Published in final edited form as:

Curr Opin Obstet Gynecol. 2016 October ; 28(5): 407–412. doi:10.1097/GCO.0000000000000298.

The Urinary Microbiota: A Paradigm Shift for Bladder Disorders?

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Abstract

Purpose of Review—A resident microbial community (the female urinary microbiota, FUM) exists within the female bladder of many adult women. Information about the FUM is likely to modify the diagnosis, prevention and treatment of adult women with urinary disorders. This review highlights key findings from recent literature relevant to adult, non-pregnant women.

Recent Findings—Similar to other human microbial communities, the FUM varies in its characteristics, including organism diversity and predominant organism identity. Recent literature reveals previously undetected organisms and community characteristics that appear associated with certain urinary symptoms, including urinary tract infection and urgency urinary incontinence. The role of individual organisms may range from beneficial to pathogenic, and may vary based on an individual's FUM characteristics. The simple dichotomy of "infected" or "sterile" no longer sufficiently captures the microbiological complexity of the female bladder.

Summary—Deeper understanding of the FUM should yield better methods to restore the microbiota to a healthy state, providing symptom relief. Opportunities to modify the FUM without antibiotic use are exciting possibilities for future research; stand-alone antibiotic use may be re-evaluated to improve treatment precision. Long-standing nomenclature for conditions such as asymptomatic bacteriuria and urinary tract infection will likely require modification.

Keywords

Urinary microbiota; urinary microbiome; urinary tract infection; asymptomatic bacteriuria; urinary incontinence

INTRODUCTION

Several years ago, the female urinary microbiota (FUM) was detected using sensitive tests that detect bacterial DNA [1,2]. With this knowledge, revisions to the traditional standard

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CONFLICT OF INTEREST

Dr. Brubaker has received editorial honoraria from UpToDate. Dr. Wolfe has received research support from Astellas Scientific and Medical Affairs, Inc for urinary microbiome research. Both authors have received funding from the NIH and Loyola University Chicago for urinary microbiome research (see funding acknowledgements).

urine culture followed, documenting the common existence of communities of living bacteria in adult female bladders, regardless of symptoms [3–5]. FUM characteristics appear related to clinical features, such as estrogen status and certain urinary symptoms [3–7]. The terms “microbiota” (the microbes themselves) and “microbiome” (the genetic material of those microbes) are becoming part of the clinical lexicon in various aspects of human health and disease. This review will highlight recent information concerning the FUM.

The Changing Clinical Paradigm

Prior concepts of microbes in the female urinary bladder were limited to a dichotomous concept of “sterile” versus “infected”, along with the poorly defined term “asymptomatic bacteriuria.” These limited concepts resulted in a limited clinical treatment algorithm, one that was dependent on antibiotic use. Documentation of the FUM provides an opportunity to improve antibiotic stewardship and clinical precision of treatment goals. Deeper knowledge of the FUM may provide etiologic insights for a wide spectrum of poorly understood lower urinary tract disorders, including simple and recurrent urinary tract infection, overactive bladder syndrome and urgency urinary incontinence. For example, previously unrecognized microbes may play pathogenic roles alone or in combination with other members of the FUM. In contrast, some microbes may play a protective, preventative role [8–10].

Improved Microbial Detection with Enhanced Urine Culture Techniques

The use of DNA sequencing, a very sensitive test, provided early evidence that bacterial DNA was present in the female urinary bladder. This technique revealed that urine obtained by transurethral catheter and suprapubic aspirate (and deemed ‘no growth’ by standard urine culture) closely resembled each other microbiologically. In contrast, the bacteria in ‘clean catch’ mid-stream urines more closely resembled the bacteria found in vaginal swabs. From these results, several conclusions were drawn: (i) urine taken directly from the bladder contains bacteria, as suprapubic aspiration bypasses the vagina; (ii) for research purposes one can use transurethral catheterization, as it samples the same microbial niche as does aspiration; and (iii) voided urine often contains vulvo-vaginal contamination, as such it is not a preferred urine sampling method for rigorously addressing questions concerning the microbiology of the bladder [2].

