

Hypothesis

Vaginal bacterial phaginosi

Anona L Blackwell

Anaerobic (bacterial) vaginosis is a vaginal syndrome of unknown aetiology in which women complain of a fishy smelling vaginal discharge and the normal lactobacillus dominated vaginal flora is replaced by a profound overgrowth of *Gardnerella vaginalis*, *Mycoplasma hominis*, and mixed anaerobes, particularly *Prevotella*, *Porphyromonas*, and *Mobiluncus* species. The vaginal pH is elevated (usually pH 4.7–5.0) and on mixing an alkali such as 5–10% potassium hydroxide with undiluted vaginal secretions an ammoniacal odour is noted (positive amine test). Anaerobic vaginosis has much of the epidemiology of a sexually transmitted disease being positively associated with gonorrhoea, chlamydia, trichomonas, genital warts, and HIV. It is rare in nuns and is more frequently found in women with multiple sexual partners and in women who use non-barrier methods of contraception.^{1–4} Lesbian couples usually have concordant vaginal floras—that is, both have a normal vaginal flora or both have anaerobic vaginosis, suggestive of a mechanical transfer of an infectious agent.⁵ The condition is also more frequently detected in black women than in white and it is independently related to cigarette smoking. Whether the typical bacterial flora found in anaerobic vaginosis are the actual cause of the condition or are merely the microbiological consequence of some other pathophysiological process is unknown, but undoubtedly a major disturbance in the vaginal ecosystem takes place which results in an anaerobic shift in the vaginal environment. The term *anaerobic* vaginosis was suggested rather than *bacterial* vaginosis because it was considered that the term bacterial vaginosis overemphasised a simple bacterial aetiology. In addition, even if bacterial vaginosis is a bacterial vaginal infection, the term *bacterial* vaginosis encompasses too broad a spectrum of the vaginal bacterial infections which do not (usually) provoke an inflammatory response—for example, group B streptococcus or *G vaginalis* infection.^{6–8} It was also felt that the anaerobic bacterial component was the most important in terms of the main symptoms, signs, and associated pathology of the condition. Treatment of anaerobic vaginosis with oral metronidazole or topical clindamycin gives good short term results but after 3 months relapse/reinfection can be as high as 69%, and, despite its “STD” epidemiology, treatment of male partners with metronidazole or oral clindamycin does not effect recurrence rate.^{9–11} This anomaly has been widely recognised but never fully explained. Cook and colleagues have suggested that relapse is more likely than reinfection.¹² In a small study of women with frequent recurrence of anaerobic vaginosis they found that clinical

cure was often associated with residual biochemical and microbial abnormalities and that the time to next clinical recurrence was related to the severity of these abnormalities. The high relapse rate of anaerobic vaginosis is of concern since it has been implicated in the pathogenesis of pelvic infection, dysfunctional uterine bleeding, adverse pregnancy outcome, and post-abortion upper genital tract infection. It may even have a role to play in the pathogenesis of cervical intraepithelial dysplasia, cerebral palsy, and in the transmission of HIV.^{1 8 13 14} Given the now well recognised pathogenic potential of anaerobic vaginosis and our lack of effective long term cures for some patients, any advance in our understanding of the pathogenesis of anaerobic vaginosis is welcomed. Two papers and an abstract published in *Infectious Diseases in Obstetrics and Gynecology* may explain why anaerobic vaginosis relapses so frequently despite treatment of male partners and may also explain why it is curiously linked with smoking. In the first paper, “Phage infection in vaginal lactobacilli: an in vitro study,” Pavlova *et al* point out that the mechanism by which the normal vaginal flora become replaced by anaerobic vaginosis organisms was poorly understood.¹⁵ They postulated that since anaerobes are sensitive to lactic acid and hydrogen peroxide produced by lactobacilli, it was logical to suggest that suppression of lactobacilli must come first and that phage mediated lysis of vaginal lactobacilli may cause profound reduction of the normal lactobacillus flora permitting subsequent overgrowth of anaerobic bacteria. An analysis of the vaginal secretions of 39 women of reproductive age for the presence of lactobacillus phages revealed that 19 of the 39 women had a normal vaginal flora, 16 had anaerobic vaginosis and four had candidiasis. Thirty seven lactobacillus strains were isolated from which seven temperate phages (phages which co-exist with the host bacterium) and ten lytic phages (phages which lyse the host bacterium) were identified. They found that the rate of phage detection was lower in healthy women than in women with anaerobic vaginosis or candida but reported that there was no obvious difference in phage sensitivity of the vaginal lactobacillus strains found in these women. The in vitro studies also showed that the phages detected could infect vaginal lactobacilli from the same woman or those from different women; this has implications for the possible sexual transmission of phages. The authors also reported that a phage isolated from a human intestinal lactobacillus strain lysed some vaginal lactobacilli and postulated that vaginal lactobacillus phages may come from the faecal urogenital route. The second paper, “Analysis of lactobacillus products for

