoided when taking metronidazole. Second line: Metronidazole 2g PO, daily for 7 days. Ensure compliance and that reinfection is not an issue. This dose will eradicate approximately 90% of the 5% of infections that fail first-line therapy. (CDC, MMWR 2015).
Trichomonas in men	Metronidazole 2 g PO, stat	There are no studies comparing single dose metronidazole to multidose metronidazole in men.
Trichomonas in pregnancy	If symptomatic, manage as for nonpregnant women. Metronidazole (category B) can be used in all trimesters.	Trichomonas have been associated with adverse pregnancy outcomes, particularly premature rupture of membranes, preterm birth, and low birthweight. If asymptomatic, consult with a sexual health physician. Some studies suggest the possibility of increased prematurity or low birthweight after metronidazole therapy. However, limitations of the studies prevent definitive conclusions regarding risks of treatment.
Complicated cases:		Treatment should be discussed

• **When oral metronidazole is not tolerated** • **Allergy to metronidazole is known or suspected**. • **Cases failing second line treatment**		with a sexual health physician. Alternatives to consider include: • Metronidazole desensitization in hospital - requires day admission for increasing doses.

- Patients should be advised to abstain from intercourse until they and their sexual partners have been adequately treated and any symptoms have resolved.
- Sexual partners should be notified, tested, and treated for trichomonas. Partners should be treated **with metronidazole 2 g PO as a single dose.**

Section 2.0 Drug Therapy in Trichomoniasis

This section comprises four subsections: the first contains the newly recommended drugs, the second covers drug modifications, the third outlines the drugs that have been withdrawn from the market, and the fourth details drugs that are approved by the FDA and/or EMA for the management of trichomoniasis but are not currently registered by the SFDA.

2.1 Additions

2.1.1 Antiprotozoal Nitroamidazole – Secnidazole

Following a thorough review of clinical guidelines, clinical trials, and the SFDA drug list, it is advisable to include the novel medication, Secnidazole, in the treatment regimen for Trichomoniasis.

Information on Secnidazole is detailed in the table below[12]:

Table 9. Secnidazole Drug Information

SCIENTIFIC NAME Secnidazole	
SFDA Classification	Prescription
SFDA	Yes
US FDA	Yes, for patients 12 years and older
EMA	Yes
MHRA	No
PMDA	No
Indication (ICD-10)	A59
Drug Class	Antiprotozoal
Drug Sub-class	Nitroimidazole
ATC Code	P01AB07
Pharmacological Class (ASHP)	N/A
DRUG INFORMATION	
Dosage Form	Tablet
Route of Administration	Oral Use
Dose (Adult) [DDD]	To reduce the development of drug-resistant bacteria and maintain the effectiveness of Secnidazole and other antibacterial drugs, Secnidazole should

	be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria: Trichomoniasis, initial treatment (index case and sexual partner) (alternative agent): Oral: 2 g as a single dose
Maximum Daily Dose Adults	N/A
Dose (pediatrics)	Trichomoniasis: Children ≥12 years and Adolescents: Oral: 2,000 mg once as a single dose; sexual partners should be treated at the same time.
Maximum Daily Dose Pediatrics	N/A
Adjustment	**Dosing: Older Adult** Refer to adult dosing. **Dosing: Altered Kidney Function: Adult and pediatric** There are no dosage adjustments provided in the manufacturer's labeling. **Dosing: Hepatic Impairment: Adult and pediatric** There are no dosage adjustments provided in the manufacturer's labeling.
Prescribing edits	MD, AGE, ST, CU, QL
AGE (Age Edit):	It is approved for patients aged more than 12 years
CU (Concurrent Use Edit):	Might be effective in combination with boric acid 600 mg suppository vaginally twice daily for 14 days for drug-resistant trichomoniasis
G (Gender Edit):	N/A
MD (Physician Specialty Edit):	Treatment should only be initiated by an infectious disease specialist
PA (Prior Authorization):	N/A
QL (Quantity Limit):	This drug is given as a single dose
ST (Step Therapy):	It is recommended as an alternative to metronidazole and tinidazole.
EU (Emergency Use Only):	N/A
PE (Protocol Edit):	N/A
SAFETY	

Main Adverse Drug Reactions (most common and most serious)	**Most common (frequency: 1-10%)** **Gastrointestinal**: Diarrhea, nausea **Genitourinary**: Vulvovaginal candidiasis **Nervous system**: Headache **Postmarketing**: **Gastrointestinal**: Dysgeusia
Drug Interactions	**Category X interactions**: • Alcohol (Ethyl) • BCG (Intravesical) • Cholera Vaccine • Fecal Microbiota (Live) (Oral and rectal) • Products Containing Ethanol or Propylene Glycol
Special Population	N/A
Pregnancy	Information related to the use of secnidazole in pregnancy is limited. Data are insufficient to recommend use of secnidazole; use of other agents in pregnant patients is preferred
Lactation	It is not known if secnidazole is present in breast milk. Due to the potential for adverse events, the manufacturer recommends breastfeeding be avoided during therapy and for 96 hours after the last dose.
Contraindications	Hypersensitivity to secnidazole, other nitroimidazole derivatives, or any component of the formulation; Cockayne syndrome.
Monitoring Requirements	Monitor for any signs and symptoms of headache, GI disturbances, alcohol intake, and Vulvovaginal Candidiasis
Precautions	**Concerns related to adverse effects**: **Carcinogenicity**: has been observed in mice and rats with nitroimidazole agents that are structurally similar to secnidazole in animal studies; it is unknown whether secnidazole is associated with carcinogenicity in

	humans. Avoid chronic use. **Disease-related concerns:** **Candidiasis**: Vulvovaginal candidiasis may occur; antifungal treatment may be necessary if the patient is symptomatic. **Other warnings/precautions:** Ethanol use: Abdominal pain, diarrhea, dizziness, headache, nausea, and vomiting have been reported with secnidazole and concomitant alcohol consumption; avoid alcoholic beverages or products containing ethanol or propylene glycol during therapy and for at least 2 days after therapy completion.
Black Box Warning	N/A
REMS	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Trichomoniasis treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations below are for Secnidazole.**

Table 10. Secnidazole HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Secnidazole	NICE	N/A
	CADTH	N/A
	HAS	**21 November 2018** Secnidazole is **recommended** for the treatment of urethritis and vaginitis caused by Trichomonas vaginalis.
	IQWIG	N/A
	PBAC	N/A

CONCLUSION STATEMENT – Secnidazole

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Secnidazole and other antibacterial drugs, Secnidazole should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. It is indicated for patients 12 years and older. The drug is given as an alternative to metronidazole and tinidazole, at 2 g PO as a single dose. Might be effective in combination with boric acid 600 mg suppository vaginally twice daily for 14 days for drug-resistant trichomoniasis. This drug should be prescribed by an infectious disease specialist. The drug has a positive recommendation from HTA body HAS for its use in vaginitis and urethritis caused by Trachomonas vaginalis.

