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The Vaginal Microbiota and Urinary Tract Infection

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Abstract

The vagina is a key anatomical site in the pathogenesis of urinary tract infection (UTI) in women, serving as a potential reservoir for infecting bacteria and a site at which interventions may decrease the risk of UTI. The vaginal microbiota is a dynamic and often critical factor in this pathogenic interplay, because changes in the characteristics of the vaginal microbiota resulting in the loss of normally protective *Lactobacillus* spp. increase the risk of UTI. These alterations may result from the influence of estrogen deficiency, antimicrobial therapy, contraceptives, or other causes. Interventions to reduce adverse effects on the vaginal microbiota and/or to restore protective lactobacilli may reduce the risks of UTI.

INTRODUCTION

Urinary tract infections (UTIs) are a common clinical problem across the lifespan of women. Although UTIs are not systematically tracked, making estimates of U.S. incidence somewhat challenging, the most recent combined National Hospital Ambulatory Medical Care Survey and National Ambulatory Medical Care Survey data from 2009–2010 suggest that approximately 10 million outpatient visits for a diagnosis of UTI occur annually in the United States among both women and men (1). Women are disproportionately affected, with an estimated lifetime risk of UTI of 60% (2). In otherwise healthy, sexually active premenopausal women, these infections occur approximately every other year (3). As women age, UTIs become more common (2). A population-based study of community-onset UTI among nearly 31,000 residents of Calgary showed that the incidence of UTI among women demonstrates an initial peak in the twenties (30 per 1,000), decreases slightly during the later reproductive years, then steadily increases with every decade of life starting in late middle age, reaching a maximum of 125/1,000 at and above age 80 (4). Although the cost of treating UTI has not been recently estimated, the last published estimate in 2010 indicated that the annual U.S. domestic cost exceeded two billion dollars (5–7).

Despite decades of studies defining the epidemiology, risk factors, and pathogenic mechanisms in UTIs, current evidence-based prevention strategies still rely upon the use of low-dose prophylactic antimicrobials as the cornerstone of prevention of recurrent UTIs in women of any age (8). For postmenopausal women, vaginal estrogen therapy may be considered, but this is often as an adjunctive to antimicrobial-based prophylaxis (8). Given

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the inexorable increase in antimicrobial resistance documented worldwide for the past few decades, antimicrobial-based preventive strategies have become less attractive and potentially contributory to worsening resistance rates (9). As discussed in detail below, the vaginal microbiota (VMB) plays a key role in the pathogenesis of UTI: alterations in the VMB are associated with risks for UTI, and effects on the VMB associated with treatment of UTIs can affect the success of this therapy. Thus, a better understanding of the role of the VMB in UTI may lead to improved interventions to prevent and treat these infections.

THE ROLE OF THE VAGINA IN THE PATHOGENESIS OF UTI

In women, the vagina plays a key role in the pathogenesis of UTIs. The intestinal microbiota is the ultimate source of bacterial strains causing cystitis and pyelonephritis in the majority of cases (10). The initial step in the pathogenesis of UTI is colonization of the vaginal introitus and periurethra with the infecting uropathogens, followed by ascension of uropathogens via the urethra to the bladder and sometimes the kidneys to cause infection (10–12). Thus, understanding factors that affect the microbiota of the vagina is key to understanding the pathogenesis of UTI and to designing interventions to prevent UTIs.

PROTECTIVE ROLE OF LACTOBACILLI IN THE VAGINA

Studies of the VMB have long indicated that certain bacterial species and/or microbial characteristics are associated with disease-free conditions, or “health,” of the genitourinary tract (13). Studies specifically related to the pathogenesis of UTI largely date from decades preceding the availability of culture-independent methodologies for characterizing microbial communities, larger-scale microbial sequencing methods, and wide-spread interest in the microbiome. In culture-based studies of vaginal samples from women without urogenital disease conditions, *Lactobacillus* species comprise 90% of the organisms present (14, 15), and 80 to 90% of these lactobacilli produced H_2O_2, mostly attributable to *Lactobacillus crispatus* and *Lactobacillus jensenii* (14, 15). Beginning with early studies utilizing DNA hybridization and quantitative real-time PCR (RT-PCR) of lactobacilli cultured from vaginal samples, numerous studies have identified *L. crispatus* as the predominant species present in healthy premenopausal women (14). Many experts view the presence of *L. crispatus* as an overall marker of a healthy VMB (16).

Several subsequent studies have characterized the VMB in states of health and disease using culture-independent methods, largely based on 16S ribosomal RNA bacterial gene sequencing (13, 17). One of the first large-scale, non-culture-dependent studies of vaginal microbial communities assessed approximately 400 asymptomatic North American women, using pyrosequencing of bar-coded 16S rRNA genes (18). This study confirmed that most vaginal microbial communities (73%) were dominated by one or more species of *Lactobacillus* and that this genus constituted over half of all sequences obtained (18). As of 2014, a systematic review of VMB studies performed using molecular characterization methodology identified 63 studies meeting criteria for inclusion and noted that these studies have definitively demonstrated that a *Lactobacillus*-dominated VMB is correlated with what was termed a “healthy vaginal micro-environment” (17).

