2011 European (IUSTI/WHO) Guideline on the Management of Vaginal Discharge

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Introduction

Three common infections are associated with vaginal discharge - bacterial vaginosis, trichomoniasis and candidiasis, of which trichomoniasis is a sexually transmitted infection. Vaginal discharge may be caused by a range of other physiological and pathological conditions including cervicitis, aerobic vaginitis, atrophic vaginitis, and mucoid ectopy. Psychosexual problems and depression can present with recurrent episodes of vaginal discharge. These need to be considered if tests for specific infections are negative. Many of the symptoms and signs are non-specific and a number of women may have other conditions such as vulvar dermatoses or allergic and irritant reactions. Occasionally cervical infection caused by chlamydia or gonorrhoea may result in vaginal discharge.

This guideline is an update of the European IUSTI vaginal discharge guideline 2001.

Aetiology and transmission

Bacterial vaginosis

Bacterial vaginosis (BV) is the commonest cause of abnormal vaginal discharge in woman of childbearing age, but may also be encountered in menopausal women, and is rather rare in children [1-8]. In Caucasian women the prevalence is 5-15%, in African and American blacks 45-55%. In Asian women the prevalence is less well studied, but in general around 20-30%. Women having sex with women share similar lactobacillary types and are at increased risk for BV[9].

It is characterised by an overgrowth of predominantly anaerobic organisms (e.g. *Gardnerella vaginalis*, *Prevotella spp., Mycoplasma hominis, Mobiluncus spp*.) in the vagina leading to a replacement of lactobacilli and an increase in vaginal pH. Recently, bacterial identification using PCR has demonstrated that previously uncultivated bacteria are highly prevalent in women with BV including bacterial vaginosis associated bacterium (BVAB) 1, 2, and 3 and Atopobium species. Since these bacteria are difficult to culture, their susceptibility to antibiotics is not known.

BV can arise and remit spontaneously and although not considered a sexually transmitted infection is associated with sexual activity. Two theories prevail to explain the existence and recurrence of this condition: 1) lactobacilli disappear due to environmental factors such as vaginal douching, or frequent pH insults due to sexual intercourse or other factors or 2) some lactobacilli are attacked by type specific viruses and are unable to recolonize the vagina, facilitating anaerobic overgrowth.

In some women the lactobacilli are also decreased and pH is elevated, but aerobic microflora derived from the gut, like *Escherichia coli*, group B streptococci, and *Staphylococcus aureus* predominate. This is termed aerobic vaginitis (AV). Mixed infections are frequent. AV is an inflammatory condition, causing long term symptoms with intermittent exacerbations.

Candidiasis

Vulvovaginal candidiasis is caused by an overgrowth of *Candida albicans* in 90% of women (remainder other species eg *C. glabrata*) [10. 11]. An estimated 75% of women will experience at least one episode during their lifetime. 10-20% women are asymptomatic vaginal carriers; this may be up to 40% during pregnancy [12,13].

Trichomoniasis

Trichomonas vaginalis (TV) is a flagellated protozoon which is a parasite of the genital tract. In adults it is almost exclusively sexually transmitted. Due to site specificity, infection only follows intravaginal or intraurethral inoculation of the organism. In women urethral infection is present in 90% of episodes, although the urinary tract is the sole site of infection in <5% of cases. The most obvious host response to infection is a local increase in polymorphonuclear leukocytes.

Clinical features

There are classical symptoms (Table 1) and signs (Table 2) but these are frequently absent or non specific [22,23]. The diagnosis of both BV and candidiasis is syndromic i.e. based on clinical symptoms and signs supported by laboratory test findings, which in themselves vary in specificity and sensitivity.