Limitations for the use of Secnidazole include being carcinogenic (hindering its prescription chronically), its interaction with ethanol, and the risk of developing vulvovaginal candidiasis with its use.

2.2 Modifications

Below are the modifications made to the list of Trichomoniasis drugs since the CHI report in May 2020, reflecting the changes and updates:

Table 11. Prescribing Edits (PE) Modifications of Certain Trichomoniasis Drugs

Drugs	PE modifications
Metronidazole gel	**ST**: recommended as an alternative to first line regimen with oral metronidazole, for pregnant women, as Metronidazole gel 0.75%, one full applicator (5 grams) intravaginally, twice a day for 7 days
Metronidazole PO	**ST:** Recommended as first line agent for women, men, pregnant women (preferably not during first trimester), sexual partners, recurrent or persistent infection and HIV or immunosuppressed patients.
Tinidazole	**ST:** recommended as an alternative agent for women and men as 2 g po single dose or 500 mg po bid for 5 or 7 days. **CU:** can be given as an alternative regime, for persistent or recurrent infection or metronidazole resistant infection, with intravaginal paramomycin or vaginal boric acid

2.3 Delisting

No drugs for the management of trichomoniasis have been delisted.

2.4 Other Drugs

The drugs detailed in table 12 are **not SFDA registered**. However, they have been recommended for the treatment of Trichomoniasis.

Table 12. Non-SFDA-Approved Drugs for the Management of Trichomoniasis

Drug	Approval	Indication	Dosing regimen
Paromomycin	Initially, the drug was given orphan designation by the **FDA and EMA** bodies for the treatment of visceral leishmaniasis[13,14]. Topical Paromomycin is not available in the USA. It is suggested to collaborate with a compounding pharmacy[12].	Trichomoniasis, refractory or resistant infection (off-label use)[5,12]	Intravaginal: 4 g (equivalent to 250 mg paromomycin) of an extemporaneously compounded 6.25% cream once daily at bedtime in combination with oral tinidazole for 14 days[5,12].

Section 3.0 Key Recommendations Synthesis

- The decision to treat trichomoniasis empirically or to wait for test results should reflect the[4]:
    - Severity of the clinical condition
    - Probability of infection
    - Person's risk factors for a sexually transmitted or blood-borne infection (STBBI)
    - Person's willingness to abstain from sex and to return for test results or follow-up.
- The 5-nitroimidazole drugs (metronidazole, tinidazole, and secnidazole) are the only class of drugs that provide curative therapy of trichomoniasis. Choice of agent is generally determined by availability, preference for single-day therapy, and cost[5].
- Recommended Regimen for Trichomoniasis Among Women[6]:
    - Metronidazole 500 mg orally 2 times/day for 7 days
- Recommended Regimen for Trichomoniasis Among Men[6]:
    - Metronidazole 2 g orally in a single dose
- Nonpregnant women's Treatment[5]:
    - An oral suspension is also available with unique dosing (metronidazole oral suspension 250 mg [2.5 mL] orally three times daily for seven days).
- Males' treatment[5]:
    - If the oral suspension is preferred to tablets or capsules, the dosing is: metronidazole oral suspension 2 g (20 mL), either as a single oral dose or in two divided oral doses of 1 g (10 mL) each, given on the same day.
- Abstinence from sexual activity – After completion of therapy (single- or multi-dose), the patient and their sex partners should abstain from intercourse until all partners have completed antibiotic therapy and symptoms have resolved[5].
- Avoid alcohol with metronidazole treatment and for 24 hours thereafter[7].
- Reinfection by sex partner is common: It is recommended to repeat treatment of the patient, and all sex partners, with the originally selected treatment regimen[4,8]:

    - Sexual partners should be notified, tested and treated for trichomonas. Partners should be treated **with metronidazole 2 g PO as a single dose.**

- Single dose secnidazole is the only oral treatment option for both trichomoniasis and bacterial vaginosis (BV) in patients with a vagina[5].
- Recurrent or persistent trichomoniasis[6,9]:
    - If a patient has persistent T. vaginalis after a single 2-g dose of metronidazole and has been re-exposed to an untreated partner, he should be retreated with a single 2-g dose of metronidazole. If he has not been re-exposed, he should be administered a course of metronidazole 500 mg 2 times/ day for 7 days.
    - If a woman has treatment failure after the 7-day regimen of high-dose oral metronidazole or tinidazole, two additional treatment options have been determined to have successful results: The first is high-dose oral tinidazole 2 g daily +/- intravaginal tinidazole 500 mg 2 times/day for 14 days. If this regimen fails, high-dose oral tinidazole (1 g 3 times/day) plus intravaginal paromomycin (4 g of 6.25% intravaginal paromomycin cream nightly) for 14 days should be considered.
    - Clinical improvement has been reported with intravaginal boric acid but not with nitazoxanide.
    - If a man has persistent trichomonas infection despite multi-dose treatment: Metronidazole 2 g orally once daily for seven days (total dose 14 g) is advised.
    - Consultation with an infectious disease specialist is recommended.
- Allergy to 5-nitroimidazole drugs[6]:
    - Desensitization to metronidazole
    - Secnidazole might be an option for a person with reported metronidazole hypersensitivity.
    - The optimal treatment for patients with T. vaginalis who are unable to be desensitized has not been systematically investigated and is based on case reports, some of which report using paromomycin or boric acid for treating *T. vaginalis*.
    - Case reports have noted microbiologic and symptomatic cure following long-term treatment with vaginal boric acid, 600 mg intravaginally twice daily, alone or in combination with other agents, for at least 60 days.