Although DNA sequencing revealed the presence of bacterial DNA in the bladder [1,2], it could not determine whether the bacteria were alive or dead. For that purpose, clinical urine cultures were needed. While the standard clinical microbiology urine culture was established and refined to detect *Escherichia coli* and a few other well-established uropathogens [11–13], this test does not detect or describe most of the microbes of the FUM, which may require special growth conditions. Simple refinements to the standard urine culture protocol (increased volume, various growth conditions, increased duration of incubation) allow a more complete description of the microbes present and show definitively that the bacteria detected by DNA sequencing are indeed alive [3–5,14]. Because the standard urine culture performs well only with respect to detection of *E. coli* and not most other uropathogens [14], we recommend all clinical laboratories adopt the Streamlined Enhanced Quantitative Urine Culture (EQUC) protocol as listed Table 1.

With improved microbial detection techniques comes the challenge of recognizing the relevance of the detected microbes, especially their relationship to clinical conditions of interest. If some microbes are protective, and indeed the evidence suggests that this is the case [6,15,16], then the simple approach of widespread antibiotic use to eradicate all bladder organisms is incorrect. Clinicians should be concerned that improper antibiotic usage could cause the urinary tract equivalent of *Clostridium difficile* infection, which is caused by antibiotic-induced disruption of the normal 'healthy' gastrointestinal microbiota [17]. For current clinical purposes, culture techniques (e.g. Streamlined EQUC) that provide additional information may be of particular relevance for women whose standard urine cultures show no growth and whose symptoms persist [14]. Further research will help refine treatment algorithms in this clinically important population.

FUM Characteristics

The typical FUM is less complex than the microbiota of the gut or oral cavity, both of which include substantially more distinct microbial organisms. The FUM tends to be dominated by a single genus, most often by *Lactobacillus*, but to a lesser degree by *Gardnerella*, *Streptococcus*, or *Corynebacteria*. Much less often, the genera *Escherichia, Aerococcus* or *Staphylococcus* dominate. In a subset of women, the FUM is diverse, having no dominant genus [1,2,5,7,14,18]. Thus, in some respects, the FUM resembles the vaginal microbiota. This similarity raises the question: Do the bladder and vagina share a common community of microbes or do these vastly different environments favor colonization by different microbes? The answer will come from sequencing the genomes of strains isolated from different pelvic floor sites of the same individual.

Prevailing Lower Urinary Research Does Not Include Microbial Interactions

In an effort to understand common lower urinary tract disorders in women, extensive research has been undertaken. This research has yielded significant insight into the function of the detrusor muscle and valuable information concerning the sensory role of the urotheium [19,20] and various urothelial receptors [21]. Each of these prior studies has provided additional insight into the understanding of a clinically relevant urinary condition. Prior research also has included multiple large studies to test efficacy and safety of oral medical for treatment of UUI, However, all these important studies were conducted without assessment of the interaction with or the potential role of the FUM. Assuming the urinary FUM has an important physiologic role, yet to be fully understood, it is likely that the microbial communities have varied and robust interactions with other urinary regulatory mechanisms.

This possibility is underscored by the knowledge that microbiota interact with the innate immune system of other organ systems, especially the gut [22] and skin [23], little is known of the innate immune system in the urinary tract and less about its interaction with the FUM. Since this highly regulated relationship maintains microbial equilibrium at the epithelial interface, it seems reasonable to assume that such interactions occur in at the urothelium-bladder lumen interface. A major component of the innate immune response are anti-microbial peptides (AMPs), which contribute to innate host defense by providing bactericidal or bacteriostatic activity prior to subsequent innate and adaptive immune

responses [24]. In a population of women undergoing pelvic prolapse (POP)/UI surgery, one research team reported a positive correlation between a greater abundance of one urinary AMP (β-defensin-1) in subjects with POP symptoms and reduced risk of post-operative UTI. They also determined that AMP activity was significantly more robust in individuals whose day-of-surgery standard urine cultures were positive for typical uropathogens or in individuals whose standard urine cultures became positive following surgery [16]. In an attempt to understand mechanism, another team reported that the cytokine interleukin-22 regulates human urothelial cell sensory and innate functions by modulating AMP synthesis [25]. Given the new knowledge that the FUM exists and the detection of AMPs within the adult urinary tract [26], it will be essential to clarify the physiologic role of urinary AMPs in health and disease.

