

CLINICAL KNOTS

Managing recurrent bacterial vaginosis

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Bacterial vaginosis (BV) is the most frequently found condition of the female genital tract. It increases a woman's risk of acquiring HIV, is associated with increased complications in pregnancy, and may be involved in the pathogenesis of pelvic inflammatory disease. Yet there are many unanswered questions about its aetiology, making management of recurrent infection difficult and often idiosyncratic. This paper discusses the current knowledge and possible management of recurrent BV.

linked BV with sexual behaviour; a recent change of sexual partner,⁷ and multiple partners compared with one partner¹⁰ increasing the risk. The increase in BV in women with new sexual partners was independent of frequency of intercourse, suggesting exposure to a new partner is a more important risk factor than the number of episodes of intercourse.^{7–10} These findings lead onto the next question about aetiology.

AETIOLOGY

Are frequent episodes of BV the result of re-infection or relapse? If it is re-infection what are the pathogens and is it related to behaviour of the women or her sexual partner? If it is relapse what triggers the disruption in the flora? The link with sexual behaviour suggests that BV is sexually transmitted and that further episodes are due to re-infection. Yet treatment of the sexual partner demonstrates no benefit in terms of recurrence rates in women. Five out of six trials, using oral metronidazole, tinidazole, or clindamycin to treat the male partner showed no benefit for the women.¹¹ These findings do not support the theory of sexual transmission and re-infection.

A study looking at risk factors for repeated episodes of BV suggests they are due to relapse. Cook *et al* studied 13 women with recurrent BV over a 9 month period, and compared them with a control group of 31 women with no current, or history of, BV.¹ There were 31 episodes of BV during the study period and each was treated with metronidazole 500 mg twice daily for 7 days. Complete clinical and microscopic cure occurred in only 23% of the episodes, in 61% there was an improvement, but in 16% there was clinical failure. Following treatment, raised vaginal pH was present in 65%, positive amine whiff test in 15%, and abnormal Gram stained flora in 24%. Anaerobic Gram negative rods were isolated from 19% of the women post-therapy compared with 3% of the control group. Women who developed early recurrence tended to complain of an abnormal discharge at the end of therapy. Some asymptomatic women considered themselves cured after treatment, but they continued to have significant abnormalities of vaginal flora, the more severe the abnormality the earlier the recurrence. These findings support the theory of relapse.

The exact mechanism for the onset of BV remains a mystery. It is associated with a reduction in lactobacilli (LB) and hydrogen peroxide production, a rise in the vaginal pH, and the overgrowth of BV associated organisms (see fig 1). But which of these happens first, and which is the most important? If we knew the

Bacterial vaginosis is characterised by a thin homogeneous white discharge, a vaginal pH of greater than 4.5, a positive amine test, and the presence of clue cells microscopically. There is also a change in vaginal flora from the normal lactobacilli (LB) dominant to flora with greatly reduced numbers of LB and an overgrowth of *Gardnerella vaginalis*, *Mycoplasma hominis*, and anaerobic bacteria such as peptostreptococci, *Prevotella* spp, and *Mobiluncus* spp. There is no universally accepted definition of recurrent bacterial vaginosis, but in the few publications on the topic the definition used is three or more proved (clinically by Amsel's criteria or microscopically) episodes of BV in 12 months.^{1–2}

A search was performed using Dialog DataStar for articles published between 1966 and September 2003, using the keywords bacterial vaginosis, recurrent bacterial vaginosis, vaginal pH, vaginal lactobacilli, probiotics, and bacteriotherapy.

Frequency of recurrent BV

Treatment trials report cure rates of 80–90% at 1 week, but recurrence rates of 15–30% within 3 months.³ In a study of long term follow up of women who had been successfully treated for BV, 48% remained BV free, and 52% had at least one further episode.⁴ The mean follow up was 6.9 years. Most relapses were during the first year and were significantly correlated with new sexual contacts.⁴ So following successful treatment, half of women will stay cured for years.

Predisposing factors

Several factors are known to increase the risk of BV, including younger age,⁵ black ethnicity,⁶ douching,⁷ smoking,⁸ and the IUD as contraception.⁹ The studies on douching and IUD use were longitudinal studies of incidence, so women with recurrent BV may benefit from stopping douching, and changing their method of contraception if they have an IUD. Many papers have

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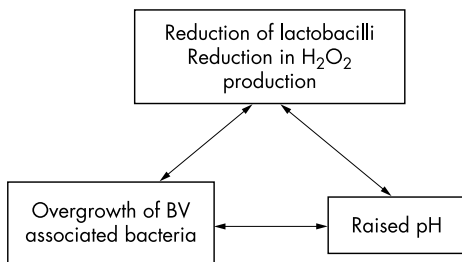


Figure 1 The inter-relationship between lactobacilli, vaginal pH, and bacterial overgrowth in the aetiology of BV.

answers to these questions, we could use this knowledge to try to prevent further recurrences of BV.