- Pregnant women[4,7–10]:
    - Preferably treat symptomatic pregnant patients. If asymptomatic, consult with a sexual health physician.
    - Ideally metronidazole should be avoided in the first trimester (metronidazole is category B2 in pregnancy).
    - Preferred – Metronidazole 500 mg orally twice daily for seven days, regardless of trimester. An oral suspension is also available (metronidazole oral suspension 250 mg [2.5 mL] orally three times daily for seven days).
    - It is recommended to avoid oral tinidazole or secnidazole, especially in the first trimester.
- Breastfeeding[7]:
    - Clinicians sometimes advise deferring breastfeeding for 12–24 hours after maternal treatment with metronidazole. Avoid high doses in breastfeeding.
    - Breastfeeding should be deferred for 72 hours after a single 2-g oral dose of tinidazole.
    - Secnidazole – Given the long half-life of the drug (approximately 17 hours), the manufacturer advises avoiding giving milk to the infant for 96 hours after a single dose.
- HIV Infection – Male patients receive the same treatment and retesting approaches regardless of HIV infection status. Treatment with metronidazole 2 g in a single oral dose is advised[5].
- Immunosuppression —immunosuppressed patients are treated with metronidazole 500 mg orally daily for seven days[5].

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI Genital Protozoal Infections report** and aims to provide recommendations to aid in the management of Trichomoniasis. These recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with Trichomoniasis. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses, and sequence of therapy

Appendix B. Genital Protozoal Infections Scope

Genital Protozoal Infections Scope

Section	Rationale/Updates
Section 1.1.1 **Trichomoniasis Treatment Guidelines Up-To Date Mar 24, 2020**	**Trichomoniasis Treatment Guidelines Up-To Date November 2023**[5] • UpToDate authors and editors thoroughly examine the existing clinical evidence and optimal clinical approaches to deliver a comprehensive overview of a particular subject. Although not commonly used as a clinical guideline, the information was extensively covered in the prior CHI report, making it pertinent to incorporate the updated version of the "Trichomoniasis Treatment," last revised in November 2023. • The recommendations were not accompanied by a grading scheme, and are presented below: • The 5-nitroimidazole drugs (metronidazole, tinidazole, and secnidazole) are the only class of drugs that provide curative therapy of trichomoniasis. Choice of agent is generally determined by availability, preference for single-day therapy, and cost. • Single-dose therapy for male patients is generally preferred because of ease of single dosing, although efficacy may be lower than that of multi-dose metronidazole therapy. However, trial data are limited. In a trial including 325 males comparing a single 2 g oral dose of metronidazole and metronidazole 400 mg three times daily for five days, treatment failure occurred in 43 percent of the single-dose patients and none of the multi-dose patients. Until data from an adequately powered trial are available, both dosing regimens are reasonable and patient preference, usually for single-dose treatment, determines treatment choice. The authors extrapolate this approach to individuals who have undergone surgical phalloplasty, although the authors are unaware of a reported case of trichomoniasis in a patient with phalloplasty. • Secnidazole is a 5-nitroimidazole with a longer half-life (17 to 19 hours) than oral metronidazole (7 to 8 hours) and tinidazole (12 to 13 hours). It is given as a single 2 g oral treatment for trichomoniasis. It is administered as a packet of granules which should be sprinkled onto a standard serving of applesauce, yogurt, or pudding and consumed within 30 minutes. Single-dose secnidazole is the only oral treatment option for both trichomoniasis and bacterial vaginosis (BV)

	in patients with a vagina. o Efficacy – Compared with placebo for treatment of trichomoniasis in females, cure rates of 92 percent were reported at 6- to 12-day follow-up, which is comparable to other 5-nitroimidazole single-dose regimens in this short-term follow-up period. o Safety - Gastrointestinal side effects were reported in <5 percent of participants in either arm, which is lower than rates reported with single-dose metronidazole. o Data for using secnidazole in males with trichomoniasis are limited. In one trial comparing ornidazole, metronidazole, or secnidazole treatment in 85 men with confirmed trichomoniasis, all three treatment groups tested negative (by microscopic evaluation and culture of discharge) and were asymptomatic at follow-up evaluation. o Limitations –there are no head-to-head efficacy comparisons of single-dose secnidazole and the seven-day metronidazole regimen for the treatment of trichomoniasis in females or males. • The authors still do not believe that patients need to be counseled to avoid alcohol while using metronidazole and extrapolate this approach to tinidazole and secnidazole. • Nonpregnant Treatment: o Nonpregnant females are preferentially treated with a multi-dose oral metronidazole regimen rather than single-day treatment because multi-dose therapy is associated with improved cure rates at one month. o Preferred – Metronidazole 500 mg, tablet or capsule, orally twice daily for seven days. The authors prefer this approach because of higher efficacy compared with single-day regimens. An oral suspension is also available with unique dosing (metronidazole oral suspension 250 mg [2.5 mL] orally three times daily for seven days). o Alternatives – Alternative treatments vary according to the source guideline (CDC compared with WHO). As direct comparative data are lacking, selection is based on availability and cost. ➔ Single-dose options – Treatment with a single 2 g oral dose of either metronidazole or tinidazole (ie, four 500 mg tablets) is associated with lower rates of cure compared with metronidazole multi-dose therapy. The authors reserve single-dose therapy for those who are unable to complete a multi-dose treatment course.

