2018 European (IUSTI/WHO) Guideline on the Management of Vaginal Discharge

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This guideline is an update of the European IUSTI vaginal discharge guideline 2011.

INTRODUCTION

Four common pathological conditions are associated with vaginal discharge: bacterial vaginosis, aerobic vaginitis, candidosis, and the sexually transmitted infection, trichomoniasis. Chlamydial or gonococcal cervical infection may result in vaginal discharge. Vaginal discharge may be caused by a range of other physiological and pathological conditions including atrophic vaginitis, desquamative inflammatory vaginitis, cervicitis, and mucoid ectopy. Psychosexual problems may present with recurrent episodes of vaginal discharge and vulval burning. 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 vulval dermatoses or allergic and irritant reactions.

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 perimenopausal women[1,2]. In Caucasian women the prevalence is 5-15%, in Black women is higher at 45-55%. Women having sex with women share similar lactobacillary types, are more likely to have concordant vaginal microbiota (flora) patterns, and are at increased risk for BV[3].

BV is a dysbiosis of the vaginal microbiota. It is characterised by an overgrowth of predominantly anaerobic organisms (e.g. *Gardnerella vaginalis*, *Prevotella spp., Atopobium vaginae, Mycoplasma hominis, Mobiluncus spp*.) in the vagina leading to a replacement of lactobacilli and an increase in vaginal pH. Bacterial identification using PCR has demonstrated that there are many different, previously uncultivated bacteria present in women with BV including bacterial vaginosis associated bacterium (BVAB) 1, 2, and 3, and *Sneathia* species [4]. Since these bacteria are difficult to culture, the antibiotic susceptibility of many is not known.

BV can arise and remit spontaneously and although not strictly considered a sexually transmitted infection it is associated with sexual activity. The exact aetiology of BV is still unclear but current evidence suggests that formation of a biofilm with *Gardnerella vaginalis* is important in the switch from normal vaginal flora to BV [5,6].

Aerobic vaginitis / desquamative inflammatory vaginitis

Aerobic vaginitis (AV) presents with a purulent discharge, some degree of atrophy and vaginitis. Lactobacilli are decreased and pH is elevated, but aerobic microbiota, like *Escherichia coli*, group B streptococci, and *Staphylococcus aureus* predominate [7]. Mixed infections are frequent. It is not known whether AV has an infectious origin, or whether it is an inflammatory process followed by a dysbiosis. It can cause long term symptoms with intermittent exacerbations, and recurrences after treatment are common [8]. Atrophic vaginitis in lactating women is probably a variant of AV. More severe forms of AV and desquamative inflammatory vaginitis (DIV) are probably the same condition.

Candidosis

More than 60% of healthy premenopausal women are colonised with *Candida*, with higher rates in pregnancy, and lower rates in children and postmenopausal women without hormonal replacement therapy [9,10]. An estimated 75% of women will experience at least one symptomatic episode during their lifetime and 6 to 9% will experience chronic recurrent vulvovaginal candidosis (at least 4 episodes per year). Vulvovaginal candidosis results from an overgrowth of *Candida albicans* in 90% of women (remainder other species eg *C. glabrata*) [11,12]. Precipitating factors include antibiotic therapy, pregnancy, and endogeneous or exogeneous immunosuppression (including diabetes mellitus and immunosuppressive medication). In some women, symptoms may occur with a low burden of *Candida* and it is thought this may be due to an allergic or inflammatory response to the yeast.

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 recognised symptoms and signs (Table 1). The diagnosis of both BV and candidosis is syndromic i.e. based on clinical symptoms and signs supported by laboratory test findings, which in themselves vary in specificity and sensitivity. The classical features of TV are frequently absent or non-specific [13,14].

