The Vaginal Microbiota

Subjects: Others
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The human vagina is a useful and accessible route for local and systemic administration of drugs, and particularly for clinical indications that are directly associated with women's sexual and reproductive health. Spurred in part by progressive societal changes to attitudes, behaviors and stigmas around the human vagina, the past twenty years has witnessed increased interest among users, clinicians, and the pharmaceutical industry in developing and using vaginal products for therapeutic benefit.

Keywords: controlled release ; drug delivery system ; silicone elastomer

1. Lactobacillus spp.

In humans, *Lactobacillus* spp. are the dominant microorganism in the healthy human vagina, found in a relative abundance of greater than 70%. Yet, lactobacilli are rarely found in greater than 1% abundance in the vaginal environment of other mammals [1]. Lactobacilli are Gram-positive, rod-shaped, anaerobic bacteria that produce lactic acid via their metabolic action on the various glycogen breakdown products found in the vagina and formed under the influence of estrogen. It is this lactic acid production that results in a healthy vaginal pH of ~4.2 [2][3]. Lactobacilli will adhere to vaginal epithelial cells, out-competing other microorganisms for surface real estate. They also produce soluble compounds, including bacteriocins, that are toxic to other bacterial species [4]. These attributes of lactobacilli contribute to their dominance in the human vagina and protect against infection with pathogenic microorganisms without themselves inducing inflammation [3]. However, studies have shown that not all lactobacilli are equal in this protective capacity. *Lactobacillus crispatus*, *Lactobacillus gasseri*, *Lactobacillus iners*, and *Lactobacillus jensenii* have been reported as the most frequently occurring species in the healthy vagina [5]. *L. crispatus* is associated with a strong protective and anti-inflammatory capabilities, whereas *L. iners* is easily displaced by other species, and is often associated with a dysbiotic environment. The picture is less clear for *L. gasseri* and *L. jensenii*, although these species appear to be less abundant in states of vaginal dysbiosis [6].

2. Gardnerella vaginalis

G. vaginalis, first described as *Haemophilus vaginalis,* a Gram-variable facultatively anaerobic rod, was proposed over half a century ago as the sole etiological agent of bacterial vaginosis (BV), the most common vaginal infection in women of reproductive age [7]. However, its presence in the vaginal microbiome of healthy women has since cast doubt on its virulence and role as a putative pathogen [8]. It has been detected at rates of 14% to 69% in asymptomatic women [9] and has been isolated as the dominant vaginal microorganism of almost all women with BV [10][11][12]. BV is associated with malodorous vaginal discharge, increased vaginal pH, and the presence of "clue cells" (vaginal epithelial cells with a heavy coating of bacteria, that can be observed microscopically in vaginal fluid). These clue cells are explained by the ability of *G. vaginalis* to form biofilms on the vaginal epithelium, providing convincing evidence for the role of the species in this condition [13]. However, its colonization in asymptomatic women, combined with phenotypic variability and limited taxonomic refinement, results in a somewhat complicated and incomplete understanding of the precise role of *G. vaginalis* within the vaginal microbiome.

G. vaginalis has been well known to display genotypic and phenotypic diversity with differing virulence potential, and at least four 'clades' (or subgroups) within the species are differentially associated with different clinical outcomes [14][15]. In recent years, biotyping and molecular methods have been applied to categorize these subgroups. In 2019, Vaneechoutte et al. formally proposed three new and distinct species based on whole-genome sequencing and biochemical analysis: *Gardnerella piotii*, *Gardnerella swidsinskii*, and *Gardnerella leopoldii* [13].

BV is also associated with increased risk of HIV infection and transmission [16][17][18][19]. Several factors are likely at play here, including decreased levels of hydrogen peroxide-producing lactobacilli, production of mucin-degrading enzymes, increased influx of HIV target cells, elevated levels of proinflammatory cytokines, elevated vaginal pH, and increased

expression of HIV in the lower genital tract. Novel drug-releasing ring formulations to treat or prevent recurrence of BV, including multipurpose devices that simultaneously administer antiretrovirals, have been reported [20][21].

3. Atopobium vaginae and Prevotella spp.

Another species strongly associated with BV is the strict anaerobe *Atopobium vaginae*, which is resistant to metronidazole and may explain why some women suffer from recurrent BV after treatment with this antibiotic. Studies have reported that *A. vaginae* is present in up to 86% of BV samples [22]. The anaerobic species *Prevotella* spp. is also negatively associated with vaginal health [23]; it has been suggested that colonization with *Prevotella*—the most heritable vaginal bacteria—is strongly associated with host genetics [24]. Women with abundant *Prevotella* in their vagina have higher levels of pro-inflammatory cytokines and increased activation of Toll-like receptors leading to downstream signaling for immune surveillance [24]. Interestingly, there is a strong association between obesity and greater abundance of both gut and vaginal *Prevotella* compared to individuals with BMIs in the healthy range [24][25].

4. Candida albicans

Candida albicans is a polymorphic fungus and a member of the normal human microbiome, residing for the most part harmlessly in the oropharynx, gastrointestinal tract, on the skin, and in the vagina of 20–30% of healthy women [26]. The yeast form (blastoconidia) is typically associated with asymptomatic colonization and transmission, while the hyphal (mycelial) form contributes to adherence and mucosal invasion seen in symptomatic disease [27]. During the switching from a commensal to a vaginal pathogen, *Candida* spp. will also produce a range of extracellular enzymes (including proteases, phospholipases, and hemolysins) that are implicated in adherence to and invasion of vaginal epithelial cells [26]. Another important virulence factor is the ability of *Candida* spp. to form biofilms that attach irreversibly to both biotic and abiotic surfaces; this trait is highly dependent on yeast to hyphal morphogenesis [26][28]. Vulvovaginal candidiasis (VVC) is defined as symptoms of inflammation caused by an overgrowth of *Candida* spp., particularly *C. albicans,* without other infectious etiologies [22]. It is estimated that approximately 75% of all women suffer from VVC at least once in their lifetime [29] and it is a common side effect of treatment with broad spectrum antibiotics, with the eradication of commensal bacteria allowing *C. albicans* to dominate the vaginal microbiota [30].

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