	• Metronidazole 2 g orally given as a single dose or metronidazole oral suspension 2 g (20 mL), either as a single oral dose or in two divided oral doses of 1 g (10 mL) each, given on the same day. OR • Tinidazole 2 g orally given as a single dose OR • Secnidazole 2 g orally given as a single dose (single-dose secnidazole is effective treatment for both trichomoniasis and bacterial vaginosis). ➔ Multi-dose tinidazole – Tinidazole 500 mg orally twice daily for five days is an alternative option listed by WHO. It is not yet known which patient groups may benefit from multi-dose tinidazole compared with single-dose for initial treatment. The authors recommend to reserve multi-dose tinidazole for patients with persistent infection despite adequate initial treatment and use a higher dose in this setting (tinidazole 2 g daily for seven days) • Not advised – Vaginal metronidazole gel is not recommended because it does not effectively treat all anatomic reservoirs of infection and should not be used to treat trichomoniasis. However, metronidazole vaginal gel remains on at least one treatment guideline. • Pregnant — Treatment of pregnant persons, with or without symptoms, is indicated as T. vaginalis infection is common in pregnant persons and has been associated with adverse pregnancy outcomes o Preferred – Metronidazole 500 mg orally twice daily for seven days, regardless of trimester. An oral suspension is also available (metronidazole oral suspension 250 mg [2.5 mL] orally three times daily for seven days) The authors believe the available evidence supports the benefits of treatment, including reduced partner and perinatal transmission, and outweighs potential risks, although at least one organization advises waiting until after the first trimester for treatment, if possible o Alternate regimens – WHO lists the following as alternative treatment options with the notation to avoid metronidazole use in the first trimester of pregnancy if possible. While data directly comparing the treatment options in pregnant persons are lacking, there is no reason to think that pregnancy would make the alternative regimens more effective than multi-dose oral metronidazole.

	• Metronidazole 2 g orally in a single dose. An oral suspension is also available (metronidazole oral suspension 2 g [20 mL], either as a single oral dose or in two divided oral doses of 1 g [10 mL] each, given on the same day). While single-day dosing is included as a first-line treatment option in the WHO sexually transmitted infection (STI) treatment guidelines, the authors view it as an alternative for the reasons discussed above. However, both single- and multiple-dose regimens are acceptable as there are no specific data comparing single-dose and multiple-dose regimens in pregnant individuals and there are no reasons to think that efficacy is different in pregnant patients. It is recommended to reserve the single-dose regimen for pregnant individuals who are unable to complete seven days of treatment or prefer single-dose therapy.
	OR
	• Metronidazole 200 or 250 mg orally three times daily for seven days. These doses may not be universally available.
	  • Not advised during pregnancy – In practice, it is recommended to not use metronidazole gel, tinidazole, or secnidazole in pregnant persons.
	  o Metronidazole vaginal gel does not effectively treat all anatomic reservoirs of infection and is not advised, although at least one guideline lists metronidazole gel as a third-line treatment option
	  o Tinidazole and secnidazole – it is recommended to avoid oral tinidazole or secnidazole, especially in the first trimester, as safety data from human pregnancies are insufficient to make a definitive conclusion regarding teratogenicity and some, but not all, animal data suggest risk
	  • Teratogenicity — While metronidazole crosses the placenta, it appears to be low risk to the developing fetus. Cross-sectional and cohort studies have not reported teratogenicity or mutagenic effects for single- or multi-dose metronidazole treatment in humans (although studies suggest the drug is mutagenic in bacteria and carcinogenic in mice). There is limited information on the safety of tinidazole or secnidazole in pregnancy and thus the authors do not advise use of these drugs during pregnancy
	  • Breastfeeding:
	  o Secnidazole – Data on safety of secnidazole use during lactation are lacking. Given the long half-life of the drug (approximately 17 hours), the manufacturer advises avoiding giving milk

to the infant for 96 hours after a single dose

- Males — While other treatment options exist, preferred treatment for male patients with confirmed trichomoniasis include:
  - Preferred – Metronidazole 2 g orally in a single dose. If the oral suspension is preferred to tablets or capsules, the dosing is: metronidazole oral suspension 2 g (20 mL), either as a single oral dose or in two divided oral doses of 1 g (10 mL) each, given on the same day
  - Alternatives

- Tinidazole 2 g orally in a single dose

OR

- Secnidazole 2 g orally given as a single dose

OR

- Metronidazole, 400 or 500 mg, orally twice daily for seven days. Dose selection is based on availability and type of oral formulation; the 500 mg dose of metronidazole is more commonly available. If the oral suspension is preferred, it is given as 250 mg (2.5 mL) orally three times daily for seven days. Although data supporting a longer course of therapy are lacking, this approach is described for individuals with recurrent or persistent infection
  - Sexual partners:
    - Abstinence from sexual activity – After completion of therapy (single- or multi-dose), the patient and their sex partners should abstain from intercourse until all partners have completed antibiotic therapy and symptoms have resolved. There are no studies on how long trichomonads remain viable after treatment is initiated or completed. counsel patients to abstain from anal intercourse as well because trichomonads have been found in rectal samples and an anal reservoir of organisms could be a source of reinfection
  - Reinfection by sex partner is common:
    - It is recommended to repeat treatment of the patient, and all sex partners, with the originally selected treatment regimen as presented above
  - Persistent infection – Persistent infection can occur despite appropriate treatment of the patient and all sex partners. Once inadequate initial treatment and/or reinfection from a sex partner have been excluded, retreat the index patient and all sex partners as follows:
    - Longer duration of treatment – Individuals with symptom recurrence after single-dose oral

	metronidazole 2 g should be treated with oral metronidazole 500 mg twice daily for seven days (total dose 7 g) • Increased dose and duration of treatment – If the patient has persistent trichomonas infection despite multi-dose treatment, then treat with higher doses of oral tinidazole or metronidazole. • Females – Metronidazole or tinidazole 2 g orally once a day for seven days (total dose 14 g) can be used. This approach can also be effective in patients with low levels of metronidazole resistance, which was noted in 4 percent of 538 T. vaginalis isolates collected from women attending STD clinics in six cities in the United States • Males – Metronidazole 2 g orally once daily for seven days (total dose 14 g) is advised • Drug-resistant infection — If the above treatment regimens fail and nucleic acid amplification tests (NAAT) confirms persistent trichomonas infection, next steps include in vitro culture and drug susceptibility testing and patient referral to a specialist. One option for culture and drug sensitivity testing is available through the United States CDC Infectious Disease Laboratories. Metronidazole-resistant T. vaginalis has been documented. Cross resistance to tinidazole is frequent but not inevitable. For secnidazole, trichomoniasis isolates requiring a minimum inhibitory concentration similar to that of metronidazole have been reported. In an in vitro study of trichomonas isolates in South Africa, resistance to metronidazole was more common (11 percent) than tinidazole (2 percent) or secnidazole (1 percent) • Treatment options for patients with metronidazole-resistant infection include: o High-dose tinidazole – Refractory disease has been successfully treated with high-dose oral tinidazole, although the optimal dose, regimen, and combination with other drugs have not been established. Choice of treatment is based on availability of the drugs below. • Tinidazole only – Oral tinidazole 2 g daily for 14 days plus vaginal tinidazole 500 mg twice a day for 14 days (total drug dose 42 g) • Tinidazole plus vaginal boric acid – Tinidazole, 1 g orally three time a day for 14 days plus vaginal boric acid, 600 mg, twice daily for 28 days successfully treated a female patient with confirmed T. vaginalis infection resistant to both metronidazole and tinidazole. Boric acid should never be given orally as it can cause death. • Tinidazole plus vaginal paromomycin – Tinidazole 1 g orally three times a day plus vaginal

