

TREATMENT OF VAGINAL INFECTIONS WITH LACTOBACILLI: A CLINICIANS REVIEW

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SUMMARY

Bacterial vaginosis (BV) and vaginal candidosis are the most common diagnoses in women with symptoms from the lower genital tract. Treatments with antibiotics and antifungals are effective but are impaired by side effects. A considerable number of women suffer recurrences and have a need for alternative treatments.

Treatment of vaginal ailments with lactobacilli has a long tradition. Published reports indicate that BV and candidosis may be treated with lactobacilli but additional studies on the microbiology of lactobacilli as well as further clinical investigations are needed to elucidate all aspects of such treatments.

INTRODUCTION

Symptoms from the lower genital tract like dysuria, itching and discharge are common in women attending outpatient clinics. Most often they are caused by a vulvo-vaginal infection (Komaroff et al., 1978). There are three common causes for vulvo-vaginal infections in women of childbearing age: candidosis, bacterial vaginosis (BV) and trichomoniasis. The relative frequencies of these infections differ considerably between and also within countries depending on the clinical situation. Since treatment of vaginal infections with lactobacilli has been reported only for candidosis and bacterial vaginosis this review will deal only with these infections.

The diagnosis and treatment of vaginitis has recently been reviewed (Sobel, 1997). Standard treatment of vaginitis is with antimicrobials or antifungals. In most clinical situations they perform perfectly. However they are not

without complications. Moreover some women suffer from frequent recurrences (Sobel, 1997). In some clinical settings there seems to be an increasing number of women with recurrent vaginal candidosis (Hallén, 1998). Some of these women encounter problems with repeated treatments. There is also an emerging problem with resistance to azole antifungals in *Candida* strains (Hallén et al., 1998). Particularly in these women there is a need for alternative treatments. With the increasing public awareness of the drawbacks of antibiotic treatments many women demand alternative cures.

Treatment of vaginal infections with lactobacilli has a long tradition starting with Döderlein's descriptions of the vaginal flora (Döderlein, 1892). The interest in this option has increased during the last ten years (Redondo-Lopez et al., 1990; Reid et al., 1990; McGroarty, 1993; Elmer et al., 1996).

Over the years there are a considerable number of reports published on treatment of vaginal infections with different forms of lactobacilli (Mohler and Brown, 1933; Butler and Beakley, 1960; Spitzbart, 1968; Gunston and Fairbrother, 1975; Collins and Hardt, 1980; Gerstner and Müller, 1987). With

today's conception of vaginal infections these studies are of very limited value for the clinician. Information on diagnostic criteria used is lacking or diagnoses are very ill defined and the different kinds of lactobacilli used are most often not characterised in any way.

TREATMENT OF CANDIDOSIS

There are two clinical studies published on the treatment and prophylaxis of vaginal candidosis. Both used commercial yoghurt orally ingested as active treatment.

Hilton and co-authors (1992) designed a crossover study for one year including 33 patients with recurrent vaginal candidosis (≥ 5 episodes per year; eight are called chronic infections). They were supposed to start either in the active arm with eight ounces of yoghurt daily for six months and then switch to a yoghurt free diet during the remaining six months or vice versa. However the protocol had to be amended due to dropouts (12 protocol violations and two with other infections) but mainly because women in the active arm refused to switch over to yoghurt free diet. Finally only 13 women, aged 24 to 50 years, completed the study and 11 of these started on the control arm. There were no diabetics among the patients.

The yoghurt used contained $>10^8$ *Lactobacillus acidophilus* per ml. The lactobacilli showed "moderate production" of H_2O_2 .

The primary efficacy variable was the number of infections on either study arm and this difference was significant: 0.38 ± 0.51 in the active arm compared to 2.54 ± 1.66 . There was also a significant difference in favour of active treatment in the number of cultures positive for *Candida*: 0.84 ± 0.90 and 3.23 ± 2.17 respectively.

The study also reported a higher

number of vaginal cultures positive for lactobacilli when there were simultaneously lactobacilli in stool. Whether this was the *Lactobacillus* given in the yoghurt is not stated.

One basic objection to this study is the lack of a placebo arm. Shalev and co-authors (1996) address this aspect in their study. The design was a blinded cross over study with one group of women eating 150 ml yoghurt with *L. acidophilus* daily for two months, followed by a two month wash out period and finally two months with pasteurised yoghurt. In the other arm the order was reversed.

The active treatment was a commercial yoghurt containing $>10^8$ CFU *L. acidophilus* per ml. It is uncertain whether any H_2O_2 producing capacity was verified.

The study included 46 women: 20 with BV, 18 with candidosis and eight women had both conditions simultaneously. Only seven women completed the full protocol and data are only given for the first four months of the study. At the visits after three and four months treatment only 22 and 17 women respectively attended. There are no data telling the initial diagnoses in these women.