Table 1

Symptoms and signs

Bacterial vaginosis	**Aerobic vaginitis**	**Candidosis**	**Trichomoniasis**
Approximately 50% asymptomatic	10-20% asymptomatic	Approx. 60% women colonised. Minority develop symptoms.	10-50% asymptomatic and 5-15% no abnormal signs
Thin white homogenous discharge, coating walls of vagina and vestibule	Purulent discharge	Vaginal discharge may be curdy (non offensive)	Offensive vaginal discharge in up to 70% - frothy and yellow in 10-30%
Offensive fishy odour	Vulval burning or stinging	Vulval soreness/itching and erythema	Vulval itching / irritation and erythema
Absence of vaginitis	Superficial dyspareunia	Vulval fissuring	Dysuria
	Vaginal erythema and oedema	Superficial dyspareunia	Rarely low abdominal discomfort
	Vaginal ulceration	Satellite skin lesions	Vaginitis
		Vulval oedema	Approx. 2% “strawberry” cervix visible to naked eye.

Complications

Women with BV are at increased risk of acquiring sexually transmitted infections. They have a 2-fold increased risk of HIV acquisition [15], 1.5 to 2-fold risk of chlamydia [16] and gonorrhoea [16], a 9-fold risk of TV [17] and a 2-fold risk of HSV-2 [18] compared to women without BV. HIV positive women with BV have a 3-fold risk of transmitting HIV [19]. Monthly prophylaxis with metronidazole reduces the incidence of STIs by almost 50% [20]. The BV-associated bacteria are probably also implicated in the aetiology of pelvic inflammatory disease. A prospective study of women with clinically suspected pelvic inflammatory disease (PID) reported significant correlations between the presence of BV associated bacteria and the presence of endometritis and recurrent PID [21].

There is an association with BV and post-hysterectomy vaginal cuff infection [22,23], post-abortion endometritis [24,25], and an increased risk of spontaneous miscarriage and preterm birth [26,27]. Symptomatic pregnant women with BV should be treated in the usual way but the latest Cochrane review concludes there is insufficient evidence to recommend routine screening and treating all pregnant women for asymptomatic bacterial vaginosis to prevent preterm birth [28].

Multiple reports support an epidemiological association between HIV and trichomoniasis. There is growing evidence that trichomonas infection enhances HIV transmission [29-32] and there may be an increased risk of TV infection in those that are HIV positive [33].

Trichomoniasis is associated with adverse pregnancy outcomes [34,35]. The literature on metronidazole treatment during pregnancy and preterm birth is not conclusive. The most recent Cochrane review found that metronidazole is effective against trichomoniasis when taken by women and their partners during pregnancy, but it may harm the baby due to early birth [36]. Screening of asymptomatic individuals for TV infection is therefore not currently recommended.

Although only recently described, moderate/severe AV is associated with an increasing number of co-infections and complications [37]. An increased risk of preterm delivery and chorioamnionitis in women with first trimester AV has been shown [38].

Several studies in the last decade have shown a decrease in preterm birth, if vaginal candida colonisation or infection had been treated with clotrimazole [39]. In a study by Holzer et al women who were colonized with *Candida* spp. during the second

trimester of pregnancy had higher rates of preterm birth and lower neonatal birthweight than those who were colonized during the first trimester of their pregnancy [40]. According to old studies the vaginal treatment of an asymptomatic Candida colonisation during the last 6 weeks of pregnancy reduces the Candida colonisation of the newborn during vaginal delivery and thus reduces oral thrush and napkin dermatitis of the baby during the first 4 weeks of life [41]. Modern studies are urgently needed to confirm these findings.

DIAGNOSIS

Women presenting with abnormal vulval or vaginal symptoms should be tested to ensure that appropriate treatment is given [42-45]. If this is not possible, then examination and testing should definitely be performed in the following situations:

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

Asymptomatic women do not require testing for BV, AV or candida. Testing asymptomatic women for TV should be guided by local prevalence data.