	paromomycin 6.25% given as 4 g intravaginally at night (ie, 250 mg of drug per dose), both for a total of 14 days, has been reported in one patient. Additional information on vaginal paromomycin is presented in the bullet below. ○ Secnidazole – Data supporting secnidazole treatment of drug-resistant trichomoniasis is limited to one case report. A patient with confirmed metronidazole- and tinidazole-resistant infection was successfully treated with an investigational protocol of secnidazole 2 g orally daily for 14 days combined with boric acid 600 mg suppository vaginally twice daily for 14 days. Four weeks after completing treatment, the patient's symptoms had resolved and test of cure was negative by wet mount, culture, and NAAT. ○ Vaginal paromomycin – Rare patients who do not have a response to 5-nitroimidazoles have been treated with the aminoglycoside paromomycin. Paromomycin 6.25% cream is given as a 4 g intravaginal dose (ie, 250 mg of drug) daily for two weeks). Dual therapy combining intravaginal paromomycin 6.25% cream, 4 g intravaginally at night, with oral tinidazole, 1 g three times daily, for a total of 14 days, has been reported. Intravaginal paromomycin can cause local side effects (pain, mucosal ulceration) but these symptoms are self-limited. Applying lubricating jelly to the vaginal tissue prior to vaginal paromomycin application has been reported to reduce ulceration in some patients. Paromomycin is not available commercially in the United States as a cream and must be compounded by a specialty pharmacy. For this reason, it is considered a third-line option when the above regimens have not worked. ○ Vaginal boric acid – Successful treatment of drug-resistant trichomoniasis has been reported with vaginal boric acid, alone or combination with other drugs (eg, secnidazole or clotrimazole). ○ Limited data – Case reports have described successful use of nimorazole, ornidazole, niridazole, furazolidone, and hamycin ○ Not advised – Other topical agents that have a limited (<50 percent) cure rate and therefore are not recommended include vaginal povidone-iodine, clotrimazole, acetic acid, furazolidone, gentian violet, nonoxynol-9, and potassium permanganate. A trial of nitazoxanide in three women with difficult to eradicate T. vaginalis reported lack of efficacy • Allergy to 5-nitroimidazole drugs:

	○ A single case report describes successful treatment with secnidazole in a person with reported metronidazole hypersensitivity. ○ Therapy with drugs other than 5-nitroimidazoles is an option, but cure rates have been low (≤50 percent). Case reports have noted microbiologic and symptomatic cure following long-term treatment with vaginal boric acid, 600 mg intravaginally twice daily, alone or in combination with other agents, for at least 60 days • HIV Infection, Male – Male patients receive the same treatment and retesting approaches regardless of HIV infection status. Treatment with metronidazole 2 g in a single oral dose is advised; retesting of male patients is not recommended at this time • Bacterial vaginosis coinfection – There is a high prevalence of BV in patients with concurrent HIV and T. vaginalis infection and an apparent association between the presence of BV and early failure of single-dose oral metronidazole treatment of trichomoniasis (See Bacterial STDs report) • Immunosuppression —immunosuppressed patients are treated with metronidazole 500 mg orally daily for seven days. As limited data are available to address the wide spectrum of immunosuppression, treatment of these patients is extrapolated from data based on patients with HIV infection. • Transgender individuals — There are no available data indicating that hormone therapy or surgery should alter trichomoniasis treatment or retesting recommendations. The authors extrapolate from the above data to transgender patients and treat or retest based on the patient's anatomy.
Section 1.1.2 **Centers of Disease Control and Prevention of America Treatment Guidelines of Trichomoniasis 2015**	**Sexually Transmitted Infections Treatment Guidelines, 2021**[6] • Recommended Regimen for Trichomoniasis Among Women: ○ Metronidazole 500 mg orally 2 times/day for 7 days • Recommended Regimen for Trichomoniasis Among Men: ○ Metronidazole 2 g orally in a single dose • Alternative Regimen for Women and Men: ○ Tinidazole 2 g orally in a single dose • Management of sex partners: ○ EPT might have a role in partner management for trichomoniasis and can be used in states

	where permissible by law o However, no partner management intervention has been demonstrated to be superior in reducing reinfection rates • Recurrent trichomoniasis: o If a man has persistent T. vaginalis after a single 2-g dose of metronidazole and has been reexposed to an untreated partner, he should be retreated with a single 2-g dose of metronidazole. If he has not been reexposed, he should be administered a course of metronidazole 500 mg 2 times/ day for 7 days. o If a patient has treatment failure after the 7-day regimen of high-dose oral metronidazole or tinidazole, two additional treatment options have been determined to have successful results for women. The first is high-dose oral tinidazole 2 g daily plus intravaginal tinidazole 500 mg 2 times/day for 14 days. If this regimen fails, high-dose oral tinidazole (1 g 3 times/day) plus intravaginal paromomycin (4 g of 6.25% intravaginal paromomycin cream nightly) for 14 days should be considered o Alternative regimens might be effective but have not been systemically evaluated; therefore, consultation with an infectious disease specialist is recommended. o Clinical improvement has been reported with intravaginal boric acid but not with nitazoxanide o The following topically applied agents have minimal success (<50%) and are not recommended: • Intravaginal betadine (povidone-iodine) • Clotrimazole • Acetic acid • Furazolidone • GV • Nonoxynol-9 • Potassium permanganate • No other topical microbicide has been reported to be effective against trichomoniasis. • Drug Allergy, Intolerance, and Adverse Reactions

