UK National Guideline for the management of Bacterial Vaginosis 2012

Clinical Effectiveness Group

British Association for Sexual Health and HIV

Guideline development group:

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What is new in the 2012 guidelines?

Advice on testing women for BV prior to termination of pregnancy

Introduction and methodology

Objectives

This guideline offers recommendations on diagnosis, treatment regimens and health promotion principles needed for the effective management of bacterial vaginosis (BV) covering the management of the initial presentation, and recurrence.

It is aimed primarily at women aged 16 years or older (see specific guidelines for those under 16) presenting to health care professionals working in departments offering level 3 care in STI management within the United Kingdom. However, the principles of the recommendations should be adopted across all levels - level 1 and 2 providers may need to develop local care pathways where appropriate.

Included in the guideline is a patient information leaflet (appendix 1)

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NHS Evidence has accredited the process used by the British Association for Sexual Health &HIV (BASHH) to produce UK national guidelines. Accreditation is valid for 3 years from January2011 and is retrospectively applicable to guidance produced using the processes described in the BASHH Framework for Guideline Development and Assessment dated September 2010.More information on accreditation can be viewed at www.evidence.nhs.uk

Search strategy

Four reference sources were used to provide a comprehensive basis for the guideline:

1. Medline and Embase Search

a.1948 – Aug 2011

The search strategy comprised the following terms in the title or abstract: 'bacterial vaginosis'. 5052 citations were identified.

2. 2010 CDC STD Treatment Guidelines (www.cdc.gov/std/)

3. 2011 European (IUSTI/WHO) Guideline on the Management of Vaginal Discharge

4. Cochrane Collaboration Databases (www.cochrane.org)

Methods

Article titles and abstracts were reviewed and if relevant the full text article obtained. Priority was given to randomised controlled trial and systematic review evidence, and recommendations made and graded on the basis of best available evidence.

Piloting and feedback

The initial draft of the guideline, including the patient information leaflet (PIL) was piloted for validation by the Clinical Effectiveness Group (CEG). A standardised feed back form was completed by each pilot site for the patient information leaflet.

The final guideline was then reviewed by the CEG using the AGREE instrument before posting it on the BASHH website for external peer review for a 3 month period. 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

Bacterial vaginosis (BV) is the commonest cause of abnormal discharge in women of childbearing age. The reported prevalence has varied from 5% in a group of asymptomatic college students to as high as 50% of women in rural Uganda. A prevalence of 12% was found in pregnant women attending an antenatal clinic in the United Kingdom (1), and of 30% in women undergoing termination of pregnancy(2).

Lactobacilli are the dominant bacteria in the healthy vagina. The pH is maintained below 4.5, and there are low levels of other bacteria. In BV the pH of vaginal fluid is elevated above 4.5 and up to 6.0. Lactobacilli may be present, but the flora is dominated by many anaerobic and facultative anaerobic bacteria, with concentrations up to a thousand-fold greater than normal. Conventional culture techniques identified *Gardnerella vaginalis*, *Prevotella spp*., *Mycoplasma hominis*, *and Mobiluncus spp*. as those most commonly found. Recent studies using molecular techniques have identified many other species including *Atopobium vaginalis, Clostridiales spp*. (BV 1-3), *Leptotrichia spp.*, *Sneathia spp.* (3). A biofilm consisting mainly of Gardnerella and Atopobium has been described more recently, implicating these two species as critical in the aetiology(4). There is debate about whether BV is merely an imbalance in vaginal ecology, or is initiated as a sexually transmitted infection (STI). Risk factors include vaginal douching, receptive cunnilingus, Black race, recent change of sex partner, smoking, presence of an STI e.g. chlamydia or herpes. However it has been described in virgins.

Clinical Features

Symptoms

- Offensive fishy smelling vaginal discharge
- Not associated with soreness, itching, or irritation
- Many women (approximately 50%) are asymptomatic

Signs

- Thin, white, homogeneous discharge, coating the walls of the vagina and vestibule.
- BV is not usually associated with signs of inflammation.

Complications

BV is not sexually transmitted but there are associations between BV, STIs and other genital infections.

- It has been linked with an increased risk of HIV acquisition in a prospective study of pregnant women(5).
- A study has shown a decrease in acquisition of Chlamydia in women treated for asymptomatic BV, but this study has limitations. (6)
- The prevalence of BV is high in women with pelvic inflammatory disease (PID), but in a prospective study BV was not predictive of subsequent PID, except in a sub-group of women with two or more concurrent partners(7) (level of evidence 11a). There are no prospective studies investigating whether treating asymptomatic women for BV reduces their risk of developing PID subsequently.
- BV is common in some populations of women undergoing elective termination of pregnancy (TOP)(2), and is associated with post-TOP endometritis and PID (level of evidence Ib)(8).
- In pregnancy BV is associated with late miscarriage, preterm birth, preterm premature rupture of membranes, and postpartum endometritis (Ib) (9-12).
- BV has been associated with an increased incidence of vaginal cuff cellulitis and abscess formation following transvaginal hysterectomy (III)(13), but it is unclear whether this is a problem in UK practice where many units administer perioperative antibiotics.
- There are no studies investigating the possible role of BV in the onset of PID following insertion of an intrauterine contraceptive device (IUCD).
- In one study BV was associated with NGU in male partners(14).