With respect to *Candida* there was a reduction in the number of positive vaginal cultures in the first two months irrespective of treatment. 60% were culture positive at inclusion and this was reduced to 28% after two months. The

number of clinical recurrences was also unaffected by treatment. In the seven women who completed the protocol there were three episodes of vaginitis in

14 visits in the yoghurt period compared to five episodes in 14 control period visits.

TREATMENT OF BACTERIAL VAGINOSIS

The hallmark of BV is the absence of lactobacilli. Consequently the idea of treating the condition with lactobacilli is compelling.

In a letter in *Lancet* *Fredricsson* and co-workers (1987) reported on treatment of BV with four different modalities. They included 61 women with BV in an open randomised study, treating them for one week with two daily doses of respectively 5 ml 0.92% v/v acetic jelly (Aci-Jel®), 5 ml Dienoestrol® cream, 5 ml yoghurt with *L. acidophilus* or 500 mg metronidazole. Thirteen of the 14 women treated with metronidazole were cured at control after four weeks compared to only one of the 14 yoghurt treated.

Hallén and co-authors (1992) performed a double blind, placebo controlled study with local treatment of BV with lyophilised H₂O₂ producing *L. acidophilus* of human origin (Vivag®, Pharma-Vinci A/S, Denmark). The vaginal capsules contained 10⁸ to 10⁹ CFU of lactobacilli. Treatment was with one capsule twice daily for six days. Sixty women with BV were included; there were three dropouts. The first control was immediately after treatment when 12 out of 28 (43%) actively treated women had normal findings compared to none of the placebo treated. Protocol design indicated treatment with metronidazole to patients with persistent BV so no relevant comparisons can be done from visit number two, performed after the next menstrual period. However 14 of the actively treated returned and 11 of these had relapsed into BV. Of the Vivag® treated women, 93%

had *Bacteroides* at inclusion and this was reduced to 35% after treatment. Whether the lactobacilli in the vagina were the strain from the vaginal capsules was not investigated.

Neri et al (1993) compared *L. acidophilus* with acetic acid in the treatment of BV in 64 pregnant women. This was an open randomised study and the women were given two daily doses for seven days of either 10-15 ml of yoghurt with *L. acidophilus* (>10⁸ CFU/ml) or a vaginal tampon soaked with 10-15 ml of 5% acetic acid. The yoghurt was introduced into the vagina with a syringe. There was also a control group of 20 women who refused treatment of their BV.

Outcome was significantly better for women treated with yoghurt compared to both acetic acid and no treatment. Twenty-eight of yoghurt treated women were free from BV one and two months after treatment compared to 12 at each visit in the acetic acid group and three and one in the control group.

In a placebo-controlled, randomised three-centre study *Parent* and co-workers (1996) investigated a vaginal tablet containing H₂O₂ producing *L. acidophilus* and 0.03 mg estriol (Gynoflor®, Medinova Ltd). They included 17 women in the active group (six pregnant) and 15 in the placebo group (2 pregnant). There were two different dosings in each group, one or two vaginal tablets daily. Since there were no differences in the outcome measures irrespective of treatment data were pooled. Of 32 included 25 returned for the first control after one

week and only 17 to the control after three weeks.

Active treatment was significantly better: 77% were free from BV at the first control and 88% at the second compared to 25% and 22% respectively in the control group.

The study by *Shalev et al* (1996) mentioned earlier also included a number of women with BV, although the outcome in the BV group is not reported separately. However, 20 women with BV were included and eight with con-

comitant BV and candidosis. During active treatment the percentage of women with BV was significantly reduced from 55% at inclusion to 25% after one month and only 10% after two months. In the placebo group the number decreased from 50% to 40%. In the seven patients completing the protocol there was only one episode of BV during active treatment compared to six of them having one or two BV episodes during the period with pasteurised yoghurt.

DISCUSSION

To the clinician the treatment of vaginal infections with lactobacilli is an area filled with questions. One basic problem is knowing the composition of the normal flora of lactobacilli in different ecological niches. And do these lactobacilli differ in aspects that are relevant to the clinician?

Information so far seems to indicate that treatment with lactobacilli might be useful in the treatment of candidosis and BV. However the reports published are weak evidence. Patient numbers are small, attrition rates often very high and it is often difficult to deduce from the reports what really happened with patients in different diagnostic groups. Furthermore lactobacilli used are poorly defined and it is never verified whether the lactobacilli used for treatment ever colonised the vagina.

There are also reports on different strains of lactobacilli producing antimicrobial substances. Whether these lactobacilli might be better candidates for

treatment, possibly in different clinical situations, is still not investigated.

So we really do not know whether lactobacilli work. What strains should we use? For what diagnoses? Should we use them for treatment or for prophylaxis?

It is also necessary for the microbiologists to help the clinicians investigate and define products with lactobacilli. The paper by *Hughes and Hillier* (1990) demonstrated that commercial products might contain no lactobacilli whatsoever or be contaminated with other bacteria.