	• The optimal treatment for patients with T. vaginalis who are unable to be desensitized has not been systematically investigated and is based on case reports, some of which report using paromomycin or boric acid for treating T. vaginalis
	• Breastfeeding:
	  • Although multiple reported case series studies demonstrated no evidence of adverse effects among infants exposed to metronidazole in breast milk, clinicians sometimes advise deferring breastfeeding for 12–24 hours after maternal treatment with metronidazole.
	  • In one study, maternal treatment with metronidazole (400 mg 3 times/day for 7 days) produced a lower concentration in breast milk and was considered compatible with breastfeeding over longer periods.
	  • Data from studies involving human subjects are limited regarding tinidazole use during pregnancy; however, animal data indicate this drug poses moderate risk. Thus, tinidazole should be avoided for pregnant women, and breastfeeding should be deferred for 72 hours after a single 2-g oral dose of tinidazole

Section 1.1.3
Guidelines for the management of symptomatic sexually transmitted infections June 2021[10]
	• The below non-graded recommendations are published by the WHO STI Guidelines 2021 for the management of Trichomoniasis vaginalis.
	• First line options:
	  ○ Metronidazole 2 grams, orally, in a single dose
	  or
	  ○ Metronidazole 400 mg or 500 mg, orally, twice daily for 7 days
	• Effective substitutes
	  ○ Tinidazole 2 grams orally, single dose
	  or
	  ○ Tinidazole 500 mg orally, twice daily for 5 days
	• Pregnancy: metronidazole should, ideally, be avoided in the first trimester:
	  ○ Metronidazole 200 mg or 250 mg, orally, 3 times a day for 7 days
	  or
	  ○ Metronidazole gel 0.75%, one full applicator (5 grams) intravaginally, twice a day for 7 days

Section 1.1.4
Canadian STI-associated syndromes guide: Vaginitis 2023[4]

- The decision to treat trichomoniasis empirically or to wait for test results should reflect the:
  - Severity of the clinical condition
  - Probability of infection
  - Person's risk factors for a sexually transmitted or blood-borne infection (STBBI)
  - Person's willingness to abstain from sex and to return for test results or follow-up
- The below table showcases the empiric treatment recommended for trichomoniasis:

The Canadian Recommendations Regarding the Empiric Treatment for Trichomoniasis	
Non-pregnant people	Metronidazole 2 g PO in a single dose [A-I] or Metronidazole 500 mg PO BID for 7 days [A-I] Notes: • Efficacy is 82-88% for both regimens; increases to 95% if partner also treated • Intravaginal metronidazole gel is not effective • Prevalence of metronidazole-resistant T. vaginalis is estimated at 5%; it usually responds to high-dose metronidazole
Pregnant people	Metronidazole 2 g PO in a single dose for symptom relief [A-I]. Notes: • Metronidazole 500 mg PO BID for 7 days [A-I] is an alternate treatment in pregnancy. • It is not recommended that those who are asymptomatic during pregnancy be treated [D-I] • It is not known whether treatment will improve pregnancy outcomes

	• Sexual partners to be treated with the same empiric treatment regimen

Section 1.1.5
Australian STI Management Guidelines for use in Primary Care 2021[7]
	• The below non-graded recommendations are published by the Australian STI Management Guidelines for use in Primary Care 2021 for the management of trichomoniasis:
	• Recommended regimen for an uncomplicated infection:
	  o Metronidazole 400 mg PO with food, twice daily for 7 days
	• Alternative regimen for an uncomplicated infection:
	  o Metronidazole 2 g PO with food, stat
	• Treatment advice:
	  o Avoid alcohol with metronidazole treatment and for 24 hours thereafter.
	  o Advise no sexual contact for 7 days after treatment is commenced, or until the course is completed and symptoms resolved, whichever is later.
	• Special considerations – complicated infection:
	  o Consider seeking specialist advice before treating any complicated presentation.
	  o Pregnancy: Category B2 in pregnancy
	  o Breastfeeding: Metronidazole may affect taste of breast milk; avoid high doses in breastfeeding
	  o Allergy to principal treatment choice: There is no effective alternative to 5-nitroimidazole compounds. Metronidazole desensitisation has been described.
	  o HIV patients: Reports indicate single-dose metronidazole is less effective than extended metronidazole.
	• Treatment for sex partners:
	  o For all sexual partners
	  o There is currently insufficient data to provide a definitive period for contact tracing, partner treatment encouraged presumptively.
	  o Partners with a penis may test negative for trichomonas as it is more likely to resolve spontaneously in these people.

Section 1.1.6 **The Royal Children's Hospital Melbourne**	• The below non-graded recommendations are published by the Royal Children's Hospital Melbourne STI Management Guidelines 2022 for the management of trichomoniasis: • Treatment

Sexually transmitted infections (STIs) 2022[11]	○ Metronidazole 2 g PO single dose (>12 years old) ○ OR ○ Metronidazole 10mg/kg (max 400 mg) PO bid for 7 days ○ Topical treatment is not advised ○ No sexual contact for 7 days after treatment ○ Current sexual partner should be treated
Section 1.1.7 **AAFP 2018 Vaginitis: Diagnosis and Treatment**[9]	• The below non-graded recommendations are published by the AAFP Vaginitis Guidelines 2018 for the management of trichomoniasis: • Initial regimens recommended: ○ Metronidazole, 2 g orally, single or divided dose on the same day or ○ Tinidazole, 2 g orally, single dose • Alternative regimens: ○ Metronidazole, 500 mg orally twice daily for seven days • Pregnancy: ○ Metronidazole, 2 g orally, single dose in any stage of pregnancy • Recurrence: ○ Differentiate persistent or recurrent infection from reinfection ○ If metronidazole, 2-g single dose fails: • Trial of metronidazole, 500 mg twice daily for seven days ○ If metronidazole, 500 mg twice daily for seven days fails: • Trial of metronidazole, 2 g daily for seven days ○ If above regimens fail: • Consider susceptibility testing • Treatment of sex partners: ○ Concurrent treatment of sex partners is recommended ○ Advise refraining from intercourse until partners are treated and symptom-free
Section 1.1.8 **Melbourne Sexual**	• The below non-graded recommendations are published by the Melbourne Sexual Health Centre Trichomonas vaginalis Guidelines 2021:

Health Centre Trichomonas vaginalis treatment guidelines 2021[8]

