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United Kingdom National Guideline on the Management of *Trichomonas vaginalis* 2014

Jackie Sherrard¹, Cathy Ison², Judith Moody³,
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Abstract

The main objective is to assist practitioners in managing men and women diagnosed with *Trichomonas vaginalis* (TV) infection. This guideline offers recommendations on the diagnostic tests, treatment regimens and health promotion principles needed for the effective management of TV, covering the management of the initial presentation, as well as how to prevent transmission and future infection.

Keywords

Trichomoniasis (*Trichomonas vaginalis*), protozoal disease, diagnosis, epidemiology, treatment, sexually transmitted infection, guideline

Date received: 1 February 2014; accepted: 4 February 2014

New in the 2014 guidelines: Updated section on diagnosis incorporating information on nucleic acid amplification tests and management of infection refractory to first-line treatment.

Introduction and methodology

Scope and purpose

It is aimed primarily at people aged 16 years or older (see specific guidelines for those under 16) presenting to health care professionals, working in departments offering specialist care in sexually transmitted infection (STI) management within the United Kingdom. However, the principles of the recommendations should be adopted across all levels (non-specialist services may need to develop, where appropriate, local care pathways). For levels or recommendations, see appendix 2.

Search strategy

This document was produced in accordance with the guidance set out in the Clinical Effectiveness Group's (CEG) document "Framework for guideline

development and assessment" at <http://www.bash-h.org/guidelines>. The 2014 guideline updates the 2007 guideline by searching PubMed 2006–2012 for *Trichomonas vaginalis* or trichomoniasis and limited to "human" and "English".

The Cochrane database was searched for *Trichomonas vaginalis*. The European (IUSTI/WHO) guideline on the management of vaginal discharge, 2011, and the 2010 US CDC guidelines for the treatment of Sexually Transmitted Diseases were reviewed.

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A general search was performed on the NHS evidence search engine as well as a Google Scholar and the BNF September 2012.

Piloting and consultation, including public and patient involvement

The initial draft of the guideline, including the patient information leaflet (PIL), was piloted for validation by the CEG and a number of BASHH pilot sites. A standardised feedback form was completed by each pilot site for the PIL. The final draft guideline was then reviewed by the CEG using the AGREE instrument before posting it on the BASHH website for external peer review for a two-month period. Concurrently it was reviewed by the BASHH Public and Patient Panel. Comments received were collated by the CEG editor and sent to the guideline chair for review and action. The final guideline was approved by the CEG and a review date agreed before publication on the BASHH website.

Aetiology

Causative organism

Trichomonas vaginalis (TV) is a flagellated protozoan. In women the organism is found in the vagina, urethra and paraurethral glands. Urethral infection is present in 90% of infected women, although the urethra is the sole site of infection in less than 5% of cases. In men infection is usually of the urethra, although trichomonads have been isolated from the subpreputial sac and lesions of the penis.

Transmission

In adults transmission is almost exclusively through sexual intercourse. Due to site specificity, infection can only follow intravaginal or intraurethral inoculation of the organism.

Clinical features (Evidence level III)

Symptoms

Females¹⁻³

- 10–50% are asymptomatic.
- The commonest symptoms include vaginal discharge, vulval itching, dysuria, or offensive odour, but these are not specific for TV.
- Occasionally the presenting complaint is of low abdominal discomfort or vulval ulceration.

Males⁴⁻⁶

- 15 to 50% of men with TV are asymptomatic and usually present as sexual partners of infected women.
- The commonest presentation in symptomatic men is with urethral discharge and/or dysuria.
- Other symptoms include urethral irritation and urinary frequency.
- Rarely the patient may complain of a copious purulent urethral discharge, or complications such as prostatitis.

Signs

Females¹⁻³

- Vaginal discharge in up to 70% – varying in consistency from thin and scanty to profuse and thick; the classical frothy yellow discharge occurs in 10–30% of women.
- Vulvitis and vaginitis are associated with trichomoniasis.
- Approximately 2% of patients will have strawberry cervix appearance to the naked eye. Higher rates are seen on colposcopic examination.
- 5–15% of women will have no abnormalities on examination.

