

REVIEW

Extra-vaginal infection caused by *Gardnerella vaginalis*

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(Accepted 1 October 1986)

INTRODUCTION

For the past 30 years there has been controversy concerning the role of *Gardnerella vaginalis* in the aetiology and pathogenesis of bacterial vaginosis (BV), a non-inflammatory condition characterized by the presence of a malodorous vaginal discharge, an elevated vaginal pH value and the presence of epithelial cells covered with cocco-bacilli (clue cells) in vaginal smears. The clinical features of BV were described in 1955 by Gardner & Dukes, who claimed that the condition was caused by infection with a hitherto unclassified bacterium which they named *Haemophilus vaginalis*, but which has since been re-classified as *G. vaginalis* (Greenwood & Pickett, 1980). Their conclusion that *G. vaginalis* was the cause of BV was based on their isolation of the organism from 92% of patients with BV, but not from women without this condition. The role played by *G. vaginalis* in the aetiology of BV has become less clear, however, with the subsequent finding that it may be isolated from the normal vaginal flora if sensitive culture techniques are employed (Hill, Eschenbach & Holmes, 1984). Quantitative studies of the vaginal microflora have shown that there is a significant increase in the number of *G. vaginalis* organisms in the genital tract of women with BV compared to women not suffering from this complaint. However, as there is also a relative increase in the anaerobic vaginal flora and the number of *Mycoplasma hominis* organisms in women with BV (Hill, Eschenbach & Holmes, 1984), the role of *G. vaginalis* is still unclear. Chen and colleagues (1979) suggested that a symbiotic relationship existed in the vagina between *G. vaginalis* and other organisms associated with BV, since *in vitro*, *G. vaginalis* produced high concentrations of pyruvic and amino acids which could be metabolized by these organisms. Chen *et al.* (1979) also identified the various amines present in vaginal fluids from BV patients which probably account for the characteristic malodour and showed that they could be produced *in vitro* during the growth of mixed vaginal bacteria, but not by *G. vaginalis* alone. Clearly the signs and symptoms of BV correlate with significant changes in the ecology of the vaginal flora, but the role that *G. vaginalis*, anaerobic bacteria and *M. hominis* play in the initiation and development of the disease is still unclear.

The finding that smears and biopsies obtained from women with BV show little or no evidence of vaginal inflammation or tissue damage tends to suggest that *G. vaginalis* and the other organisms associated with this condition are not invasive. There is, however, increasing evidence that *G. vaginalis* may be isolated from

extra-vaginal sites such as the blood stream, endometrium, chorioamnion and urinary tract, and that it may be involved in complications of pregnancy, such as pre-term labour.

ISOLATION FROM THE BLOODSTREAM

Reports of the isolation of *G. vaginalis* from the bloodstream are listed in Table 1. The majority of cases occurred in obstetric patients, which indicates that *G. vaginalis* is not intrinsically virulent, but is an opportunistic pathogen, spreading to the bloodstream following trauma to the tissues of the genital tract. The one case of bacteraemia seen in an adult male patient occurred after transurethral prostatectomy (Patrick & Garnett, 1978). It is of interest to note that in many patients with *G. vaginalis* bacteraemia, other organisms found in the female lower genital tract were also isolated from blood cultures, which further suggests that the bacteraemia reflects spread of the vaginal flora into areas of tissue damage with subsequent spread into the bloodstream. The low inherent virulence of *G. vaginalis* was commented on by some authors, who noted that most bacteraemic patients recovered, even if appropriate anti-microbial therapy was not given (Reimer & Reller, 1984) and that there was no evidence of patients developing meningitis, endocarditis or other metastatic septic complications (Venkatramani & Rathbun, 1976).

One group of workers have suggested that the incidence of bacteraemia caused by *G. vaginalis* may be higher than the number of reported cases would indicate (Reimer & Reller, 1985). These workers found that sodium polyanetholesulfonate, an anticoagulant routinely added to most blood culture media, inhibits growth of *G. vaginalis* unless gelatin is also present. The apparently benign course of *G. vaginalis* bacteraemia, coupled with a failure to culture the organism on blood culture media, clearly suggests that many cases may not be recognized.