- The 5-nitroimidazoles, which include metronidazole (MTZ) and tinidazole (TDZ), are the only class of drug known to be effective against Trichomonas vaginalis.
- The table below showcases the guidelines' recommended regimens:

Condition	Recommended regimen	Comments
Trichomonas in women	Metronidazole 400 mg PO, twice daily for 7days	Recent studies have shown multi-dose metronidazole to be significantly more effective than single dose metronidazole in women, with a cure rate of approximately 95%. Alcohol should be avoided when taking metronidazole. Second line: Metronidazole 2g PO, daily for 7 days. Ensure compliance and that reinfection is not an issue. This dose will eradicate approximately 90% of the 5% of infections that fail first-line therapy. (CDC, MMWR 2015).
Trichomonas in men	Metronidazole 2 g PO, stat	There are no studies comparing single dose metronidazole to multidose metronidazole in men.
Trichomonas in pregnancy	If symptomatic, manage as for nonpregnant women. Metronidazole (category B) can be used in all trimesters.	Trichomonas has been associated with adverse pregnancy outcomes, particularly premature rupture of membranes, preterm birth and low birthweight. If asymptomatic, consult with a sexual health physician. Some studies suggest the possibility of increased prematurity or low birthweight after metronidazole therapy. However, limitations of the studies prevent definitive conclusions regarding risks of treatment.
Complicated cases:		Treatment should be discussed with a

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- **When oral metronidazole is not tolerated**
- **Allergy to metronidazole is known or suspected**
- **Cases failing second line treatment**

</td><td></td><td>sexual health physician.

Alternatives to consider include:
• Metronidazole desensitization in hospital - requires day admission for increasing doses.</td></tr>
</table>

Patients should be advised to abstain from intercourse until they and their sexual partners have been adequately treated and any symptoms have resolved.
Sexual partners should be notified, tested and treated for trichomonas. Partners should be treated with metronidazole 2 g PO as a single dose.

</td></tr>
<tr><td>HTA Pharmacoeconomics Analysis</td><td>Recommendations from HTA bodies should be added under each drug therapy section as they are missing from the previous/initial document.</td></tr>
</table>

Appendix C. MeSH Terms PubMed

C.1 PubMed Search for Genital Protozoal Infections:

Query	Filters	Search Details	Results
((((((Trichomonas Infections[MeSH Terms])) OR (Trichomoniasis[Title/Abstract])) OR (Trichomoniases[Title/Abstract])) OR (Infections, Trichomonas[Title/Abstract])) OR (Infection, Trichomonas[Title/Abstract])) OR (Trichomonas Infection[Title/Abstract])	Guideline, in the last 5 years	("trichomonas infections"[MeSH Terms] OR "Trichomoniasis"[Title/Abstract] OR "Trichomoniases"[Title/Abstract] OR "infections trichomonas"[Title/Abstract] OR "infection trichomonas"[Title/Abstract] OR "trichomonas infection"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	2
(((((((Trichomonas Vaginitis[MeSH Terms]) OR (Trichomonas Vaginitides[Title/Abstract])) OR (Vaginitides, Trichomonas[Title/Abstract])) OR (Vaginitis, Trichomonas[Title/Abstract])) OR (Trichomoniasis, Human[Title/Abstract])) OR (Human Trichomoniases[Title/Abstract])) OR (Human Trichomoniasis[Title/Abstract])) OR (Trichomoniases, Human[Title/Abstract])	Guideline, in the last 5 years	("trichomonas vaginitis"[MeSH Terms] OR (("Trichomonas"[MeSH Terms] OR "Trichomonas"[All Fields] OR "trichomona"[All Fields]) AND "Vaginitides"[Title/Abstract]) OR (("vagina"[MeSH Terms] OR "vagina"[All Fields] OR "vaginal"[All Fields] OR "vaginally"[All Fields] OR "vaginals"[All Fields] OR "Vaginitis"[MeSH Terms] OR "Vaginitis"[All Fields] OR "Vaginitides"[All Fields]) AND "Trichomonas"[Title/Abstract]) OR "vaginitis trichomonas"[Title/Abstract] OR "trichomoniasis human"[Title/Abstract] OR (("human s"[All Fields] OR "humans"[MeSH Terms] OR "humans"[All Fields] OR "Human"[All Fields]) AND "Trichomoniases"[Title/Abstract])	2

		OR "human trichomoniasis"[Title/Abstract] OR (("trichomonas infections"[MeSH Terms] OR ("Trichomonas"[All Fields] AND "infections"[All Fields]) OR "trichomonas infections"[All Fields] OR "Trichomoniases"[All Fields]) AND "Human"[Title/Abstract])) AND ((y_5[Filter]) AND (guideline[Filter]))	