Diagnosis

Two approaches are available

• Amsel's criteria(15).At least three of the four criteria are present for the diagnosis to be confirmed.
(1) Thin, white, homogeneous discharge
(2) Clue cells on microscopy of wet mount

(3) pH of vaginal fluid >4.5
(4) Release of a fishy odour on adding alkali (10% KOH).

• A Gram stained vaginal smear, evaluated with the Hay/Ison criteria(16) or the Nugent criteria(17).

The Hay/Ison criteria are defined as follows:
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. Few or absent Lactobacilli.

There are additional grades which have not been correlated with clinical features: grade 0 No bacteria present; grade 4 Gram-positive cocci predominate.

The Nugent score is derived from estimating the relative proportions of bacterial morphotypes to give a score between 0 and 10. A score of <4 is normal, 4-6 is intermediate, and >6 is BV.

The Bacterial Special Interest group of BASHH recommend using the Hay/Ison criteria in genitourinary medicine clinics. (grade of recommendation C).

• Isolation of Gardnerella vaginalis cannot be used to diagnose BV because it can be cultured from the vagina of more than 50% normal women (IIa). In research studies a high concentration of Gardnerella vaginalis is associated with the presence of BV (IIa)(18).

Commercially available tests are available such as the OSOM BVBlue which measures sialidase levels, a prolineaminopeptidase test card (Pip Activity TestCard, Quidel, San Diego, California), and a DNA probe-based test that detects high concentrations of G. vaginalis (Affirm VP III, Becton Dickinson). These perform adequately when assessed against Amsel and Gram stain criteria. Detection of combinations of BV associated bacteria by PCR may offer highly sensitive and specific diagnosis in the future but is not yet available(19).

BV may co-exist with other causes of abnormal discharge such as candidiasis, trichomoniasis and cervicitis.

Management

General advice
Patients should be advised to avoid vaginal douching, use of shower gel, and use of antiseptic agents or shampoo in the bath (grade of recommendation C).

Treatment
Treatment is indicated for:

• Symptomatic women (A)

• Women undergoing some surgical procedures (A)

• Women who do not volunteer symptoms may elect to take treatment if Offered. They may report a beneficial change in their discharge following treatment. (C)

Recommended regimens

Metronidazole 400mg twice daily for 5-7 days (A)
Or
Metronidazole 2 g single dose (A).
or
Intravaginal metronidazole gel (0.75%) once daily for 5 days (A)
or
Intravaginal clindamycin cream (2%) once daily for 7 days (A)

Alternative regimens
Tinidazole 2G single dose (A).
Or
Clindamycin 300 mg twice daily for 7 days (A).

Rationale
All these treatments have been shown to achieve cure rates of 70-80% after 4 weeks in controlled trials using placebo or comparison with oral Metronidazole(9;20-23). Oral metronidazole treatment is established, usually well tolerated, and inexpensive (Ia). Dosage and duration used in trials have varied from 400 mg twice daily for 5 days to 500 mg twice daily for 7 days. The 2 g immediate dose may be slightly less effective at 4 week follow up(24) (Ib).
Intravaginal metronidazole gel and clindamycin cream have similar efficacy (Ib), but the latter is more expensive. Theoretically, metronidazole has an advantage because it is less active against lactobacilli than clindamycin. Conversely, clindamycin is more active than metronidazole against most of the bacteria associated with BV. Oral

clindamycin has only been evaluated in one study with short term follow up(25), and in pregnant women (Ib, IIa)(26;27). It is more expensive than metronidazole. Tinidazole has similar antibacterial activity to metronidazole *in vitro*, and efficacy was equivalent but is also more expensive(28).

Non-antibiotic based treatment with probiotic lactobacilli or lactic acid preparations have not yielded consistently reproducible evidence of efficacy as treatments for BV and no recommendation on their use can be made at present(29).

Caution
• With metronidazole treatment alcohol should be avoided because of the possibility of a disulfiram-like action. There are no data on the risks from consuming alcohol with intravaginal metronidazole gel, but it is not recommended at present.
• Clindamycin cream can weaken condoms, which should not be used during such treatment. Pseudomembranous colitis has been reported with both oral clindamycin and clindamycin cream(30) (21).

Allergy
Allergy to metronidazole is uncommon. Use 2% clindamycin cream for metronidazole allergic women.