Clinical Relevance of the FUM

There is insufficient evidence in the current literature to confirm any etiologic relationships between the FUM and most lower urinary tract symptoms; we lack normative data about the FUM from large, longitudinal studies across diverse populations. Yet, certain associations deserve further study. Some of these are discussed below.

Clinical Treatment Possibilities for UUI—Urgency urinary incontinence (UUI) is a common disorder, affecting many adult women who experience bothersome urinary urgency, frequency and urgency incontinence. Symptoms of urinary urgency incontinence (UUI) are highly variable within individuals and among affected women. Persistence of symptoms is typical, despite some treatment efficacy from behavioral techniques, oral mediations and a variety of other modalities. For many years, clinicians have suspected that UUI is a heterogeneous disorder. In one of the first studies to describe variability in the FUM of study participants seeking UUI treatment, the investigators reported an association between symptom severity and certain FUM characteristics, including the number and variety of microbes detected. They also detected a protective relationship between the pre-treatment FUM and UTI following urinary tract instrumentation with or without intravesical onabotulinumtoxin A [6,15]. In another study, researchers compared the baseline FUM of women with and without UUI symptoms. They identified statistical associations between UUI symptoms and several bacterial species, including *Actinomyces neuii, Actinotignum schaalii* (formerly *Actinobaculum schaalii*), *Aerococcus urinae, Corynebacteria coylae, Corynebacteria riegelii, Oligella urethralis*, and *Streptococcus anginosum*. Several of these species are considered uropathogens; however, most would not be detected by standard urine culture. *Lactobacillus* species are common dominant members of the vaginal microbiota and are considered to be protective. Intriguingly, while *Lactobacillus crispatus* in the FUM was associated with the non-symptomatic controls, *Lactobacillus gasseri* in the FUM was associated with UUI. This gives rise to the possibility that the roles of these organisms may differ in the bladder compared to their roles in the vagina [5]. In a third study of UUI-affected women planning UUI treatment with oral medication, investigators detected differences in UUI medication treatment response that appeared dependent on certain FUM characteristics that were detected in the baseline (pre-treatment) urine samples. Specifically, women who responded to oral medication UUI treatment had less microbial diversity than those who did not or responded only to increased medication doses [7]. Together, these

studies suggest that FUM heterogeneity may hold important clues to the roles played by microbes in both the etiology and treatment of UUI. In addition, these small studies suggest the possibility of a more personalized approach to UUI treatment that takes into account FUM characteristics, perhaps modulating these relevant characteristics for a more favorable treatment response.

Another clinically relevant patient group reports various lower urinary tract symptoms of unclear etiology, with urinary urgency, frequency and/or bladder pain; typically, the work-up is negative, including the standard urine culture. Most clinicians suspect that these patients are an etiologically heterogeneous group. The spectrum of bladder pain conditions has long been suspected to have an “infectious” etiology, although previous culture-based microbial detection methods have not confirmed this suspicion. More recent studies, using DNA-based approaches and voided urine samples, suggest that there may be a microbial component to these symptoms [27,28]. Confirmation, however, will require the use of catheterized samples, to distinguish vulvo-vaginal contaminants from true members of the resident bladder community. Until such studies are completed, the role of the FUM will remain uncertain in these patients with refractory lower urinary symptoms. Affected patients and their clinicians may benefit from the additional information provided by improved detection techniques, as some microbes not generally recognized as uropathogens may contribute to symptoms [29,30].

Clinical Treatment Possibilities for UTI—Simple UTIs are common and often require treatment. The interpretation of the standard urine culture is becoming increasingly nuanced [31]. The current clinical concept of a UTI is based on a single uropathogen invading the otherwise sterile bladder environment. Treatments are then based on eradicating the uropathogen. Much research has focused on the characteristics of well-known uropathogens, predominantly uropathogenic *Escherichia coli* (UPEC), and the cellular mechanisms that UPEC uses to attach to the urothelium and establish intracellular communities [32]. However, the emerging knowledge concerning the FUM may improve treatment precision with diminished over-reliance on systemic antibiotic use. Potential for probiotics and other microbial altering interventions will require assessment with a broader understanding of their effects on the FUM, as well as the clinical condition of interest. Clinicians also may find the simple diagnosis of UTI insufficient, as investigators have reported specific associations between uropathogens and UTI symptoms (Dune et al., submitted).