Table 1

Symptoms

Bacterial vaginosis	Candidiasis	Trichomoniasis
approximately 50% asymptomatic	10-20% asymptomatic	10-50% asymptomatic
Offensive fishy smelling discharge	Vulval itching	Offensive vaginal discharge
	Vulval soreness	Vulval itching / irritation
	Vaginal discharge (non offensive)	Dysuria
	Superficial dyspareunia	Rarely low abdominal discomfort

Table 2

Clinical signs

Bacterial vaginosis	Candidiasis	Trichomoniasis
Thin white homogenous discharge, coating walls of vagina and vestibule	Vulval erythema	Vulval erythema
Absence of vaginitis	Vulval fissuring	Vaginitis
	Vaginal discharge may be curdy (non offensive)	Vaginal discharge in up to 70% - frothy and yellow in 10-30%
	Satellite skin lesions	Approx. 2% “strawberry” cervix visible to naked eye.
	Vulval oedema	5-15% no abnormal signs

Complications

There is an association with BV and post-hysterectomy vaginal cuff infection [14-16], post-abortion endometritis [17-21], increased risk of spontaneous miscarriage ranging from 13 to 24 gestational weeks [24-27] and preterm birth [28-43] and increased risk of acquiring STI, especially genital herpes and HIV [44-52] . In one large RCT treating women with BV, metronidazole did not show any benefit in the prevention of preterm birth compared to placebo [53], while in 2 other RCT the use of metronidazole showed an increased risk for preterm birth [54,55]. Furthermore in at least 2 meta-analyses, metronidazole was found to increase the risk of adverse pregnancy outcome [56,57]. On the other hand, although older RCT studies with vaginal clindamycin did not seem to influence the preterm birth rate [58-61], 3 more recent RCT using clindamycin provided beneficial evidence of reduced preterm birth rates, either given orally, of vaginally [62-64]. As the results of clinical trials investigating the value of screening for and treating BV in pregnancy have been conflicting it is difficult to make firm recommendations. Symptomatic pregnant women should be treated in the usual way (Grade B) but there is insufficient evidence to recommend routine treatment of asymptomatic pregnant women who are found to have BV.

Vaginal trichomoniasis has been associated with adverse pregnancy outcomes, particularly premature rupture of membranes, preterm delivery, and low birth weight [65,66]. However, further research is needed to confirm these associations and to prove that the association is causal. Moreover data do not suggest that metronidazole treatment results in a reduction in perinatal morbidity and some trials suggest the possibility of increased prematurity or low birth weight after metronidazole treatment, limitations of the studies prevent definitive conclusions regarding risks of treatment [54, 67]. Screening of asymptomatic individuals for trichomoniasis is therefore not currently recommended. (Evidence Level I & II, Grade A) Some specialists would defer therapy in asymptomatic pregnant women until after 37 weeks’ gestation. In addition, these pregnant women should be provided with careful counselling regarding condom use and the continued risk of sexual transmission**.** There is evidence that trichomoniasis may enhance HIV transmission[68-70].

Diagnosis

Ideally all women presenting with abnormal vulval or vaginal symptoms should be tested (Evidence level III, grade C) [71-77]. If this is not possible then examination and testing should definitely be performed when:

- Finding of TV on cervical cytology
- Diagnosis of TV in sexual partner
- Failure of vaginal discharge to respond to empirical treatment
- Severe or recurrent symptoms

Asymptomatic women do not require testing for BV or candida.

Laboratory diagnosis

The definitive diagnosis of each infection is based upon laboratory tests (Table 3). A sample of the discharge is removed from the vaginal wall with a swab. The type of fibre is not important. Direct microscopy can be done immediately at the clinic, if available.

Criteria for diagnosis of bacterial vaginosis (Evidence level II, grade B) [77-82]

A. Clinical diagnosis (Amsel): (the presence of three of the 4 criteria is required)
   1. Homogeneous gray-white discharge
   2. pH of vaginal fluid > 4.5;
   3. Fishy odour (if not recognizable, use few drops of 10% KOH)
   4. Clue cells present on wet mount microscopy

B. Nugent score - This is used as a gold standard for studies and relies upon estimating the relative proportions of bacterial morphotypes on a Gram stained vaginal smear to give a score between 0 and 10. A score of <4 is normal, 4-6 is intermediate and >6 is BV. However, it does not take abnormal flora types other than full blown BV into account and the nature of the so called 'intermediate flora' is unclear.