ISOLATION FROM THE ENDOMETRIUM

In the late 1950s Edmunds (1959) reported an association between the isolation of *G. vaginalis* from high vaginal swabs and the presence of puerperal pyrexia and leucorrhoea. Subsequently, several workers have reported the isolation of *G. vaginalis* from endometrial samples from women suffering from post-partum or post-caesarian-section infections and septic abortion (Hegamey & Schoenknecht, 1973; Monif & Baer, 1974). Most recently, Eschenbach and colleagues (1984) reported a study of 101 patients with clinical signs of endometritis. BV-associated organisms were isolated from endometrial samples from 61 patients, with *G. vaginalis* being the most commonly isolated species (38 patients). These findings led the authors to suggest that BV may contribute to post-partum infection morbidity.

ISOLATION FROM THE URINARY TRACT

The male urethra. In view of the fact that *G. vaginalis* occurs in the lower genital tract of women, it is not surprising that several groups of workers have reported the isolation of *G. vaginalis* from urethral swabs or mid-stream urine samples from men, particularly those who are the sexual partners of infected or colonized women

Table 1. Reports of bacteraemia caused by *Gardnerella vaginalis*

Reference	Total no. of patients	No. of patients in indicated category				No. of patients with polymicrobial bacteraemia
		Obstetrics*	Gynaecological	Neonatal	Surgical	
Adeniyi-Jones <i>et al.</i> (1980)	4	3	—	1	—	1
Carney (1973)	8	8	—	—	—	—
Eschenbach <i>et al.</i> (1984)	1	1	—	—	—	—
LaScolea <i>et al.</i> (1984)	13	13	—	—	—	7
Monif & Baer (1974)	1	—	—	—	1	—
Patrick & Garnett (1978)	6	3	—	3	—	—
Platt (1971)	1	1	—	—	—	—
Regamey & Schoenknecht (1973)	30	25	5	—	—	16
Reimer & Reller (1984)	5	5	—	—	—	4
Rotheram & Schick (1969)	29	22	2	4	1	—
Venkataramani & Rathbun (1976)	14	14	—	—	—	—
Vontner & Eschenbach (1981)						

* Includes post-partum endometritis, post-partum fever, chorioamnionitis, post caesarian-section infection and septic abortion.

Table 2. *Isolation of Gardnerella vaginalis from bladder urine*

Reference	Study population	No. patients culture-positive/ no. patients tested
Abercrombie <i>et al.</i> (1978)	Man with cystitis	1/1
Birch <i>et al.</i> (1981)	Renal allograft recipients	7/123
Fairley & Birch (1983)	Patients with urinary-tract disease	22/190
Fairley & Birch (1983)	Healthy women without history of urinary-tract disease	2/35
McDonald <i>et al.</i> (1982)	Patients with symptoms of urinary tract infection	7/101
McDowall <i>et al.</i> (1981)	Pregnant women with renal disease	26/44
McDowall <i>et al.</i> (1981)	Asymptomatic pregnant women	9/50
McFadyen & Eykyn (1968)	Asymptomatic pregnant women	159/1000
Savage <i>et al.</i> (1983)	Women with acute urinary symptoms	5/40

(Leopold, 1953; Gardner & Dukes, 1955; Dawson *et al.* 1982). This finding, and the observation that many women whose sexual partners are untreated become re-infected, clearly indicate that *G. vaginalis* may be transmitted from person to person by sexual contact. The clinical significance of urethral colonization with *G. vaginalis* is, however, not completely clear. Leopold (1953) reported that all the men from whose urines he isolated a Gram-negative rod (which from the description he gave appeared to be *G. vaginalis*) had symptoms of mild to moderate prostatitis. In a more recent study, however, Dawson and colleagues (1982) showed that there was not an association between urethral carriage of *G. vaginalis* and symptoms of urethritis.