Reduction in lactobacilli and hydrogen peroxide production

The main hydrogen peroxide producing strains of lactobacilli (LB+) are *L crispatus* and *L jensenii*.¹² The presence of these has been positively associated with being white, aged over 20 years, using barrier contraception, and low frequency of BV and gonorrhoea.¹² A cohort study showed that lack of LB+ gave a twofold risk of acquiring BV and no LB gave a fourfold risk.⁷ Klebanoff *et al* showed in vitro that combining myeloperoxidases with hydrogen peroxide and a halide produced a potent oxidant, which was toxic to BV associated bacteria.¹³ Myeloperoxidase activity has been found in vaginal fluid and cervical mucus, and chloride is present in cervical mucus in amounts in excess of that required for this system. In vitro testing showed LB+ in high concentration (but compatible with the levels found in the vagina) were toxic to *G vaginalis* and *Prevotella bivia*. This toxicity was inhibited by catalase indicating that hydrogen peroxide was the toxic agent. When the concentration of LB+ was lowered so that growth of the bacteria was not inhibited the addition of myeloperoxidase and chloride reinstated the toxicity.¹³ The toxic effect of this LB+/myeloperoxidase/chloride system was rapid, with reduction in numbers of *G vaginalis* at 15 minutes and complete loss of viability at 60 minutes.

It is not known what causes the reduction in LB+ in BV. Pavlova *et al* suggest that as BV associated organisms are sensitive to lactic acid and hydrogen peroxide, suppression of LB must come before overgrowth of BV associated bacteria. Phage mediated lysis of LB may cause such a reduction. Phages from one woman can infect LB from a different woman so they could be the sexually transmitted agent,¹⁴ which would explain the lack of benefit of treatment of the male partner with antibiotics.¹¹

However, some studies suggest that LB may not totally protect against BV. A study in pregnant women revealed that 63% with BV had LB+ isolated from the vagina, yet despite these they still had BV. Rosenstein *et al* suggest that abnormal bacteria start to appear and increase before disappearance of LB+, and that BV may develop in some women despite the presence of hydrogen peroxide producing LB.¹⁵ This suggestion is supported by another study of women with BV where 33% had LB present at days 1–5 of the menstrual cycle, rising to 54% at days 19–24.¹⁶ It is known that broad spectrum antibiotics reduce the numbers of LB.¹⁷ If reduction in LB was the initiating factor for BV, broad spectrum antibiotics should predispose to BV, and yet this has not been described.

Change in pH

The low pH of the vagina is attributable to production of lactic acid by LB metabolism, and by the conversion of glycogen to lactic acid by oestrogenised vaginal epithelial cells.

In vitro LB acidify their growth medium to a pH of 3.2–4.8 (that is, similar to normal vaginal pH). At that pH a steady state of equilibrium develops where the acidity becomes autoinhibitory. Anaerobes grow poorly at pH 4.5 or less; the optimum pH for *Prevotella* spp and *G vaginalis* growth is 6–7. In vitro studies show that the concentrations of these bacteria increase with increasing pH, but both are susceptible to low pH.¹⁸ McClean and McGroarty found that lactic acid and low pH had a greater inhibitory effect on *G vaginalis* than hydrogen peroxide.¹⁹ The in vitro experiments by Klebanoff *et al* showed that the LB+/myeloperoxidase/chloride system had maximum toxicity at a pH of between 5 and 6, with inhibition falling as pH increased beyond 6. This suggests that pH has an additional effect to the LB+/myeloperoxidase/chloride system. At pH 4.5, the growth of *G vaginalis* was inhibited, and the addition of LB+ produced no extra inhibition. The LB+/myeloperoxidase/chloride system did have some additional inhibitory effect on growth, but less so than at pH 5–6 when there was a highly significant reduction in *G vaginalis*.¹³ One interpretation of these findings is that at pH 4.5 or less the LB+/myeloperoxidase/chloride system is less important as the low pH produces an inhibitory effect on bacterial growth. However, at times of a rise in vaginal pH, such as after sex and during menses, when bacterial overgrowth could occur, the LB+/myeloperoxidase/chloride system rapidly kicks in to inhibit bacterial growth.