Appendix D. Treatment Algorithm of Trichomoniasis

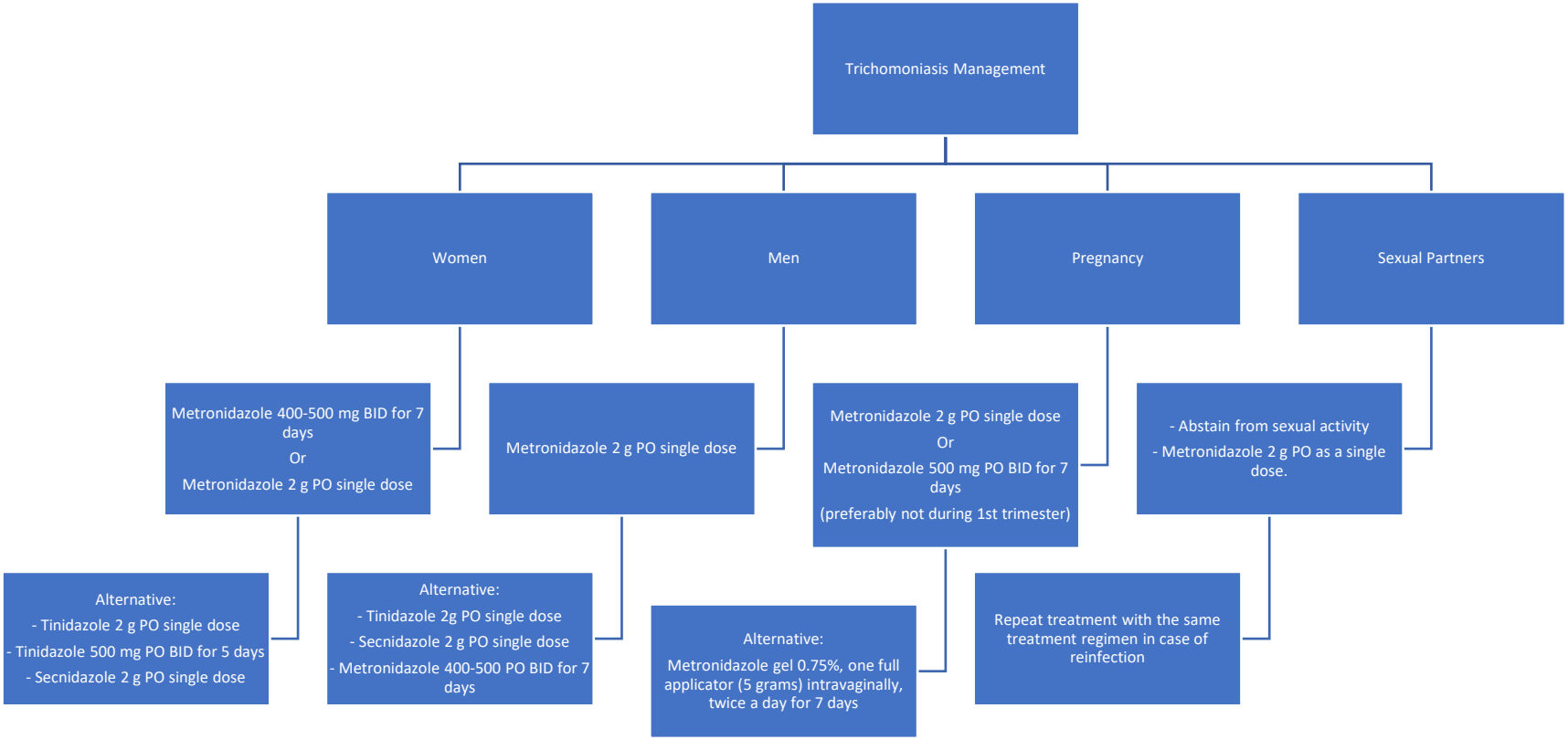

Figure 1. *Trichomoniasis treatment algorithm*

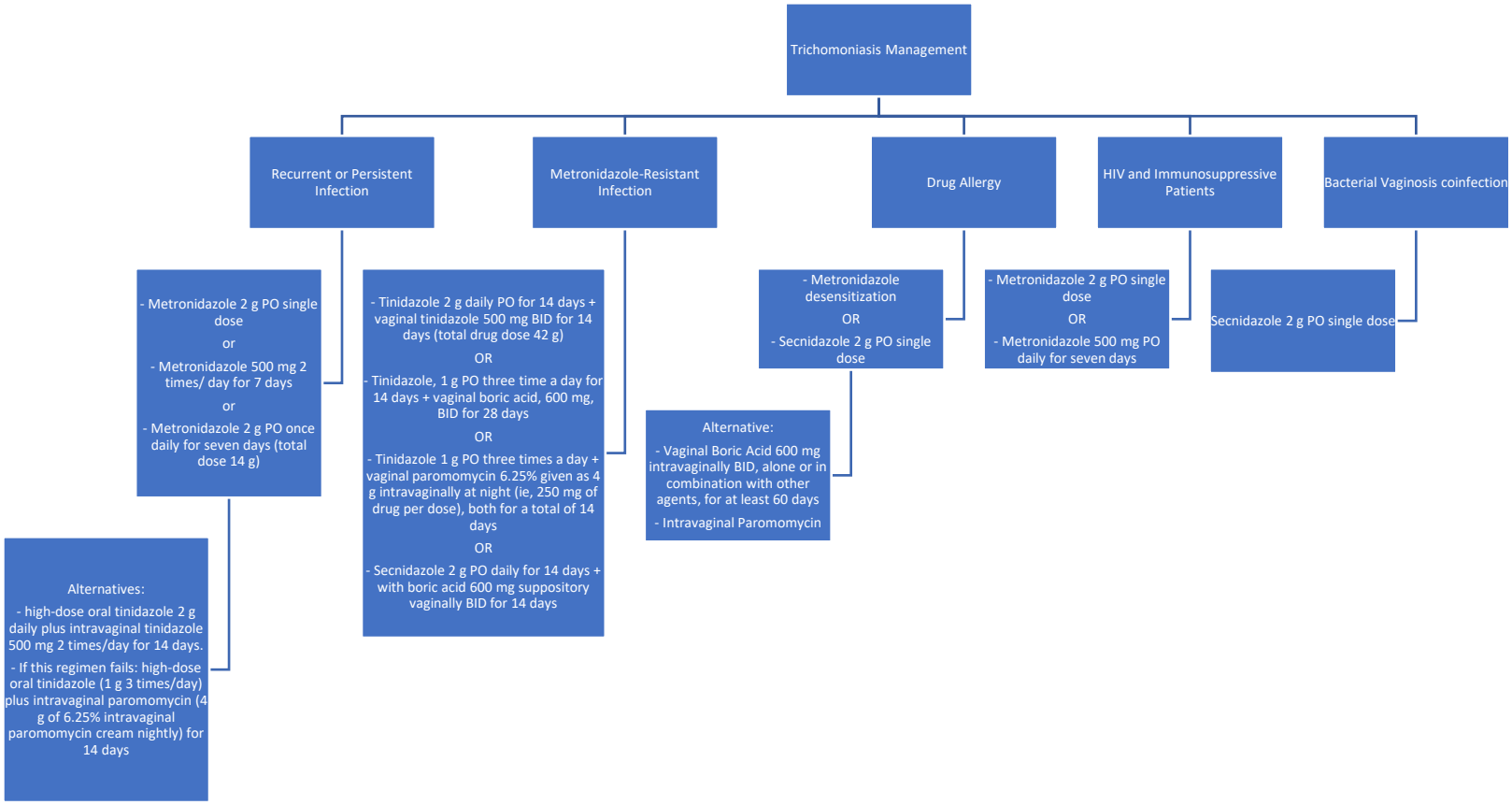

Figure 2. *Trichomoniasis treatment algorithm (cont'd)*