The definitive diagnosis of each infection is based upon clinical symptoms, examination, the pH and the microscopic findings of the vaginal secretions, and for TV additionally by laboratory tests. A sample of the discharge is removed from the vaginal wall with a swab. This can be performed by the clinician or be self-collected by the woman [46]. The type of swab is not important. An elevated pH (>4.5) is suggestive of BV or trichomoniasis and is almost always normal in candida infections. Direct microscopy should be done immediately, if available.

Bacterial vaginosis

Gram-stained microscopy is the reference method for diagnosing BV.

A. Nugent score [47] - 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 bacterial morphotypes other than those associated with BV into account. The clinical implications of 'intermediate flora' are unclear but they are associated with complications [48].

B. Hay Ison criteria [49] – These are also based on the findings on a Gram stained smear but are easier and quicker to use in clinical practice and do include non-BV associated bacteria.
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)

Clinical criteria for diagnosis of BV (Amsel) [50]

The presence of three of the 4 criteria is required; as three are clinical criteria it is possible to make a diagnosis of BV without microscopy or the use of a microbiology laboratory. Compared to Gram-stained microscopy, the presence of three of the four clinical criteria has a sensitivity of 60-72% for the diagnosis of BV [51,52].

1. Homogeneous grey-white discharge
2. pH of vaginal fluid > 4.5 (measured using narrow gauge pH paper)
3. Fishy odour (if not recognizable, use few drops of 10% KOH)
4. Clue cells present on wet mount microscopy (>20% of all epithelial cells)

Other methods of diagnosing BV

Commercial tests for BV are also available. OSOM BV Blue (Sekisui Diagnostics, Framingham, MA, USA) is a point of care test which measures sialidase levels and has sensitivity of 91.7% compared to microscopy [53]. The BD MAX™ Vaginal Panel is a microbiome-based, nucleic acid amplification assay that detects BV, TV and several Candida species. The manufacturer insert quotes a sensitivity of 90.7% for the diagnosis of BV [54].

The Guidelines Group recommends that the current best test to diagnose BV in women is microscopy using the Hay Ison Criteria.
Strength of recommendation: Grade 1, quality of evidence: Grade A.

Aerobic vaginitis

Microscopy

- The gold standard for diagnosis is wet mount microscopy [55]. The AV score combines information about bacterial flora, epithelial disruption and inflammation creating a score from 0-10: 0-2 (no AV), 3-4 (mild AV), 5-6 (moderate AV) or 7-10 (severe AV) (Table 2).

Table 2 Abbreviated template for assessing the aerobic vaginitis score [8]

		ENTER SCORE
Background Flora		
Unremarkable	0	
Small coliforms	1	
Cocci or chains	2	
Lactobacillary grade		
Predominant lactobacilli	0	
Reduced lactobacilli	1	
No lactobacilli	2	
Number of leucocyte		
<10/high power field	0	
≤ 10/epithelial cell	1	
>10/epithelial cell	2	
Toxic leucocyte proportion		
None or sporadic	0	
≤ 50% leucocyte	1	
>50% leucocyte	2	
Parabasal cells proportion		
None	0	
≤10% of epithelial cells	1	
>10% of epithelial cells	2	

Cultures

Although most women with AV have positive cultures for aerobic bacteria such as *S. agalactiae, S. aureus, E. coli,* a positive vaginal culture does not indicate the woman has AV and is not recommneded for diagnosis. However, culture with antimicrobial susceptibility testing may aid in treatment.

Molecular detection

Tests based on molecular biology are being developed which correlate well with moderate to severe AV compared with microscopy but need confirmation in larger trials assessing sensitivity and specificity [56].

The Guidelines Group recommends that the current best test to diagnose AV in women is microscopy.
Strength of recommendation: Grade 2, quality of evidence: Grade B.