A low pH also appears to be important for LB adherence to the epithelial cells. In vitro testing showed at pH of 4.4, a mean of 5.5 LB adhered per vaginal cell, compared with 1.4 at pH of 6.2.²⁰

Overgrowth of BV associated organisms

The initial work by Gardner and Dukes showed that BV can be produced by inoculating BV associated bacteria into a healthy vagina. *G vaginalis* alone caused BV in only one of 13 women, but when vaginal secretions from women with BV were inoculated 11 of 15 women developed BV.²¹ This suggests that the inter-relationship between the different groups of bacteria is important for overgrowth. *P bivia* and *G vaginalis* have a symbiotic association. Growth of *G vaginalis* is enhanced by ammonia which is produced by *P bivia*. Amino acids are produced during *G vaginalis* growth, which are stimulatory to the growth of *P bivia*.²² It is therefore possible that the symbiotic relationship between these bacteria is because the byproducts of metabolism of one fuel the growth of the other.

A microbiological study throughout the menstrual cycle showed that in women with or without BV the rate of recovery of LB increased over the cycle and the concentration of non-LB species was higher at menses, suggesting instability of the vaginal flora at that time with the potential for bacterial overgrowth.¹⁶

THERAPEUTIC OPTIONS TO PREVENT BV RECURRENCES

What therapeutic options do we have to manage or try to prevent further recurrences of BV?

Bacteriotherapy

Bacteriotherapy, using harmless bacteria to displace pathogenic organisms is considered “natural” and without any side effects, but there is lack of efficacy data with few randomised controlled trials (RCT). The LB used need to be able to adhere to vaginal epithelial cells, and to produce hydrogen peroxide. If given orally the LB need to pass through the intestinal tract and ascend from the perianal area into the vagina.

There have been several publications of attempts to restore vaginal flora by recolonising with LB using both intravaginal and oral administration. However, the LB used have not been

vaginal strains. LB strains from yoghurt adhere less well to vaginal cells than clinical isolates. In a double blind RCT looking at LB as a treatment for BV, vaginal pessaries containing *L acidophilus* were used for 6 days. With active therapy 57% of women cleared their infection compared with 0% of those given placebo, but only three remained BV free after menstruation.²³ It was thought there was a problem with LB adherence. One group of researchers has published case reports and small case series of vaginal and oral LB replacement. They report successful vaginal colonisation following administration by both routes.^{24,25} This group have recently published a RCT of oral capsules of *L rhamnosus* GR-1 and *L fermentum* RC-14 for 60 days. Microscopy showed restoration to normal flora from asymptomatic BV in 37% women receiving LB treatment compared with 13% receiving placebo. This significant improvement in vaginal flora was also accompanied by a significant increase in LB at day 60.²⁶ These results are encouraging but we do not know if the non-vaginal LB will remain in the vagina to protect against further episodes of BV. A RCT of oral *Lactobacillus* GG drink for the prevention of recurrent urinary tract infection (UTI) showed no reduction in UTIs over 12 months.²⁷ The principles of UTI prevention by this method are similar to that of BV prevention—that is, LB replacement to protect against bacterial overgrowth, so it is unlikely that oral *Lactobacillus* GG would be beneficial for BV prevention. In a study looking at mechanisms of LB blockage of uropathogen adherence to vaginal epithelial cells, *L crispatus* showed greater capacity to block uropathogen adherence than other LB.²⁸ A study looking at sustained vaginal colonisation of LB showed 40% of women remained colonised with *L crispatus* and *L jensenii* for over 8 months compared with 5% of women colonised with other LB spp indicating better ability to adhere to vaginal cells.¹⁷ There is currently a RCT using vaginal pessaries containing *L crispatus* to attempt to recolonise the vagina with LB (S Hillier, personal communication). This is the first study of replacement with one of the main vaginal hydrogen peroxide producing LB.

Maintaining vaginal pH at 4.5

The main goal of therapy here is to keep the vaginal pH at 4.5 or less, in order to prevent overgrowth of pathogens until the normal LB are re-established and able to maintain the pH themselves. In a RCT of 42 women with recurrent BV using intravaginal lactate gel to try to prevent BV recurrences, 17 women used lactate gel for 3 days immediately after menstruation for 6 months, the remainder used placebo. The 6 months on-treatment analysis showed that 88% were clear of BV with active treatment compared with only 10% with placebo. Intent to treat analysis at 6 months showed 71% were clear with treatment and 4.8% were clear with placebo.²⁹ The treatment was well tolerated but there was a large dropout rate, particularly in the placebo arm because of malodour. The authors suggested more intensive treatment might have improved this.