Males⁴⁻⁶

- Urethral discharge (20–60% men) – usually small or moderate amounts only, and or dysuria.
- No signs, even in the presence of symptoms suggesting urethritis: one recent prospective study of infected TV contacts found 77.3% were asymptomatic.
- Rarely balanoposthitis.

Complications

There is increasing evidence that TV infection can have a detrimental outcome on pregnancy and is associated with preterm delivery and low birth weight. (Evidence level III).⁷⁻⁹ However, further research is needed to confirm these associations and to prove that the association is causal. TV infection at delivery may predispose to maternal postpartum sepsis.¹⁰

Some studies have shown treatment of TV infection in pregnancy to have a negative impact on the pregnancy¹¹⁻¹³ but others have shown no association between treatment for TV and pre-term delivery or low birth weight.¹⁴ Screening of asymptomatic

individuals for TV infection is therefore not currently recommended. (Evidence Level I & II, Grade A)

Multiple reports support an epidemiological association between HIV and trichomoniasis. There is growing evidence that trichomonas infection may enhance HIV transmission^{15–18} and there may be an increased risk of TV infection in those that are HIV positive.¹⁹

Diagnosis

Testing for TV should be undertaken in women complaining of vaginal discharge or vulvitis, or found to have evidence of vulvitis, and/or vaginitis on examination. Testing in men is recommended for TV contacts, and should be considered in those with persistent urethritis.

Sites sampled

Females (Evidence level III, Grade B).^{1,2,20,21}

- Swab taken from the posterior fornix at the time of speculum examination.
- Self-administered vaginal swabs have been used in many recent studies, and are likely to give equivalent results.^{22,23}
- Urine has been used for evaluation with some nucleic acid amplification tests.

Males (Evidence level III, B)²⁴

- Urethral culture or culture of first-void urine will diagnose 60–80% cases, sampling both sites simultaneously will significantly increase the diagnostic rate using microscopy or culture.

Laboratory investigations

Microscopy. Detection of motile trichomonads by light-field microscopy can be achieved by collection of vaginal discharge using a swab or loop, which is then mixed with a small drop of saline on a glass slide and a coverslip placed on top. The wet preparation should be read within 10 min of collection, as the trichomonads will quickly lose motility and be more difficult to identify.²⁵ The slide should be scanned, firstly at low magnification (100×), and then at a higher magnification (400×) to confirm the morphology of any trichomonads and to visualise the flagella. Microscopy as a diagnostic aid for TV has the advantage that it can be performed near to the patient and in a clinic setting. The sensitivity is highest in women presenting with vaginal discharge and a visualisation of motile

trichomonads in these women indicates the presence of infection. However, the sensitivity is reported to be as low as 45–60% in women^{20,21,24,26–29} in some studies and lower in men,^{29,30} and so a negative result should be interpreted with caution. The specificity with trained personnel is high.

Detection of TV by staining dead organisms with acridine orange can give a higher sensitivity than wet microscopy^{31,32} but is not widely used.

Point of care tests Level of evidence: IIb, B

A number of point of care tests that have the advantages of microscopy have been described^{29,30,33} of which the OSOM Trichomonas Rapid Test (Genzyme Diagnostics, USA) has demonstrated a high sensitivity and specificity.^{29,30} The sensitivity and specificity has been reported to be 80–94% and greater than 95%, respectively, depending on the comparator.^{27,28,34,35} This test requires no instrumentation and provides a result within 30 min and is a suitable alternative to culture or molecular testing. Although these tests are more sensitive than those requiring vaginal wet preparation, false positives might occur, especially in populations with a low prevalence of disease, so consideration should be given to confirming positives in that situation.

Culture level of evidence: IIb, B

Culture of TV has a higher sensitivity compared to microscopy^{27,28,30} and can detect TV in men.^{29,30} A commercially available culture system (InPouch TV; BioMed Diagnostics, USA) offers many advantages over previous culture media such as Diamond's medium.^{36–39} Once inoculated, the pouches can be transferred to the laboratory for incubation and the entire pouch read microscopically each day for five days, negating the need to prepare wet preparations every day that only sample a portion of the culture medium. Culture was considered “the gold standard” but the molecular testing has proven to have a higher sensitivity.