Conversely, the absence of vaginal lactobacilli has been associated with several disease states. In earlier clinical studies, vaginal samples collected from women with and without various urogenital disease conditions were cultured using standard microbiological methods for isolating lactobacilli and were compared for characteristics such as the presence or absence of *Lactobacillus* spp., especially H_2O_2-producing lactobacilli. Women lacking vaginal lactobacilli per vaginal cultures, particularly those with vaginal samples with decreased relative amounts of or total absence of peroxide-producing lactobacilli, were found to be at increased risk for a variety of urogenital disease conditions, including bacterial vaginosis, HIV infection, and *Neisseria gonorrhoeae*, as well as vaginal colonization with *Escherichia coli*, the most common cause of UTI in women (19–24).

Proposed mechanisms through which lactobacilli may prevent vaginal colonization by uropathogens include competitive exclusion of uropathogens by adherence of *Lactobacillus* species to uroepithelial cells; lowering of vaginal pH by production of lactic acid; production of bacteriocins, surfactants, and other antimicrobial products; and finally, production of H_2O_2 (25–32). *L. crispatus* is highly adherent to vaginal epithelial cells and produces high quantities of H_2O_2 (29, 33, 34). Lactic acid concentrations are high in a lactobacillus-dominated VMB, and these conditions produce a potently antimicrobial environment *in vitro* (35). Hydrogen peroxide alone is microbicidal for many bacterial species, and this microbicidal activity is 10- to 100-fold greater when it is combined with chloride anion and myeloperoxidase, both of which are found in the vagina (36, 37). This vaginal antimicrobial defense system (H_2O_2, chloride anion, and myeloperoxidase) has potent *in vitro* activity against *E. coli* as well as other microorganisms (38). Lactobacilli also produce surfactants that inhibit growth of *E. coli* and other uropathogens (27, 28).

ALTERATIONS IN MICROBIOTA ASSOCIATED WITH UTI

The VMB has been demonstrated to be altered at the time of UTI, in women with recurrent UTI, and following treatment of the infection, even in women without a history of recurrent UTI. As noted above, the critical event preceding UTI is colonization of the vaginal introitus with intestinal microbiota, most commonly *E. coli* (36, 39, 40). Multiple culture-based studies showed that women with recurrent UTI often have increased rates of colonization with *E. coli* and depletion of the normally predominant H_2O_2-producing lactobacilli (39, 41–43), suggesting that vaginal colonization with H_2O_2-producing lactobacilli may prevent *E. coli* vaginal introital colonization and UTI. In a case-control study, we found that women with recurrent UTI who lacked vaginal H_2O_2-producing lactobacilli had a 5-fold increased risk of *E. coli* vaginal colonization compared to women with H_2O_2-producing lactobacilli (41). In another study of reproductive-age women, 15% of 301 women who had vaginal colonization with *L. crispatus* or *L. jensenii*, both H_2O_2-producers, were colonized with *E. coli*, compared with 27%of womenwho did not have these lactobacilli species present (P = 0.01) (14). A Canadian study showed that the VMB of women with recurrent UTI demonstrated a diminished lactobacillus morphotype composition resembling bacterial vaginosis pathophysiology (44). Finally, data from studies of premenopausal women in Seattle demonstrated that only 50% of women have H_2O_2-producing lactobacilli in the vagina at the time of presentation with recurrent UTI (45).

ALTERATIONS OF THE VMB ASSOCIATED WITH LOSS OF ESTROGEN

Among the manifold effects of the loss of estrogen at the time of menopause are changes in the vaginal microbiome of most women, decreasing the relative amounts of *Lactobacillus* present (46–49). As noted above, rates of UTI begin to rise at the climacteric, and recurrent UTIs are considered among the features of the genitourinary syndrome of menopause, which is characterized by thinning of the vaginal epithelium, various symptoms associated with vulvovaginal atrophy, and relative loss of lactobacilli in the VMB (50). In a study of 463 community-dwelling postmenopausal women, colonization with *E. coli* was more frequent in women without estrogen replacement and inversely associated with the presence of *Lactobacillus* (51). Further, these alterations of the VMB were associated with having a history of recurrent UTI (51).