C. Hay Ison criteria – based on findings on a Gram stained smear and reflects the flora possibilities better than Nugent score.
   Grade 0: Not related to BV, epithelial cells only, no lactobacilli, indicates recent antibiotics
   Grade 1: (Normal): Lactobacillus morphotypes predominate
   Grade 2: (Intermediate): Mixed flora with some Lactobacilli present, but Gardnerella or Mobiluncus morphotypes also present
   Grade 3 (BV): Predominantly Gardnerella and/or Mobiluncus morphotypes, clue cells. Few or absent Lactobacilli.
   Grade 4: Not related to BV, Gram +ve cocci only, no lactobacilli (Aerobic vaginitis flora) [83]

Criteria for diagnosis of vaginal candidosis (Evidence level III, grade B) [71-76, 84-87]

- Absence of smell (in "whiff test" on speculum and in amine odour test on slide) are supportive, since candidiasis and BV/TV do not usually co-exist, but not diagnostic.
- Yeasts or pseudohyphae on wet preparation (40 - 60% sensitivity) of vaginal discharge.
- Yeasts or pseudohyphae on Gram stain (up to 65% sensitivity) of vaginal discharge
- Vaginal culture positive for a Candida species. If possible this should be delineated as albicans or non-albicans. If directly inoculated to a Sabouraud's plate results should be reported as light, medium or heavy growth as this correlates with specificity.
- Repeated culture of the same species of non-albicans candida (usually *C. glabrata*) may indicate reduced antifungal sensitivity.

Criteria for diagnosis of *Trichomonasis vaginalis* (TV) (Evidence level III, grade B) [88-96]

A. Direct observation of the organism by a wet smear (normal saline) or acridine orange stained slide from the posterior vaginal fornix (sensitivity 40-70% cases). Microscopy for *T. vaginalis* should be performed as soon as possible after the sample is taken as motility diminishes with time.
B. Culture media are available and will diagnose up to 95% cases.
C. Nucleic acid amplification tests (NAATs) have been developed and sensitivities and specificities approaching 100% have been reported.

Trichomonads are sometimes reported on cervical cytology, however a meta-analysis has shown that while cytology has good specificity, the weighted mean sensitivity is only 58% [95]. If the population prevalence of TV is high it is appropriate to treat in these circumstances however where a woman is unlikely to have trichomoniasis (prevalence less than or equal to 1%) it is prudent to confirm the diagnosis, preferably by the culture of vaginal secretions or NAATs if available. (Evidence level Ia, Grade A)

Management
Information, explanation and advice for the patient.

TV: As TV is a sexually transmitted organism screening for coexistent infections should be undertaken. Sexual abstinence should be advised until treatment of all partners is completed.

BV: It should be explained that the cause is unclear and that although there is an association with sexual activity, it is not a sexually transmitted infection.

Therapy
Indications for treatment of bacterial vaginosis:

- Symptoms
- Positive direct microscopy with/without symptoms in some pregnant women (those with a history of prior idiopathic preterm birth or second trimester loss)
- Women undergoing some surgical procedures
- Optional: positive direct microscopy in women without symptoms. They may report a beneficial change in their discharge following treatment.
- Male partners do not require treatment

Indications for therapy of candida

- Symptomatic women found to have candida on either microscopy or culture.
- Asymptomatic women do not require treatment.
- Asymptomatic male partners do not require treatment
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Indications for therapy of TV:

- Positive test for trichomoniasis regardless of symptoms
- Epidemiological treatment of sexual partners