Molecular detection Level of evidence: IIb, B

Nucleic acid amplification tests (NAATs) offer the highest sensitivity for the detection of TV. They should be the test of choice where resources allow and are becoming the current “gold standard”. In-house PCRs have shown increased sensitivity in comparison to both microscopy and culture,^{31,32,40–52} which has been found to be even greater using the commercial FDA-approved platform which can detect TV DNA in vaginal or endocervical swabs and in urine samples

from women and men with sensitivities of 88%–97% and specificities of 98%–99%, depending on the specimen and reference standard (APTIMA TV, Genprobe).^{28,53–57} In-house PCRs need validation before use on clinical specimens and are unlikely to be offered by many laboratories. However, the APTIMA TV uses the same technology as testing for chlamydia and gonorrhoea, so that additional hardware will not be necessary and is becoming more widely available.

Management

General advice

Sexual partner(s) should be treated simultaneously. Patients should be advised to avoid sexual intercourse for at least 1 week and until they and their partner(s) have completed treatment and follow-up.

Patients should be given a detailed explanation of their condition with particular emphasis on the long-term implications for the health of themselves and their partner(s). This should be reinforced by giving them clear and accurate written information. (See www.bashh.org/guidelines for patient information leaflet).

Further investigations

Screening for coexistent sexually transmitted infections should be undertaken in both men and women.

Treatment^{57–59}

Systemic antibiotic therapy is required to effect a permanent cure due to the high frequency of infection of the urethra and paraurethral glands in females. A Cochrane review has found that almost any nitroimidazole drug given as a single dose or over a longer period results in parasitological cure in >90% of cases. Oral single-dose treatment with any nitroimidazole seems to be effective in achieving short-term parasitological cure, but is associated with more frequent side effects than either longer oral or intravaginal treatment. Intravaginal treatment showed parasitological cure rates around 50%, which is unacceptably low. There is a spontaneous cure rate in the order of 20–25%.

Recommended regimes (Evidence level Ia, Grade A)

- Metronidazole 2 g orally in a single dose
- or
- Metronidazole 400–500 mg twice daily for 5–7 days

Alternative regimens

Tinidazole 2 g orally in a single dose. Tinidazole has similar activity to metronidazole but is more expensive.

Pregnancy and breast feeding

Metronidazole is likely to cure trichomoniasis, but it is not known whether this treatment will have any effect on pregnancy outcomes.⁶⁰ Meta-analyses have concluded that there is no evidence of teratogenicity from the use of metronidazole in women during the first trimester of pregnancy (Evidence level Ia).^{60–63} Metronidazole can be used in all stages of pregnancy and during breast feeding. Symptomatic women should be treated at diagnosis, although some clinicians have preferred to defer treatment until the second trimester. The British National Formulary advises against high-dose regimens in pregnancy. Metronidazole enters breast milk and may affect its taste. The manufacturers recommend avoiding high doses if breast feeding or if using a single dose of metronidazole, breast feeding should be discontinued for 12–24 h to reduce infant exposure. Tinidazole is pregnancy category C (animal studies have demonstrated an adverse event, and no adequate, well-controlled studies in pregnant women have been conducted), and its safety in pregnant women has not been well-evaluated. The manufacturer states that the use of tinidazole in the first trimester is contraindicated.

HIV-positive individuals

There are few data available to guide management of TV infection management in HIV-positive individuals. The standard treatment recommendations are based on studies conducted in HIV-negative persons. However, a recent randomized clinical trial demonstrated that a 2-g single oral dose of metronidazole was not as effective as 500 mg of metronidazole twice daily for 7 days for trichomoniasis among HIV-infected women.⁶⁴

Reactions to treatment

Patients should be advised not to take alcohol for the duration of treatment and for at least 48 h (72 h for tinidazole) afterwards because of the possibility of a disulfiram-like (Antabuse[®] effect) reaction.