Candidosis

Microscopy

- Budding cells (and a positive *Candida* culture) can exist in asymptomatic, colonised women or in women with candidosis. The diagnosis should be based on a combination of the clinical signs and microscopic findings. Pseudohyphae/mycelia are evidence of candidosis [56-59].
- Yeasts or pseudohyphae on wet preparation with either saline or 10-20% KOH solution (40 - 60% sensitivity) of vaginal discharge.
- Yeasts or pseudohyphae on Gram stain (up to 65% sensitivity) of vaginal discharge

Culture

- Vaginal culture positive for a *Candida* species. If possible this should be delineated as *C. 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.
- As a high number of women carry candida asymptomatically, the significance of light and medium growths should be interpreted with caution.
- Repeated culture of the same species of non-albicans *Candida* (usually *C. glabrata*) indicates reduced antifungal susceptibility to azoles.

The Guidelines Group recommends that the current best test to diagnose *Candida* in women is microscopy.
Strength of recommendation: Grade 1, quality of evidence: Grade B.

Trichomoniasis

Microscopy
Direct observation of the organism by a wet smear (normal saline) or acridine orange stained slide from the posterior vaginal fornix. The wet preparation should be read within 10 minutes of collection, as the trichomonads quickly loose motility and will be more difficult to identify [60]. The sensitivity is highest in women presenting with vaginal discharge. However, the sensitivity is reported to be as low as 45-60% [61-63] so a negative result should be interpreted with caution. The specificity with trained personnel is high.

Point of care tests
A number of point of care tests that have the advantages of microscopy have been described. The OSOM Trichomonas Rapid Test (Genzyme Diagnostics, USA) has demonstrated a sensitivity of 80-94% and a specificity greater than 95% [64,65]. This test requires no instrumentation and provides a result within 30 mins and is a suitable alternative to culture or molecular testing. Although these tests are more sensitive than 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
Culture of TV has a higher sensitivity compared to microscopy, but is not widely available. A commercially available culture system (InPouch TV; BioMed Diagnostics, USA), offers many advantages over previous culture media such as Diamond's medium [66-68]. 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.

Molecular detection
Nucleic acid amplification tests (NAATs) offer the highest sensitivity for the detection of TV in comparison to both microscopy and culture [69,70]. They should be the test of choice where resources allow. NAATs can detect TV in vaginal or endocervical swabs and in urine samples from women with sensitivities of 88%-97% and specificities of 98%-99%, depending on the specimen and reference standard [71-74].

The Guidelines Group recommends that the current best tests to diagnose TV in women are NAATs.
Strength of recommendation: Grade 1, quality of evidence: Grade A.

MANAGEMENT

Bacterial vaginosis
It should be explained that the cause is unclear and that although there is increasing evidence of an association with sexual activity, and of sexual transmissibility, it is not yet proven to be a sexually transmitted infection.

Indications for treatment of BV:
- Symptoms
- Positive direct microscopy with/without symptoms in some pregnant women (those with a history of prior idiopathic preterm birth or second trimester loss)
- BV in women undergoing gynaecological surgical or invasive diagnostic procedures

Optional: positive direct microscopy in women without symptoms. They may report a beneficial change in their discharge following treatment.

Recommended regimens for BV
- Metronidazole 400 - 500 mg orally twice daily for 5 to 7 days
  or
- Intravaginal metronidazole gel (0.75%) once daily for 5 days
  or
- Intravaginal clindamycin cream (2%) once daily for 7 days

Alternative regimens for BV
- Metronidazole 2 gram orally in a single dose
  or
- Tinidazole 2 g orally in a single dose
  or
- Tinidazole 1 g orally for 5 days
  or
- Clindamycin 300 mg orally twice daily for 7 days
  or