Recommended regimens
Trichomonas: The nitroimidazoles comprise the only class of drugs useful for the oral or parenteral therapy of trichomoniasis and most strains are highly susceptible. Due to the high rates of infection of the urethra and paraurethral glands in women systemic chemotherapy should be given to effect a cure and the use of metronidazole gel is not recommended. The single dose has the advantage of improved compliance and being cheaper, however there is some evidence to suggest that the failure rate is higher, especially if partners are not treated concurrently. There is a spontaneous cure rate in the order of 20-25%. In patients with true metronidazole allergy, desensitisation has been used. [97-98]

Recommended regimens for *T. vaginalis* and bacterial vaginosis (Evidence level Ia, grade A) [99-115]
1st choice:

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

With metronidazole or tinidazole, alcohol should be avoided because of the possibility of a disulfiram-like (antabuse) reaction. Abstinence from alcohol use should continue for 24 hours after completion of metronidazole or 72 hours after completion of tinidazole.

Alternative regimens for bacterial vaginosis ONLY

- Intravaginal metronidazole gel (0.75%) once daily for 5 days
  or
- Intravaginal clindamycin cream (2%) once daily for 7 days
  or
- Clindamycin 300 mg orally twice daily for 7 days

For BV, clindamycin and metronidazole have equal efficacy, comparing oral and vaginal formulations, both after one week (combined RR 1.01, 95% CI 0.69 to 1.46) and after one month (combined RR 0.91, 95% CI 0.70 to 1.18). Roughly 58 to 88% will be cured after 5 days treatment with metronidazole or clindamycin. No difference in

treatment failures was seen after one week or one month when oral versus local applications where compared. However, in terms of side effects, in most studies clindamycin tended to have less adverse effects than metronidazole (RR 0.75, 95% CI 0.56 to 1.02).

Vaginal versus oral application. As bioavailablity for both metronidazole and clindamycin are only 50% of the oral intake after vaginal application, less side effects are to be expected. When compared to oral intake 400mg twice a day for 7 days, the use of 500 mg metronidazole vaginally at night for 7 days was equally effective, resolving 74% and 79% after 4 weeks in the oral versus the vaginal group respectively. In one randomized trial comparing the oral and the vaginal form, clinical eradication was present after one month in 71% of both modalities.

A number of randomized studies addressed the efficacy of vaginal clindamycin versus oral metronidazole Eradication at one month after vaginal clindamycin cream were 66 to 83% versus 68% to 87% for metronidazole . Also when oral metronidazole, 0.75% metronidazole vaginal cream and 2% vaginal clindamycin cream where compared in a randomized trial, equal efficacies (respectively 85, 75, 86%) and side effects were noted. Vaginal versus oral clindamycin also showed similar efficacy and but somewhat less side effects.

Clindamycin cream as well as metronidazole gel contain mineral oils that are known to diminish the strength of condoms. Therefore, use of barrier contraception is not considered safe during the treatment with any of these vaginal products.

<u>Recommended regimens for vaginal candidiasis</u> (Level of evidence: II, grade A) [13, 116, 117]
Intravaginal and oral therapy provide equally effective treatment for vaginal candidiasis. Treatment with azoles results in relief of symptoms and negative cultures among 80-90% of patients after treatment is completed, whether administered orally or topically. Only topical preparations should be used during pregnancy.

Overall standard single dose treatments are as effective as longer courses. In a severely symptomatic attack there is proven to be better symptomatic benefit in repeating fluconazole 150mgs after 3 days. This does not affect relapse rates.

Oral preparations include

- Fluconazole 150mg as a single dose
- Itraconazole 200mg twice daily for one day

Intravaginal treatments include

- Clotrimazole vaginal tablet 500mg once or 200mg once daily for 3 days
- Miconazole vaginal ovule 1200mg as a single dose or 400mg once daily for 3 days.
- Econazole vaginal pessary 150mg as a single dose

There are a number of other intravaginal preparations available. These are now all either azoles or of limited availability e.g. nystatin, or unlicensed. Topical treatment to the vulva is of no proven added benefit to intravaginal treatment but some patients prefer this. Where itch is a significant symptom a hydrocortisone containing topical preparation may provide more rapid symptomatic relief. Any benefit may be from the emollient effect. If oral antifungals are used then a moisturising cream is cheaper and may be less likely to give an irritant reaction.