Conversely, in the same study of community-dwelling postmenopausal women, retention of lactobacilli in the VMB at menopause was associated with having received systemic or topical vaginal hormone replacement therapy in the preceding year (51). Studies of treatment of menopause-associated estrogen deficiency with topical estrogen preparations such as estrogen cream or an estradiol-releasing vaginal ring (Estring) has been demonstrated to reduce the rate of recurrent UTI and restore vaginal lactobacilli in most women (46–49, 52). A recent study of microbial communities in postmenopausal women with atrophic vaginitis showed depletion of *Lactobacillus* spp. prior to therapy, with low-dose estrogen therapy increasing the relative amounts of *Lactobacillus* spp. and decreasing vaginal pH (53). As a result, topical vaginal estrogen therapy is recommended in the management of recurrent UTI in older women, in addition to low-dose antimicrobial therapy (54).

ALTERATIONS OF THE VMB ASSOCIATED WITH ANTIMICROBIAL THERAPY

Exposure to antimicrobials has been demonstrated in multiple studies to alter the VMB, such as during pregnancy (55, 56) or after therapy for bacterial vaginosis (56, 57). In one study, use of antimicrobials in the preceding weeks was associated with increased risk of UTI (58). The choice of antimicrobial for treatment of UTI may also affect the VMB. For example, beta lactam antibiotics are associated with less efficacy in eradicating vaginal colonization with *E. coli*, and clinically, these agents are more associated with rapid recurrence of UTI after therapy compared with other agents (45, 59). Of note, the Infectious Diseases Society of America considered adverse ecological effects of antimicrobials, termed collateral damage, as key factors in ranking recommended therapies for acute uncomplicated UTI (60).

EFFECT OF CONTRACEPTIVE METHOD ON THE VMB AND RISK OF UTI

Numerous studies have demonstrated that spermicidal products containing compounds such as nonoxynol-9 disrupt the VMB by depleting lactobacilli and increasing *E. coli* colonization and increasing the risk of UTI (8, 61–64). This adverse effect appears to be mediated by a direct toxic effect on vaginal *Lactobacillus* spp. (65). Data regarding other methods of contraception are more limited. Oral contraceptives appear to reduce the rate of

bacterial vaginosis (66) but are neutral with respect to risk of UTI (61, 63, 64). Data regarding the intrauterine device and effects on the VMB overall are conflicting, with no published studies considering the effect of this method on the risk of UTI at the time of this review (66).

CLINICAL IMPLICATIONS

The interactions between the VMB and the risks of UTI, treatment choices, and possible means of UTI prevention lead to several fairly evident clinical implications. First, lifestyle considerations may be discussed with patients. Though spermicidal contraceptives are less commonly used at present, these may be substituted with methods having a neutral effect on UTI, such as hormonal contraceptives (8). Patients and their providers may be counseled regarding current knowledge of adverse effects of antimicrobial agents and their effect upon risk of UTI. Postmenopausal women without contraindications to the use of topical hormone therapies may be offered such medications for primary or secondary prevention of UTI (8). In clinical practice, UTI episodes and subsequent clusters of recurrent UTI that are the hallmark of the natural history of recurrent UTI (67) may arise apparently spontaneously, for no known reason. However, given the evidence that alterations in the VMB are likely associated with these clinical events, the clinician may still attempt to identify and ameliorate known causes of VMB alterations.

Finally, the use of oral or intravaginal probiotics to attempt to restore protective vaginal lactobacilli is an attractive option that would, in theory, likely help reduce the use of antimicrobials in preventive strategies. Unfortunately, data on this approach are limited overall, and studies regarding reduction of UTI by means of oral probiotics are conflicting (8). An alternative approach of a vaginal *L. crispatus* probiotic directly administered to the vagina has shown promise in a small randomized, double-blind, placebo-controlled phase 2 study, in which receiving the lactobacillus probiotic ($n = 50$) was associated with decreased rates of recurrent UTI compared with placebo ($n = 50$) (68). Unfortunately, in a recent Cochrane review of all probiotic approaches to UTI prevention, few studies were adequate for inclusion, and the above-described study of a vaginal probiotic was the only one of its kind (69). Additional randomized, double-blind, placebo-controlled studies of adequate sample size using a carefully selected probiotic strain are needed to ascertain whether this approach is effective.

SUMMARY

The vagina is a key anatomical site in the pathogenesis of UTI, serving as a potential reservoir for infecting bacteria ascending from the intestinal source of uropathogenic bacteria. The vagina is also an important site at which interventions that positively affect the VMB can be instituted to attempt to decrease risk of UTI. The VMB is a dynamic and often critical factor in this pathogenic interplay, because changes in the characteristics of the VMB resulting in the loss of normally protective *Lactobacillus* spp. increase the risk of UTI. These alterations may result from estrogen deficiency, antimicrobial therapy, contraceptives, and episodes of UTI itself. Interventions designed to maintain homeostasis of the VMB and/or to ameliorate adverse effects of exposures such as antimicrobials or menopause hold promise

for future preventive or therapeutic options, potentially avoiding additional use of antibiotics.

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