- Dequalinium chloride 10mg vaginal tablet one daily for 6 days

For BV, single dose therapies have lower cure rates than prolonged treatment. Oral metronidazole for 7 days has a significantly higher cure rate than single dose treatment (88% versus 54% [75] and 82% versus 62% [76] at 3-4 weeks after completion of therapy). Fourteen days of oral metronidazole compared with 7 days showed improved cure initially but there was no difference in cure rates 21 days after completion of therapy [77]. A systematic review of trials comparing clindamycin versus metronidazole concluded they have equal efficacy, whether oral or 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. 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). Combining 7 days of oral metronidazole with vaginal clindamycin cream did not improve the cure rate compared with 7 days oral metronidazole with placebo[78]. Vaginal dequalinium seems to have similar cure rates to vaginal clindamycin cream [79]. The effectiveness of metronidazole and clindamycin are the same, but the cost of oral metronidazole is significantly less than vaginal metronidazole which is less cheaper than clindamycin vaginal cream with dequalinium being the most expensive. Oral metronidazole has more side effects than the other treatments but post-treatment symptomatic candida is more common with intravaginal treatments.

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.

The Guidelines Group recommends that 5 to 7 days of topical or oral metronidazole or 7 days of intravaginal clindamycin can be considered first line for uncomplicated BV in women depending on personal choice and circumstances. Cost-effectiveness of the recommended regimens should be considered when adapting the guideline for local use.
Strength of recommendation: Grade 1, quality of evidence: Grade A.

Recurrent bacterial vaginosis

A longitudinal study of women, following treatment of BV with oral metronidazole for 7 days, reported BV recurrence rates of 23% at 1 month, 43% at 3 months and 58% at 12 months [80]. BV is associated with smoking and vaginal douching [81] but there is no evidence that stopping these reduces BV. Studies of consistent condom use have shown a 50% reduction in BV incidence; the combined oral contraceptive pill is associated with a 16% reduction and progestogen depot injections/implants are associated with a 19% reduction in BV Incidence [82]. Small studies have reported an increased incidence of BV with the copper intrauterine contraceptive device but it is not know what effect, if any, progestogen-containing levonorgestrel intrauterine system has on BV incence. Recurrence of BV is associated with a new or multiple male partners and having had a female partner.

A number of trials have evaluated intravaginal and oral therapies to reduce BV recurrences.

Intravaginal metronidazole

A placebo-controlled trial using twice weekly metronidazole vaginal gel or placebo for 16 weeks reported a significant reduction in BV recurrence. The relative risk at 16 and 28 weeks was RR 0.43 (95% CI 0.25-0.73) and RR 0.68 (95% CI 0.49-0.93) with 70% and 39%, and 34% and 18% of women being BV free at 16 weeks and 28 weeks respectively. Episodes of candidosis were more common with metronidazole gel [83]. Another placebo controlled trial assessed vaginal pessaries containing metronidazole 750mg plus miconazole 200mg with matched placebo for 5 nights per month for 12 months. The women were evaluated every two months and the proportion of visits with BV compared to placebo were 21.2% and 32.5%; RR 0.65 (95% CI 0.48-0.87). There was no increase in candidosis with the intervention [84].

Oral metronidazole

A placebo-controlled trial assessed the effect of monthly oral treatment (metronidazole 2g plus fluconazole 150mg) versus placebo for 12 months: the intervention reduced the incidence of BV (hazard ratio 0.55 (95% CI 0.49–0.63) [85].

Intravaginal lactate gel

In a small placebo-controlled trial of intravaginal lactate gel 5mls used for 3 days after menses for 6 months, 88% of women using the lactate gel were BV-free compared with 10% using placebo [86].

Probiotics

In a systematic review of probiotics for the treatment of bacterial vaginosis the authors concluded that the results do not provide sufficient evidence for or against recommending probiotics for the treatment of BV [87]. A subsequent meta-analysis concluded probiotic interventions were effective for treatment and prevention of BV but the quality of the studies varied[88]. More good quality research is needed to strengthen the body of evidence needed for application by clinicians.

The Guidelines Group recommends that the current best treatment for persistent and recurrent BV in women is intravaginal metronidazole.

Strength of recommendation: Grade 2, quality of evidence: Grade B.

Aerobic vaginitis/DIV

Indications for treatment of AV/DIV

In one study, 5% of women presenting with vaginal discharge had AV scores of 5 and over [8]. However, these were a very heterogeneous group and specific pathologies such as atrophic change, lichen planus and lichen sclerosus should be identified and treated appropriately.

