Could Bacterial Vaginosis Be Due to the Competitive Suppression of Lactobacilli by Aerobic Microorganisms?

B.	Bengt	Fredricsson ^a
K.	Katarina	Englund ^a
C.E.	Carl Erik	Nord ^b
L.	Leon	Weintraub ^a

Department of ^aObstetrics and Gynecology and ^bMicrobiology, Karolinska Institutet Huddinge Hospital, Huddinge, Sweden

Key Words

Bacterial vaginosis
Lactobacilli
Ciprofloxacin

Abstract

Bacterial vaginosis (BV) is characterized by lack of lactobacilli and predominance of anaerobic species. Ciprofloxacin is active against a great number of aerobic bacteria. The effect of ciprofloxacin on the vaginal microbial flora was studied both in healthy subjects and in patients with BV in order to test if BV may be due to competitive suppression of lactobacilli by aerobic species. About half of the patients were relieved of their symptoms. No adverse effects on the microbial profile or colonization by lactobacilli were produced by the drug. Lactobacilli known to be able to produce hydrogen peroxide were found to be significantly more common in healthy women than in women with BV. The species most frequently related to vaginal health were *Lactobacillus jensenii* and *Lactobacillus rogosae*.

B. Fredricsson, MD, Department of Obstetrics and Gynecology, Huddinge Hospital, S-141 86 Huddinge (Sweden)

Introduction

Bacterial vaginosis (BV) has challenged many clinicians and microbiologists. Gardnerella vaginalis was first [1] and Mobiluncus last [2] suggested as the microorganism more or less specifically causing BV. Also, the possibility that BV is an expression of an ecological disturbance has been suggested [3].

BV is very probably the result of suppression of lactobacilli in the vagina followed by an overgrowth of a variety of anaerobic bacteria [4-9]. The reason for the lactobacilli to lose their predominance could be a disorder of their own or a disorder of the vaginal epithelial cells, which by improper hormonal stimulation or otherwise may lose proper attachment sites. With this in mind we tried to change the environmental conditions of the vagina in BV patients by introducing lactobacilli or estrogens or by lowering the intravaginal pH, but all these measures were inadequate [3].

Now, the possibility remains to be tested that aerobic, probably nonpathogenic, microorganisms, capable to attach to the same sites as lactobacilli, could competitively suppress the lactobacilli. This might then result in more favorable conditions for the growth of various anaerobic bacteria, thus secondarily resulting in the picture of BV. Such a view may have support in a study by Rabe et al. [10] who claimed association between the facultative viridans group streptococci and BV. Also, G. vaginalis has been shown to be able to interfere with the adherence of lactobacilli to vaginal cells in vitro [11]. We, therefore, have given ciprofloxacin to BV patients and to healthy

volunteers as well in order to test the effects of this drug on symptoms and microbial colonization of the vagina. The drug is almost exclusively effective against aerobes and lacks significant effects on those anaerobes connected with BV [12]. It penetrates easily into gynecological tissues, including the vagina [13].

Table 1. Clinical findings in untreated (n = 15) and treated (n = 8) healthy women, and in treated symptomatic women (n = 14), before (A), and 1 week (B) and 3 weeks (C) after treatment
 Table 2. Microbiological findings in untreated (n = 15) and treated (n = 8) healthy women, and in treated symptomatic women (n = 14), before (A), and 1 week (B) and 3 weeks (C) after treatment

Healthy
 Symptomatic Species
 Healthy
 Symptomatic

un- treated treated
 B C
 un- treated treated
 B
 B C

Material and Methods

The present study was approved by the local committee of ethics of the Karolinska Institute. The clinical material comprised three groups. All women were regularly menstruating, none was pregnant and none used an intrauterine device. The mean age of the subjects was 32 years (range 20-51).

Group 1 consisted of 15 healthy women without any of the criteria of BV [(1) no complaints of discharge; (2) pH < 4.5; (3) amine test negative; (4) no clue cells present in the wet vaginal smear]. These women were defined with respect to their vaginal microorganisms.

Group 2 consisted of 8 healthy women as above. They were given oral ciprofloxacin, 250 mg twice a day for 7 days. The day after the last dose they were clinically examined and samples for microbiological analysis were taken as before the start of the experiment. Three weeks later they were reexamined and new samples for microbial cultivation were taken.

Group 3 comprised 14 women with clinical findings characteristic of BV. Cases with chlamydial, neisserial or trichomonal infections were excluded. They were treated and examined as the cases of group 2.

On each examination the clinical characteristics of BV were evaluated and samples were taken from the lateral vaginal fornix in order to define the bacteria being present, as previously described [5]. The patients were scheduled for examination in intermenstruum.

Aerobic

Lactobacillus1
 1 1 3
 1

1

1 2 31

1 1 2

L. acidophilus (+/-) *L. buchneri* (-) *L. casei* (ND) *L. cateniforme* (+) *L. crispatus* (+) *L. fermentum* (-) *L. jensenii* (+) *L. minutus* (ND) *L. plantarum* (ND) *L. rogosae* (+) *L. salivarius* (-) *L. vitulinus* (ND)

Results

The results are given in table 1 (clinical findings) and 2 (microbiological findings).

One of the healthy subjects had a slight pH elevation; otherwise none of the signs included in the BV concept were recorded. The number of bacterial species found in

Results are number of cases with findings.

1 +, – and ND (not determined) indicate capability of %C% production [15, 16].

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Bacterial Vaginosis and Ciprofloxacin

Treatment

Species

Healthy

Symptomatic Species

Healthy

Symptomatic

un- treated treated

ABC

ABC

un- treated treated

ABC

ABC

Anaerobic

Others

Peptostreptococcus *P. anaerobius* *P. asaccharolyticus* *P. magnus* *P. micros* *P. prevotii* sp.