Allergy

There is no effective alternative to 5-nitroimidazole compounds. Hypersensitivity reactions have been reported in patients using metronidazole and tinidazole and it is unknown whether there is cross-reactivity between the two agents. There are no data to suggest that tinidazole

would be safe to use in a patient with metronidazole allergy. It is important to take an accurate history to establish that a true allergy exists. Adverse reactions which may occur include anaphylaxis, skin rashes, pustular eruptions, pruritis, flushing, urticaria, and fever.⁶⁵ In cases of true allergy, desensitization to metronidazole has been described in case reports and could be considered^{66,67} (see Appendix 1⁶⁸). Recently, Helms et al.⁶⁹ reported data collected from clinicians who consulted the CDC on 59 patients with suspected hypersensitivity to metronidazole. All 15 patients who underwent metronidazole desensitization and were treated with metronidazole had their infections eradicated. Alternative treatment regimens were used for 17 study subjects with a cure rate of only 29.4%.

Treatment failure

Persistent or recurrent TV is due to inadequate therapy, re-infection, or resistance. Therefore check:

- Compliance and exclude vomiting of metronidazole
- Sexual history for possibility of re-infection and ask if partner(s) have been treated

A study investigating repeat TV infections at 1 month following the metronidazole 2g stat dose found that 7% of HIV-negative women and 10% of HIV-positive women were still infected due to treatment failure, suggesting a significant number of women do not respond to single-dose therapy.⁷⁰

Development of resistance against metronidazole and other nitroimidazoles can be due to aerobic and anaerobic resistance. In the USA, it is estimated that 5% of clinical isolates of TV exhibit some degree of metronidazole resistance, predominantly low level.⁷¹ Resistance tests can be of clinical benefit. Clinical and microbiological cure rates were higher in women with previous treatment failure who were treated in accordance with a treatment protocol utilising the results of a resistance test.⁷² Resistance data from the UK are lacking due to the absence of a metronidazole resistance testing service; however in 2002, one group found a 3.5% prevalence of non-response to standard dose metronidazole in the absence of re-infection and non-adherence.⁷³ Clinical isolates resistant to metronidazole can be resistant to tinidazole but usually with significantly lower minimal lethal concentrations to tinidazole than metronidazole.^{74,75} In vitro resistance may not predict clinical response to treatment,⁷⁴ which may be relative rather than absolute and may be overcome by high-dose metronidazole or tinidazole therapy. Tinidazole has a longer serum half-life,⁷⁶ good tissue penetration, a better side-effect profile and lower levels of resistance than metronidazole so should be

used when infections have not responded to metronidazole even though it is more expensive.^{71,75}

Treatment protocol for non-response to standard TV therapy (having excluded re-infection and non-adherence)

1. Repeat course of 7-day standard therapy

Metronidazole 400–500 mg twice daily for 7 days (Evidence level III) – in those who failed to respond to a first course of treatment, 40% responded to a repeat course of standard treatment.⁷³

For patients failing this second regimen:

2. Higher-dose course of nitroimidazole

Metronidazole or tinidazole 2 g daily for 5–7 days^{72,77} or Metronidazole 800 mg three times daily for 7 days⁷³ (Evidence level III) – in those who failed to respond to a second course of treatment, 70% responded to a higher dose course of metronidazole.⁷³

For those failing this third regimen, resistance testing should be performed if available as improved outcomes were reported with a treatment protocol guided by the results of a resistance test.⁷² If resistance testing is not available, high-dose tinidazole regimens are recommended, as in the above study 65% of women with clinical treatment failure did not have tinidazole-resistant isolates and 83% of those receiving the recommended high-dose treatment were cured compared with 57% of women receiving a lower-than-recommended dose.⁷²

3. Very high-dose course of tinidazole

Tinidazole 1 g twice or three times daily, or 2 g twice daily for 14 days ± intravaginal tinidazole 500 mg twice daily for 14 days^{72,78,79} (Evidence level III) – in those who had failed other treatments, 92%⁷⁸ and 90%⁷⁹ responded to a very high-dose course of tinidazole.