Recommended regimens for AV

- 2% clindamycin cream 5g intravaginally for 7 - 21 days [8, 89]
- Combination use of intravaginal clindamycin and intravaginal steroids [89] e.g. Hydrocortisone 300–500 mg intravaginally for 7 - 21 days or Predfoam enema applied intravaginally (off-label use) for more severe cases
- In cases with a significant atrophy component, local oestrogens can be added

Clindamycin is active against staphylococci and streptococci as well as anaerobes. Other antimicrobials which are used with success in AV include kanamycin ovules or moxifloxacin.

The Guidelines Group recommends that the current best treatment for uncomplicated AV in women is clindamycin cream.
Strength of recommendation: Grade 2, quality of evidence: Grade C.

Vaginal candidosis

Indications for therapy of candidosis

- Symptomatic women found to have candida on either microscopy or culture.

Asymptomatic women do not require treatment
Asymptomatic male partners do not require treatment

Recommended regimens for vaginal candidosis [9,90,91]

Oral preparations include

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

Intravaginal treatments include

- Clotrimazole vaginal tablet 500mg as single dose 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

Treatment with azoles results in relief of symptoms and negative cultures among 80-90% of patients after treatment is completed, whether administered orally or intravaginally. 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 [92]. This does not affect relapse rates.
There are a number of other intravaginal preparations available which are all either azoles, of limited availability e.g. nystatin, or unlicensed. There is limited data to suggest that vulval treatment maybe of added benefit to intravaginal treatment [93]. 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.

The Guidelines Group recommends that the current best treatment for uncomplicated Candida in women is a single dose azole (oral or vaginal).
Strength of recommendation: Grade 1, quality of evidence: Grade A.

Recurrent candidosis

Defined as four or more symptomatic episodes per year [94-95]

- Document frequency, establish diagnosis and confirm by culture: all such women should have at least one speciated culture.
- Exclude risk factors (e.g. diabetes, underlying immunodeficiency, corticosteroid use, frequent antibiotic use
- Consider other diagnoses - vulval dermatitis/eczema/vestibulodynia are common either co-existing or as a differential diagnosis.

Maintenance therapy needs to be given frequently enough to prevent vaginal regrowth, but the optimal dosing interval is not clear. There are differing opinions on how aggressive maintenance therapy should be – weekly or monthly treatments [94,96] and comparative trials have not been undertaken. The long-term antifungal regimen aims to prevent two essential pathogenetic mechanisms: increased risk of recolonization and increased risk of transformation to a symptomatic state primarily as a function of pathologic host intolerance of the candida [97].

Current recommendations are for an initial intensive regime of fluconazole 150mg – 200mg daily for 3 days to attempt mycologic remission before initiating a maintenance regime. Published maintenance regimens include oral fluconazole (i.e., 100-mg, 150-mg, or 200-mg dose) weekly for 6 months [94] or 200 mg fluconazole weekly for 2 months, followed by 200 mg biweekly for 4 months, and 200 mg monthly for 6 months, according to the individual response to therapy [96]. If these regimens are not feasible, topical treatments used intermittently can also be considered.

Treatment of persistent vaginal yeast infection due to species other than *Candida albicans* is particularly challenging [98]. General advice includes the use of a vulval moisturiser applied to dry skin and washed off as a soap substitute. Ovulation suppressing progesterone contraception e.g. medroxyprogesterone acetate (Depo provera), nomegestrol or desogestrel, may have some benefits in particular women but the evidence for this is poor[99].

The Guidelines Group recommends that the current best treatment for persistent and recurrent Candida in women is a 3 day induction course of an azole followed by long term maintenance suppressive regime for at least 6 months.
Strength of recommendation: Grade 2, quality of evidence: Grade C.

Trichomonas vaginalis

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.