Pregnancy and breast feeding
Meta-analyses have concluded that there is no evidence of teratogenicity from the use of metronidazole in women during the first trimester of pregnancy (Ia)(31-33).
The results of clinical trials investigating the value of screening for and treating BV in pregnancy have been conflicting. It is therefore difficult to make firm recommendations. A detailed discussion of trials in pregnancy is outside the scope of this guideline. The most recent Cochrane review concluded that there is little evidence that screening and treating all pregnant women with asymptomatic BV will prevent preterm birth and it consequences. However there is some suggestion that treatment before 20 weeks gestation may reduce the risk(34).
In conclusion:

- Symptomatic pregnant women should be treated in the usual way (B).
- There is insufficient evidence to recommend routine treatment of asymptomatic pregnant women who attend a G-U clinic and are found to have BV.
- Women with additional risk factors for preterm birth may benefit from treatment before 20 week gestation.

Metronidazole enters breast milk and may affect its taste. The manufacturers recommend avoiding high doses if breast feeding. Small amounts of clindamycin enter breast milk. It is prudent therefore to use

an intravaginal treatment for lactating women (C).

Termination of pregnancy (TOP)
Three studies have investigated whether antibiotics can reduce the rate of infectious morbidity in women with BV, following termination of pregnancy. A Scandinavian study of 231 women demonstrated a reduction in post-TOP infection by treating BV with oral metronidazole before termination (Ib)(8). Another demonstrated a reduction in infective complications following the use of clindamycin cream (Ib)(35). A UK study of 273 women again found a reduction in post-operative upper genital tract infection from 16% to 8.5%, but did not quite reach statistical significance(36). There are no data on the effectiveness of treatment administered at the time of TOP.

- These studies support screening for and treating BV with either metronidazole or clindamycin cream, to reduce the incidence of subsequent endometritis and PID (Ia).

HIV Infection
Women with HIV have not been shown to respond differently to treatment for BV than those without. In an as yet unpublished study BV was a risk factor for female to male HIV transmission (adjusted OR 3.06, 1.35-6.95) so there may be rationale for attempting to suppress BV or treat recurrence rapidly in discordant couples(37).

Sexual partners

- No reduction in relapse rate was reported from two studies in which male partners of women with BV were treated with metronidazole, one study of tinidazole, and one of clindamycin(21;38)(Ib). Routine screening and treatment of male partners are therefore not indicated.

- Two studies reported a high incidence of BV in female partners of lesbians with BV (II)(39;40). No study has investigated the value of treating the female partners of lesbians simultaneously.

Follow up
A test of cure is not required if symptoms resolve.

Recurrent bacterial vaginosis
Several published studies have evaluated treatments for women with frequent recurrences of BV.

- Suppressive 0.75% metronidazole vaginal gel. In one placebo controlled randomized trial 0.75% metronidazole vaginal gel twice a week for 16 weeks was superior to placebo with 70% of women being relapse-free compared to 39% in the placebo group(41). However, only 34% of patients remained cumulatively free of recurrence 12 weeks after stopping treatment, compared to 22% of controls. There was an excess of

vulvovaginal candidosis in those receiving metronidazole: 43% compared to 21%. (p=0.02)

• Probiotic therapy.
A double blind RCT of probiotic lactobacilli applied daily on days 1 -7 and 15 -21, in 117 women showed significantly lower recurrence rates over the ensuing two months in women with at least two episodes of BV in the preceding year: BV (15.8% [9/57 women] vs. 45.0% [27/60 women]; P . .001)(42).

Antibiotics and probiotic therapy
A Swedish study of 76 women whose BV resolved following a course of clindamycin cream were randomised to receive human lactobacilli or placebo(43). At the end of the study, 65% (24/37) of the lactobacilli treated women remained BV-free compared to 46% (18/39) of the placebo treated women.

• Lactic acid gel and acetic acid gel (the latter is no longer available in the UK) have not been evaluated adequately in well designed RCTs.

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General advice

• A detailed explanation of bv should be provided, reinforced with clear and accurate written information (Grade C [IV]). A patient information leaflet is included in appendix 1 of this guideline.

When giving information to patients, the clinician should consider the following:

• an explanation of what treatment is being given, how to take it, and its possible adverse effects

• that following treatment BV can recur, but will respond to standard treatments.

• Partners do not need to be screened routinely. Some clinicians recommend screening male partners of women with recurrent BV for urethritis, as it was associated with BV in one study (14)

Further Investigation

Routine STI screening should be offered in accordance with current testing guidelines.

Auditable Outcome Measures

Appropriate short term audit outcomes include:

- Interpretation of Gram-stained smear in clinical practice. Review results initially reported with those from a consensus of experienced slide readers.

- Screening or treatment of women planning termination of pregnancy. This should also include testing for *Chlamydia trachomatis* (see guideline).

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.

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.

D. Phillip Hay has received payment for research conducted in his unit, sponsorship to attend conferences, fees for consultancy from Bayer pharmaceuticals PLC, BBI Healthcare, Unipath, Pharmacia and Upjohn, 3M pharmaceuticals.

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