If very high-dose tinidazole has been unsuccessful it is difficult to recommend one specific further treatment. Treatment of such cases can be a therapeutic challenge as treatment options are limited with little evidence to support them. The largest published case series have been with intravaginal paromomycin and intravaginal furazolidone. There are anecdotal reports of treatment success with a number of other treatments. The reports are based on success in one or two women who had usually received a wide variety of prior treatments. Consequently for each successful anecdote there are a number of reports of treatment failure.

4. Other treatments with some reported success (Evidence level IV or anecdotal)

Paromomycin* intravaginally 250 mg once or twice daily for 14 days – 56–58% cure rate reported^{78,80}

Furazolidone* intravaginally 100 mg twice daily for 12–14 days – 33% cure rate reported^{72,81}

Acetarsol* pessaries 500 mg nocte for 2 weeks

6% Nonoxynol-9* pessaries nightly for 2 weeks

Availability

*The medicines suggested for use in treatment failure are unlicensed products and may not be readily available for purchase in the UK. The pharmacy purchasing department may be able to source some of these products from specialist manufacturers. At the time of writing this guideline, Acetarsol 500 mg pessaries and Nonoxynol-9 75 mg pessaries were available from Pharmarama International Ltd. The lead time for ordering these products for the first time may be up to 8 weeks.

Follow up

Tests of cure are only recommended if the patient remains symptomatic following treatment, or if symptoms recur. (Evidence level: IV, C)

Contact tracing and treatment

Current partners and any partner(s) within the 4 weeks prior to presentation should be screened for the full range of STIs and treated for TV irrespective of the results of investigations^{82–84} (Evidence level Ib A). (See www.bashh.org/guidelines for partner notification statement). In a male contact of TV, found to have urethritis on screening, it is reasonable to treat initially for TV and repeat the urethral smear before treating additionally for non-gonococcal urethritis (Level III).⁸⁵

There are no data available to guide treatment of the male partners of women with nitroimidazole treatment failure. Expert opinion suggests male partners should be evaluated and treated with either metronidazole 400–500 mg twice daily for 7 days or tinidazole 2 g single dose. There has been one report of a male partner requiring very high-dose tinidazole therapy before re-infection was prevented.⁷⁹

Organisational and financial considerations

The first-line treatments are cheap and easy to administer (for e.g. 21-tablet pack 200 mg metronidazole costs £1.37). For allergy and resistant case management the relative costs, time to obtain drug and access to safe

desensitisation facilities will incur additional costs and resources, or appropriate referral.

Auditable outcome measures

- First-line treatment for all patients found to have TV infection should be with metronidazole (with allergy as an exception), either as a single dose of 2 g or 400 mg twice daily for at least 5 days. Performance standard: 97%.
- Individuals should be provided with written information about their diagnosis and treatment. Performance standard: 97%.
- Partner notification should be performed and documented according to BASHH Statement on Partner Notification for Sexually Transmissible Infections (see www.bashh.org/guidelines). Performance standard: 97%.

Qualifying statement

The recommendations in this guideline may not be appropriate for use in all clinical situations. Decisions to follow these recommendations must be based on the professional judgement of the clinician and consideration of individual patient circumstances and available resources. All possible care has been undertaken to ensure the publication of the correct dosage of medication and route of administration. However, it remains the responsibility of the prescribing physician to ensure the accuracy and appropriateness of the medication they prescribe.

Statement of editorial independence

This guideline was commissioned, edited and endorsed by the BASHH CEG without external funding being sought or obtained.

Declarations of interest

All members of the guideline writing committee completed the BASHH conflict of interest declaration detailed below at the time the guideline's final draft was submitted to the CEG. JW has received research grant funding in the form of equipment from Gen-Probe.

Membership of the CEG

From October 2012 the membership of the CEG is: Dr Keith Radcliffe (Chair); Consultant Physician in Genitourinary Medicine, Whittall Street Clinic, Birmingham

Dr Mark FitzGerald, Consultant Physician in Genitourinary Medicine, Musgrove Park Hospital, Taunton

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