In my opinion clinicians need alternatives to the well-defined antimicrobials and antifungals we have access to. Particularly for patients with recurrent symptomatic BV and chronic candidosis we urgently need additional treatment options to be able to better address these difficult clinical situations. More investigations are needed to prove the position for lactobacilli in this area.

LITERATURE

Butler, B.C. and Beakley, J.W.: Bacterial flora in vaginitis. A study before and after treatment with pure cultures of Döderlein's bacillus. *Am. J. Obst. Gynec.* 79: 432-440

(1960).

Collins, E.B. and Hardt, P.: Inhibition of *Candida albicans* by *Lactobacillus acidophilus*. *J. Dairy Sci.* 63: 830-832 (1980).

- Döderlein, A.: Das Scheidensekret und seine Bedeutung für das Puerperalfieber. Leipzig, (1892).
- Elmer, G.W., Surawicz, C.M., and McFarland, L.V.: Biotherapeutic agents. A neglected modality for the treatment and prevention of selected intestinal and vaginal infections. *JAMA* 275: 870-876 (1996).
- Fredricsson, B., Englund, K., Weintraub, L., Ölund, A., and Nord, C-E.: Ecological treatment of bacterial vaginosis. *Lancet* i: 276 (1987).
- Friedlander, A., Druker, M.M., and Schachter, A.: *Lactobacillus acidophilus* and vitamin B complex in the treatment of vaginal infection. *Panminerva Med.* 28: 51-53 (1986).
- Gerstner, G.J. and Müller, G.: Intravaginale lyophilisierte Laktobazille zur Therapie des "unspezifischen" Fluor vaginalis. *Gynäk. Rdsch.* 27: 71-78 (1987).
- Gunston, K.D. and Fairbrother, P.F.: Treatment of vaginal discharge with yoghurt. *S. Afr. Med. J.* 49: 675-676 (1975).
- Hallén, A., Jarstrand, C., and Pålsson, C.: Treatment of bacterial vaginosis with lactobacilli. *Sex. Transm. Dis.* 19: 146-148 (1992).
- Hallén, A. Unpublished observations (1998).
- Hilton, E., Isenberg, H.D., Alperstein, P., France, K., and Borenstein, M.T.: Ingestion of yogurt containing *Lactobacillus acidophilus* as prophylaxis for candidal vaginitis. *Ann. Int. Med.* 116: 353-357 (1992).
- Hughes, V.L., and Hillier, S.: Microbiologic characteristics of *Lactobacillus* products used for colonisation of the vagina. *Obstet. Gynecol.* 75: 224-228 (1990).
- Komaroff, A.L., Pass, T.M., McCue, J.D., Cohen, M.S., Hendricks, T.M., and Friedland, G.: Management strategies for urinary and vaginal infections. *Arch. Intern. Med.* 138: 1069-1073 (1978).
- McGroarty, J.A.: Probiotic use of lactobacilli in the human female urogenital tract. *FEMS Immunol. Med. Microbiol.* 6: 251-264 (1993).
- Mohler, R.W. and Brown, C.P.: Döderlein's bacillus in the treatment of vaginitis. *Am. J. Obstet. Gynecol.* 25: 718 (1933).
- Neri, A., Sabah, G., and Samra, Z.: Bacterial vaginosis in pregnancy treated with yoghurt. *Acta. Obst. Gynecol. Scand.* 72: 17-19 (1993).
- Österlund, A., Hallén, A., and Strand, A.: Resistens mot *Candida* redan ett bekymmer. *Läkartidningen* 95: 4476-4477 (1998).
- Parent, D., Bossens, M., Bayot, D., Kirkpatrick, C., Graf, F., Wilkinson, F.E., and Kaiser, R.R.: Therapy of bacterial vaginosis using exogenously-applied *Lactobacilli acidophili* and a low dose of estriol. *Arzneim. -Forsch. / Drug Res.* 46: 68-73 (1996).
- Redondo-Lopez, V., Cook, R.L., and Sobel, J.D.: Emerging role of lactobacilli in the control and maintenance of the vaginal bacterial microflora. *Rev. Inf. Dis.* 12: 856-872 (1990).
- Reid, G., Bruce, A.W., McGroarty, J. Cheng, K.-J., and Costerton, J.W.: Is there a role for lactobacilli in prevention of urogenital and intestinal infections? *Clin. Microbiol. Rev.* 3: 335-344 (1990).
- Shalev, E., Battino, S., Weiner, E., Colodner, R., and Keness, Y.: Ingestion of yogurt containing *Lactobacillus acidophilus* compared with pasteurized yogurt as prophylaxis for recurrent candidal vaginitis and bacterial vaginosis. *Arch. Fam. Med.* 5: 593-596 (1996).
- Sobel, J.D.: Vaginitis. *N. Engl. J. Med.* 337: 1896-1903 (1997).
- Spitzbart, H.: Indikation zur vaginalen Applikation von Laktobakterien. *Zentralbl. Gynäkol.* 90: 1189-1191 (1968).