Indications for therapy of TV:

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

Recommended regimens for TV [100-102]
1st choice:

- Metronidazole 400 - 500 mg orally twice daily for 7 days

Alternative

- Metronidazole 2 gram orally in a single dose
  or
- Tinidazole 2 g orally in a single dose

The nitroimidazoles are the only class of drugs useful for the oral or parenteral therapy of trichomoniasis and most strains are highly susceptible. Due to high rates of infection of the urethra and paraurethral glands in women systemic chemotherapy should be given to effect a cure. The use of metronidazole gel is not recommended. Oral single dose treatment is associated with more frequent side effects than longer treatment and a recent meta-analysis [100] indicated higher treatment failure for single dose compared to multidose. In patients with true metronidazole allergy, desensitisation has been used. [103,104].

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

The Guidelines Group recommends that the current best treatment for uncomplicated TV in women is a 7 day course of oral metronidazole.
Strength of recommendation: Grade 1, quality of evidence: Grade A.

Persistent TV
Persistent or recurrent TV is due to inadequate therapy [105], re-infection, or resistance. Check for compliance and exclude vomiting of metronidazole and exclude the possibility of re-infection from new or untreated partners

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 400-500mg twice daily for 7 days - in those who failed to respond to a first course of treatment, 40% responded to a repeat course of standard treatment [105].

2. Higher dose course of nitroimidazole
    - Metronidazole or tinidazole 2g daily for 5-7 days [106]
    - Metronidazole 800mg three times daily for 7 days - in those who failed to respond to a second course of treatment, 70% responded to a higher dose course of metronidazole [105].

For those failing this 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 [105]. If resistance testing is not available high dose tinidazole regimens are recommended as in the above study 65% of women with clinical treatment 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 [106]. Tinidazole has a longer serum half-life, good tissue penetration, a better side-effect profile and lower levels of resistance than metronidazole. Tinidazole has become more difficult to source and is more expensive but should be used if available, when infections have not responded to metronidazole.

3. Very high dose course of tinidazole
    - Tinidazole 1g twice or three times daily, or 2g twice daily for 14 days +/- intravaginal tinidazole 500mg twice daily for 14 days [106-108] - in those who had failed other treatments 92% and 90% responded to a very high dose course of tinidazole.

If very high dose tinidazole has been unsuccessful it is difficult to recommend specific further treatment. 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.

The Guidelines Group recommends that the current best treatment for persistent and recurrent TV in women is repeated course of metronidazole at a higher dose.
Strength of recommendation: Grade B, quality of evidence: Grade B.

MANAGEMENT DURING PREGNANCY AND BREAST FEEDING

A recent retrospective, case-control study found an association between the use of a number of antibiotics prescribed in the first trimester of pregnancy and spontaneous abortion. Statistically significant associations were found with metronidazole. Clindamycin was not tested in this study. Sexually transmitted genital infections themselves can cause pregnancy loss so failure to treat them effectively may also result in spontaneous abortion. The associations found might result from women being prescribed the antibiotics for genital infections with the increased risk of pregnancy loss being due to the infections rather than the antibiotics i.e. confounding by indication [109].

Meta-analyses have concluded that there is no evidence of teratogenicity from the use of metronidazole in women during the first trimester of pregnancy [110-113]. Metronidazole can be used in all stage of pregnancy and during breast feeding. Symptomatic women with TV and BV 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 breastfeeding or if using a single dose of metronidazole, breastfeeding should be discontinued for 12-24 hours 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.

Topical azoles can be used at any stage of pregnancy for treatment of symptomatic candidosis. Oral fluconazole is associated with early abortions and Fallot tetralogy, if administered in the first weeks of pregnancy [114, 115]. There appears to be less risk with oral preparations after the first trimester.

The Guidelines Group recommends that the current best treatment for TV in pregnant women is metronidazole.
Strength of recommendation: Grade 1, quality of evidence: Grade A.

The Guidelines Group recommends that the current best treatment for BV in pregnant women is clindamycin.
Strength of recommendation: Grade 2, quality of evidence: Grade C.