<u>Special situations [118-120]</u>
Metronidazole is pregnancy category B (animal studies have revealed no evidence of harm to the fetus, but no adequate, well-controlled studies among pregnant women have been conducted). Multiple studies and meta-analyses have not demonstrated a consistent association between metronidazole use during pregnancy and teratogenic or mutagenic effects in infants. Metronidazole can be used in all stage of pregnancy and during breast feeding, however high dose regimens are best avoided in these circumstances. In lactating women who are administered metronidazole, withholding breastfeeding during treatment and for 12–24 hours after the last dose will reduce the exposure of metronidazole to the infant.

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.

Oral anti-candidal preparations should not be used in pregnancy. Nystatin, which is not an azole, gives a cure rate of 70 –90% for candida, but may be useful in women with an organism with reduced sensitivities to azole drugs. The dose as a pessary is 100,000 units, 1 – 2 pessaries nightly for 14 nights. Availability is limited in some European countries.

Severe candidiasis should be treated with Fluconazole 150mgs repeated after 3 days. Chronic *C. glabrata* infection requires longer duration of therapy with non-licensed treatments. Nystatin for 21 days is the first line treatment and topical flucytosine, either alone or in combination with amphotericin should also be considered. Boric acid vaginal suppositories 600mgs daily for 14-21 days may otherwise be used. Response should be based on speciated culture results as symptomatic response may sometimes take several months.

- **Partner notification**

BV and Candida [121-123]
Routine screening and treatment of male partner(s) is not indicated.

Trichomoniasis (Evidence level Ib A) [124,125]
Current sexual partners should be screened for STIs and treated for TV regardless of the results of their tests. In a male contact of TV, found to have non-gonococcal urethritis (NGU) on screening, it is reasonable to treat for TV initially and then repeat the urethral smear before making a diagnosis of NSU. Patients should be instructed to avoid sex until they and their sex partners are cured (i.e., when therapy has been completed and patient and partner(s) are asymptomatic).

- **Follow-up**

BV
Only in women with persistent symptoms. If treatment is prescribed in pregnancy to reduce the risk of preterm birth, a repeat test should be made after one month and further treatment offered if BV has recurred.

Recurrent BV, therapy[126-130]
Most patients will have recurrences within 3 to 12 months, whatever treatment has been used. In one placebo controlled randomized trial weekly vaginal metronidazole was compared to placebo during 16 weeks, showing a significant difference of 70% of women being symptom-free in the treatment group, versus only 30% in the placebo group. However, even with metronidazole maintenance therapy only 35% of patients were still recurrence free 12 weeks after stopping the treatment, versus 20% of controls. Furthermore, patients receiving vaginal metronidazole cream suffered from vulvovaginal candidosis more often than placebo users (p=0.02) [103]. Studies have found that the adjuvant vaginal application of probiotics were effective in preventing recurrences of BV over a 6 months period. In one study twice daily oral metronidazole was compared with a regimen of daily intravaginal application of lactobacilli showing similar results after 4 weeks and fewer failures at 3 months. In a non-randomised uncontrolled study of 49 women with a mean of 4.4 recurrences of BV per year, acidifying gel reduced the number of recurrences to 0.6 per year. In another randomized study acidifying gel was as efficient as 0.75% metronidazole gel.