The bladder. Reported isolations of *G. vaginalis* from the bladder are listed in Table 2. The isolation of *G. vaginalis* from the bladder was first described by McFadyen & Eykyn (1968), who reported its recovery from supra-pubic aspirates from 159 of 1000 healthy pregnant women. A similar finding was subsequently reported by McDowell *et al.* (1981), who isolated *G. vaginalis* from 18% of healthy pregnant women and 58% of pregnant women with underlying renal disease. These authors were unsure as to the clinical significance of finding *G. vaginalis* in bladder urine, since the organisms were not usually associated with pyuria in asymptomatic pregnant women, most of whom remained asymptomatic despite not being treated for bacteriuria. Rather, these authors felt that the presence of these and other fastidious bacteria in the bladder may indicate an increased susceptibility of patients to bacterial invasion of the lower urinary tract, and may, in some cases, indicate the presence of underlying renal disease. In a more recent study (Fairley & Birch, 1983), however, the interesting observation was made that bladder aspirates from women who were culture-positive for *G. vaginalis* showed squamous epithelial cells with numerous adherent bacteria which appeared to resemble closely the 'clue' cells seen in BV. These workers suggested that *G. vaginalis* may adhere readily to both squamous epithelium in the vagina and squamous epithelium, which covers the floor of the urethra and the bladder trigone in post-pubertal females. Such an ability to adhere to squamous mucosal surfaces might provide an effective mode of spread from the vagina to the urinary tract.

Since similar areas of squamous epithelium are not seen in the bladder of males, this concept may also possibly go some way towards explaining the far greater rate of isolation of *G. vaginalis* from the bladders of women as compared to men.

Another finding of interest that has been made in studies with renal transplant patients (Birch, D'apice & Fairley, 1981), patients with urinary symptoms (McDonald *et al.* 1982; Savige, Birch & Fairley, 1983) and pregnant women (McDowall *et al.* 1981) is that *G. vaginalis* was frequently found in bladder urine in conjunction with *Ureaplasma urealyticum*. Clearly, the possibility that interaction between these and possibly other micro-organisms may assist in their becoming established in the urinary tract is an area worthy of further study.

Isolation from semen

There have been two reported studies on the isolation of *G. vaginalis* from semen. In one study (Ison & Easmon, 1985), 22 of 53 men (38%) attending an infertility clinic produced semen samples from which *G. vaginalis* was isolated. Nine of the samples containing *G. vaginalis* were also culture-positive for anaerobic bacteria. The prevalence of *G. vaginalis* and anaerobic bacteria was similar in men with varying sperm counts. By way of contrast, in a subsequent study of 120 men attending an infertility clinic, only one semen sample was culture-positive for *G. vaginalis* (Naessens *et al.* 1986).

DISCUSSION

Interest in the role of *G. vaginalis* as a potential human pathogen has centred primarily on its controversial role in the aetiology and pathogenesis of BV. As outlined in this review, however, there is a significant body of evidence which shows that *G. vaginalis* may spread from the vagina to infect other anatomical sites, in particular the blood stream, endometrium and urinary tract. The finding that endometritis and/or bacteraemia tend to occur during or after parturition suggests that such infections occur as the result of opportunistic spread of *G. vaginalis* (often with other members of the vaginal microflora) from the vagina. Recent studies have shown that *G. vaginalis* organisms are resistant *in vitro* to the bactericidal activity of human serum (Boustouller & Johnson, 1986), which may explain how organisms are able to survive in the bloodstream during bacteraemic episodes. The fact that bacteraemia with *G. vaginalis* does not appear to persist for prolonged periods may be due to the clearance of the organisms from the bloodstream by phagocytic leucocytes (Easmon *et al.* 1985). Clearly, there is little evidence to suggest that *G. vaginalis* is invasive under normal conditions, and it would appear that extra-vaginal infections reflect underlying predisposing host conditions. Nevertheless, *G. vaginalis* may be associated with extra-vaginal infection, particularly in obstetric patients, more commonly than is generally realized.

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