The Guidelines Group recommends that the current best treatment for Candida in pregnant women are topical azole preparations.
Strength of recommendation: Grade 1, quality of evidence: Grade B.

MANAGEMENT OF SEXUAL PARTNERS

Bacterial vaginosis

A systematic review assessing the effectiveness of antibiotic treatment for male sexual partners of women treated for BV concluded that antibiotic treatment does not lead to a lower recurrence rate in the women [116]. Routine screening and treatment of male partners is therefore not indicated.

In women who have sex with women (WSW), regular female partners frequently have concordant vaginal microbiota so if one has BV the partner is more likely to also have BV. It is thought this is from sexual behaviours that transfer vaginal secretions between them [3]. If a WSW is found to have BV, and she has a regular female partner, it would be reasonable to suggest that her partner be checked for BV and be treated if positive although there is no evidence that this will reduce BV recurrences.

The Guidelines Group recommends that the current advice for women diagnosed with BV, is that male sexual partners do not require treatment. Female partners may be treated if they have BV.
Strength of recommendation: Grade 2, quality of evidence: Grade B.

Candidosis and aerobic vaginitis

Routine screening and treatment of male partner(s) is not indicated [117,118].

The Guidelines Group recommends that the current advice for women diagnosed with candidosis or AV, for their sexual partners is that partner treatment is not required.
Strength of recommendation: Grade 1, quality of evidence: Grade B.

Trichomoniasis

Current sexual partners should be screened for STIs and treated for TV regardless of the results of their tests [119,120]. 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).

The Guidelines Group recommends that the current advice for women diagnosed with TV, for their sexual partners is that they should be treated for TV.
Strength of recommendation: Grade 1, quality of evidence: Grade A.

FOLLOW-UP

Bacterial vaginosis

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.

Aerobic vaginitis

Women with persistent or recurrent symptoms.

Candida

Only in women with persistent or recurrent symptoms. Consider other diagnoses e.g. vulval dermatitis.

Trichomoniasis

Follow-up is unnecessary for men and women who become asymptomatic after treatment or who are initially asymptomatic. Tests of cure are only recommended if the patient remains symptomatic following treatment, or if symptoms recur.

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121.

Appendix 1

Review of the literature

An extensive literature review was performed using Medline for the years 2009 - 2017. MEDLINE search-keywords: vulvovaginal candidosis, 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 candidosis, vaginal candidosis, vaginal candida, *Trichomonas vaginalis* in women, bacterial vaginosis.

The 2015 US CDC guidelines for the treatment of Sexually Transmitted Diseases and the related UK national guidelines (www.bashh.org) were reviewed.

Tables of levels of evidence and grading of recommendations**:**
(see: http://www.iusti.org/regions/Europe/pdf/2017/ProtocolForProduction2017.pdf)

Appendix 2

Declarations of interests

Jackie Sherrard: JS has received consultancy fees from Becton Dickinson

Janet Wilson: JW has received speaker fees from BD Diagnostics; unconditional research grants in the form of diagnostic tests from Hologic; and remuneration for contract research from Starpharma.

Werner Mendling: WM declares in the last 3 years royalties by Aristo Pharma GmbH Berlin, Dr. August Wolff GmbH & Co. KG Arzneimittel Bielefeld, Dr. Kade Pharmazeutische Fabrik GmbH Berlin, Pierre Fabre Pharma GmbH Freiburg, SymbioPharm Herborn and Johnson & Johnson GmbH Neuss (all Germany), and Medinova AG Zurich/Switzerland

Gilbert Donders: received consultancy fees and/or speakers fees form Medinova, Alfa-Wasserman, Bayer, Phacobel and GSK.

Jørgen Skov Jensen: JSJ has received speaker fees from Hologic and SSI has received remuneration for contract research from Hologic, SpeeDx, NYtor, Diagenode, Nabriva, Angelini, GSK, and Osel