Swansea NHS Trust,
Department of GU
Medicine, Singleton
Hospital, Sketty Lane,
Swansea SA2 8QA
A L Blackwell

Accepted for publication
16 August 1999

phages and bacteriocins that inhibit vaginal lactobacilli," sheds further light on the possible pathogenesis of anaerobic vaginosis.¹⁶ Tao and colleagues looked for lactobacilli, phages, and bacteriocins (non-viable proteins or peptides which inhibit the growth of bacteria) in 20 yoghurts, three lactobacillus pills, two acidophilus milks, and one vaginal douche mix. Forty three lactobacillus strains were detected and 11 of these (obtained from yoghurt only) were found to release phages, seven of which inhibited vaginal lactobacilli. It was suggested that the phages or bacteriocins released from lactobacillus products, including widely available dairy products, could inhibit the growth of vaginal lactobacilli and may be involved in the pathogenesis of anaerobic vaginosis. If the authors' theory is correct, then given the widespread use of dairy products which may contain phages, one would expect many more women to have anaerobic vaginosis. Diet mediated anaerobic vaginosis would also fail to explain the "sexually transmitted" epidemiology of the condition. Temperate diet acquired lactobacillus phages may be induced to become lytic by some other factor related to sexual activity but it is also possible that lactobacillus phages may be directly inoculated into the vagina from the male (or female) partner.

Further insight into the pathogenesis of anaerobic vaginosis is found in an abstract by Tao *et al* which reported on factors which could affect phage induction in lysogenic strains of vaginal lactobacilli.¹⁷ They found that the cigarette carcinogen, benzol(a)pyrene diol epoxide (BPDE) strongly promoted phage induction and, given that other tobacco products have been shown to be concentrated in cervical mucus,¹⁸ it is conceivable that women who smoke or those whose partners smoke may be at greater risk of anaerobic vaginosis via induction by tobacco products of endogenous or sexually acquired temperate lactobacillus phages. These may then destroy the normal lactobacillus flora and would explain why anaerobic vaginosis is more common in women who smoke.

The hypothesis that a sexually transmitted lactobacillus phage may specifically destroy the endogenous healthy lactobacillus vaginal flora and secondarily permit overgrowth of endogenous anaerobic bacteria and *G vaginalis* may explain why anaerobic vaginosis behaves epidemiologically as a sexually transmitted agent but recurrence rate is unaffected by antibacterial treatment of male partners. Unfortunately this hypothesis raises as many questions as answers. Are phages capable of destroying lactobacilli carried on the penis or are the lactobacillus

phages derived from the woman's own gut flora and merely transferred into the vagina by sexual activity? Are there any phage resistant strains of lactobacilli which could be of therapeutic use? Is there any possibility that a vaccine could be developed that could be given to women with recurrent anaerobic vaginosis, particularly perhaps, those who smoke or who have cervical intraepithelial neoplasia. Until the pathogenesis of anaerobic vaginosis is more fully understood, argument will undoubtedly remain concerning the best name for the condition (?vaginal bacterial phaginosi) and treatment will be unsatisfactory. As a result some women will be burdened not only by the social consequences of recurrent genital mal-odour but may also be at risk of a plethora of complications.

Professor Ian Phillips is thanked for his helpful comments in the preparation of this paper.

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