Streptococcus *S. constellatus* *S. intermedius* *S. morbillorum*

Veillonella *V. parvula*

1 1

1

1 1

4

1 1 2

2 1

3 1 2

1 3

Candida C. albicans

Summary of microbiological findings

Megasphaera M. elsdenii

1 1

Eubacterium E. aerofaciens E. combesi E. fissicatena E. lentum

these subjects was low. Ciprofloxacin treatment of the 8 healthy volunteers resulted in no significant change of their vaginal microbial spectrum. Different lactobacilli were often present on the different occasions. The change of species from time to time within the same individual showed no systematic pattern.

Of the 14 symptomatic patients, 6 were not cured by the treatment, whereas 2 were partly cured (only 2 of the BV criteria present) at both posttreatment visits. Thus, 8 of the 14 patients were cured using the same criteria as in our previous studies. Those patients that were not cured got additional therapy with metronidazole. In spite of clinical cure, no significant change in the microbial spectrum was seen, thus *G. vaginalis*, anaerobic cocci and bacteroides did not change their prevalence. *Candida albicans* was found in culture in 3 cases before treatment but was not recognized in the wet smear. The yeasts were not increased by the ciprofloxacin treatment. *Mobiluncus* spp. were not identified by cultivation but their characteristic movement pattern was seen in the wet smears of 3 patients before institution of treatment, in 3 others immediately after stopping treatment and 3 weeks later in 3 cases (table 1). In 1 of these latter patients, this observation was not made before; in another patient *Mobiluncus* spp. were seen before treatment but not immediately after, and in yet another patient the mobile microorganisms were also seen the day after treatment.

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Discussion

Ciprofloxacin was effective in giving symptomatic relief to about half of the patients (table 1). This is to some extent remarkable although not clinically acceptable, particularly since metronidazole has given cure rates of about 80% in our hands employing identical criteria [3-6]. Of course, the present study was not designed to define treatment efficacy with this drug, but it may be of interest that in a previous study [3] treatment with three different vaginal preparations other than metronidazole cured only 5 out of 43 patients. Since this is less than was obtained with ciprofloxacin, some benefit from the drug cannot be excluded. This may be of particular interest since no significant changes in the vaginal colonization were induced by the drug (table 2). Thus, symptoms may not necessarily be due to the type of vaginal colonization. This further stresses the concept that no specific pathogen may be assigned to the clinical entity of BV, and that the disorder is rather due to disturbed function of the mucosal membrane or of the lactobacilli normally present.

Recently, the view has been expressed that lactobacilli may not be able to protect against BV unless they are capable to produce hydrogen peroxide [14]. Although many of the species which were identified in our material are not defined in this respect, some are defined in the literature [15, 16]. Thus, we found in the present study altogether 18 isolates of lactobacilli that are known to be able to produce hydrogen peroxide (*Lactobacillus crispatus*, *L. jensenii* and *L. rogosae*) among the symptom-free women, and only 1 in those who had findings consistent

Table 3. Colonization with lactobacilli capable of hydrogen peroxide production [16, 17] in women with and without findings consistent with BV

with BV. This prompted us to reexamine our protocols of all the cases reported upon previously [3-6]. Among those lactobacilli recognized to produce H_2O_2 [15, 16], 15 isolates of *L. jensenii* were found in women without symptoms and only 1 in a woman with BV. *L. rogosae* was the second most common with 10 isolates in healthy versus 2 in symptomatic women. Of other species of lactobacilli, only occasional isolates were found. Thus, the proposal by Eschenbach et al. [14] gets support from our data, showing that very few peroxide-producing species of lactobacilli were identified in women with symptoms of BV (table 3).

The fact that we have not been able to cure patients with BV with a milk product obtained by fermentation by *L. acidophilus* [3] may now be explained. This species of lactobacilli is known to be sometimes a H_2O_2 producer, sometimes not [15]; but the product we used was unfortunately not defined in this respect. On the other hand, most milk products except those based on *L. delbrueckii* ssp. *bulgaricus* are reported to be H_2O_2 producers [17].

Ciprofloxacin did not significantly affect the profile of lactobacillar colonization. The drug should then not be expected to have adverse effects or produce symptoms referred to the vagina. Nor did the drug affect the prevalence of *C. albicans* in our patients, in contrast to other antimicrobial agents, including metronidazole [3].

In conclusion, we could not find evidence that aerobic species may compete with lactobacilli on attachment sites. If, on the other hand, aerobic microorganisms contribute significantly to the normal environment of the human vagina supporting the growth of lactobacilli, then their suppression by ciprofloxacin would be expected to result in an increase of symptoms and findings characteristic of BV. This was not at all the case in the present study. We would rather support the view that BV reflects a suppression of hydrogen-peroxide-producing lactobacilli, in particular *L. jensenii* and *L. rogosae*, which in our experience was significantly more predominant in the healthy vagina than any other species of lactobacilli.

Acknowledgements

The ciprofloxacin drug was furnished by Bayer Sverige AB, by courtesy of Vimala Rahm, MD. The skilful assistance by nurses and technicians in various parts of the study was much appreciated.

It may be noted that on only 4 occasions 2 isolates were found and on the remaining 135 only 1 each. (Summary of findings in the present and previous studies by the authors.) $\chi^2 = 10.024$, d.f. = 2, $p = 6.659 \times 10^{-3}$. ND = Not determined.

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Treatment

Bacterial Vaginosis and Ciprofloxacin

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