Candida [131-137]
Only in women with persistent or recurrent symptoms. All such women should have at least one speciated culture. Consider other diagnoses e.g. vulvar dermatitis

Recurring candidiasis, therapy
Definition – four or more symptomatic episodes per year

- document frequency, establish diagnosis and confirm by culture
- exclude risk factors (e.g. diabetes, underlying immunodeficiency, corticosteroid use, frequent antibiotic use

Ongoing trials are addressing optimal therapy, which is not established, in these individuals. Current recommendations are for an initial intensive regime of 10 – 14 days followed by a maintenance regime, probably weekly for 6 months. Vulval dermatitis/eczema is common either co-existing or as a differential diagnosis. General advice includes permission to use a vulval moisturiser applied to dry skin and washed off as a soap substitute. Ovulation suppressing progesterone contraception e.g. Depo-Provera or Cerazette, may have some benefits

TV

Follow-up is unnecessary for men and women who become asymptomatic after treatment or who are initially asymptomatic.

Persistent / recurring symptoms, therapy[138-141]
- Check compliance and exclude vomiting of metronidazole.
- Check possibility of re-infection from new or untreated partners

Patients who fail to respond to first course of treatment often respond to a repeat course of standard treatment.

If this fails and above excluded, then consider a HVS or empirical treatment with erythromycin or amoxycillin to reduce B-haemolytic streptococci before retreating with metronidazole as some organisms present in the vagina may interact and reduce effectiveness of metronidazole.

Low-level metronidazole resistance has been identified in 2%–5% of cases of vaginal trichomonas, however, infections caused by the majority of these organisms respond to tinidazole or higher doses of metronidazole. High-level resistance is rare. Tinidazole has a longer serum half-life and reaches higher levels in genitourinary tissues than metronidazole. In addition, many *T. vaginalis* isolates have lower minimum inhibitory concentrations (MICs) to tinidazole than metronidazole.

For patients failing either of these regimens, Anecdotal treatments include
- Metronidazole 400mg tds for 7 days with metronidazole Ig PR or Ig PV(unlicensed) daily for 7 days
- Metronidazole (or tinidazole) 2g daily for 3 days to 5 days
- High dose intravenous metronidazole
- Nimorazole 2g orally with sulphonamide (Sultrin) pessaries bd for 10 days.

- **Prevention/health promotion**

TV: Patients should be advised that using condoms consistently will reduce the risk of acquiring trichomonal infection.

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Appendix 1

Review of the literature

An extensive literature review was performed using Medline for the years 1966-2009. MEDLINE search-keywords: vulvovaginal candidiasis, vaginal candidosis, vaginal candida, *Trichomonas vaginalis*, trichomoniasis, Bacterial vaginosis, non-specific vaginitis, abnormal vaginal flora, vaginal dysbiosis. The resulting articles were handsearched and sorted. Further references were obtained from these articles.

The Cochrane Library was searched; search-keywords were:
vulvovaginal candidiasis, vaginal candidosis, vaginal candida, *Trichomonas vaginalis* in women, bacterial vaginosis.

The 2009 US CDC guidelines for the treatment of Sexually Transmitted Diseases and the related UK national guidelines (www.bashh.org) were reviewed.

Appendix 2

Levels of evidence and grading of recommendations

Levels of Evidence

Ia Evidence obtained from meta-analysis of randomised controlled trials.

Ib Evidence obtained from at least one randomised controlled trial.

IIa Evidence obtained from at least one well designed study without randomisation.

IIb Evidence obtained from at least one other type of well designed quasi-experimental study.

III Evidence obtained from well designed non-experimental descriptive studies such as comparative studies, correlation studies, and case control studies.

IV Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.

Grading of Recommendations

A (Evidence levels Ia, Ib)	Requires at least one randomised control trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.
B (Evidence levels IIa, IIb, III)	Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.
C (Evidence IV)	Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality.

Appendix 3

Declarations of interests

Jackie Sherrard: none

Gilbert Donders: The author has no direct financial interest in any of the subjects addressed in this paper, but he is involved in consultancy and/or member of the advisory board of Alfa Wasserman, Bayer- Schering, Medinova and Glaxo Smith Kline

David White: none

Jørgen Skov Jensen: None

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