Preventing overgrowth of BV associated organisms

Although intermittent therapy, on an episodic or prophylactic basis, is frequently used for recurrent BV, there are very few publications on this. Hay *et al* advised women with recurrent BV to collect daily vaginal specimens for between 1–12 months, to try to identify the times of recurrence. BV recurrences most often arose within the first 7 days of the menstrual cycle, and frequently followed candida infection.² Consequently they advised oral or intravaginal metronidazole for 3 days at the onset of menstruation for 3–6 months, and add antifungal treatment if there is a history of candidiasis.³⁰

Better treatments and/or combined treatments

Using oral or vaginal preparations of metronidazole and clindamycin, 80–90% of women will have an initial response to treatment but 15–30% will get a recurrence within 3 months.³ In women with recurrent BV the initial response rate appears to be lower.¹ The heterogeneity of microorganisms involved in BV may contribute to treatment failure and high recurrence rates. Clindamycin has better activity against *M hominis*, *Mobiluncus* spp, and *G vaginalis* than metronidazole, but metronidazole has the advantage of not affecting LB. In trials comparing treatments, cure rates for metronidazole 400 mg or 500 mg twice daily for 7 days have been equivalent to clindamycin vaginal cream daily for 3–7 days, and to metronidazole vaginal gel once or twice per day for 5 days.³¹ In the absence of better treatments would women with recurrent BV benefit from longer courses of current treatment? This question remains unanswered.

In view of the association between lactobacilli, hydrogen peroxide production, vaginal pH, and overgrowth of BV associated bacteria, just trying to adjust one of these may help some women with recurrent BV, but it may not be enough to resolve all cases. Would a combined approach work better? There are very few publications on this, but they do suggest that the answer might be yes. A small study using single dose oral metronidazole followed by vaginal lactate tablets compared to no vaginal maintenance treatment reported an improved rate of normal vaginal flora of 94% compared to 71%.³² Another small study compared tinidazole 2 g single oral dose followed by acidic vaginal gel for 3 weeks with 2% clindamycin vaginal cream 5 g per night for 7 nights. At 4 weeks the clinical cure rate was 94% versus 77%. The vaginal pH was <4.5 in 78% and 38% respectively.³³

CONCLUSIONS

There is an important inter-relation between lactobacilli, hydrogen peroxide production, vaginal pH, and overgrowth of BV associated bacteria, but the initiating factor for BV remains a mystery. From current evidence it appears that a rise in vaginal pH allowing the overgrowth of bacteria may be more important than reduction of LB+. However long term

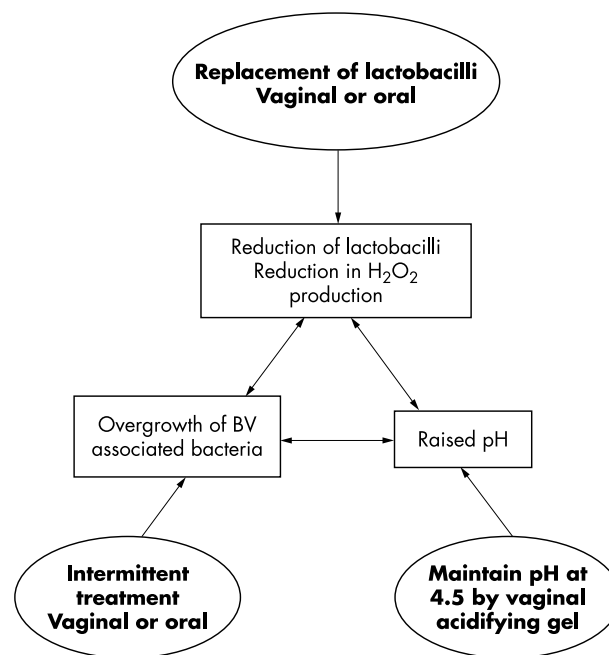


Figure 2 The therapeutic options in the prevention of BV: a combined approach might work better.

colonisation with LB+ is necessary to help maintain an acidic pH and support the LB+/myeloperoxidase/chloride system. Therapies aimed at one aspect of this inter-relation may help some women with recurrent BV, but a combined approach might work better. Probably the ideal way of managing recurrent BV would be to tackle all aspects of the inter-relation by replacing the lactobacilli, at the same time maintaining the vaginal pH at 4.5, and if necessary also adding in prophylactic treatment to control overgrowth of bacteria (see fig 2). If the current RCT of vaginal LB+ replacement proves successful this approach may soon be possible.

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