For all patients who use commonly prescribed systemic antibiotics, it is desirable to reduce their collateral undesired effects, including deleterious consequences to the “good” bacteria in the bladder and other microbial niches (e.g. vagina, bowel). In addition to improved detection and improved precision of treatment, the new FUM knowledge raises the possibility that clinicians could restore the healthy urinary microbiota following necessary antibiotic treatment (whether for urinary disorders or other clinically indicated uses). There is ample discussion of microbial restoration of the gut microbiota, an area of bacterial abundance. To advance microbial optimization of the urinary tract, additional knowledge about the desired characteristics of the healthy urinary microbiota will be needed. This is particularly important in the subpopulation of women affected by recurrent urinary tract

infection who are subjected to frequent doses of systemic antibiotics and/or low-dose antibiotic regimens for prevention of UTI recurrence [32].

Certain microbes have characteristics that protect against uropathogens. These microbes produce antibiotics, antimicrobial peptides and/or other antimicrobial compounds that inhibit or kill other microbes. For example, certain *Lactobacillus* species that colonize the vagina excrete lactic acid and hydrogen peroxide, inhibiting the growth of uropathogenic *E. coli* [33]. Microbes can also inhibit pathogens by outcompeting them for host receptors [34] or scarce nutrients [35]. Thus, optimization and/or restoration of the healthy FUM are likely aided by enhancement of the "good" bacteria.

In a study of women undergoing surgery for uncomplicated Stress Urinary Incontinence (SUI), hormonal status appeared related to FUM diversity. Menopausal women not on exogenous hormones had increased microbial diversity and their FUM was less likely to be predominated by a single microbe. A similar relationship was observed between microbial diversity and UUI symptoms. These results suggest that predominance (most often by *Lactobacillus* species) is typical of hormone-positive women and that loss of that predominance might be associated with UUI symptoms (Thomas-White et al., in review). That hormonal status has associations with certain FUM characteristics is consistent with the clinically useful role estrogen has in suppressing recurrent UTI in certain hypoestrogenic women [36].

Clinical Treatment Possibilities for Other Populations with Urinary Conditions—The scope of this review did not include male, pediatric, neurogenic, or obstetric populations, nor did it include upper urinary tract conditions, e.g. urinary stones. Investigators are beginning promising research to evaluate the FUM of these and other populations [1,4,37–41].

CONCLUSION

Improved techniques for microbial detection are available to advance the etiologic understanding, prevention, diagnosis and treatment of lower urinary disorders in adult women. The FUM may impact common lower urinary tract disorders, such as urinary incontinence and urinary tract infection. These effects could plausibly arise due to effects based on the characteristics of the whole community or effects of individual microbes. Refinements to our current nomenclature will be needed in order to adequately describe the FUM of healthy states, as well as the spectrum of vulnerable, dysbiotic microbial communities that may predispose women to lower urinary tract disorders.

Acknowledgments

We would like to thank the members of the Loyola Urinary Education and Research Collaborative for their contributions to the work described.

FUNDING

AJW and LB have been supported by NIH grants 2U10 HD41250, U01 DK58229, R21 DK097435, R56 DK104718 and P20 DK108268, a translational grant from the Falk Foundation and by RFC LU206998 from Loyola University Chicago. AJW has received funding for an Investigator Initiated Study VESI-12D01 from Astellas Scientific and

Medical Affairs Inc. Our funding sources have had no role in design or conduct of our studies; collection, management, analysis, and interpretation of our data; or in preparation, review, or approval of this or any other manuscript.

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- Traditional methods of microbial detection do not account for the majority of microbes present in the adult female bladder.
- Current nomenclature does not adequately describe the female urinary microbiota, including healthy states and the spectrum of vulnerable, dysbiotic microbial communities.
- Female urinary microbiota vary across multiple characteristics, including predominant organism and microbial diversity.
- The urinary microbiota of adult women may impact common lower urinary tract disorders, such as urinary incontinence and urinary tract infection.
- Insights into prevention, diagnosis and treatment of lower urinary tract disorders in adult women may be refined based on emerging knowledge of the female urinary microbiota.

TABLE 1

Recommended Streamlined Enhanced Quantitative Urine Culture[1]

Volume (μl) of Urine	Media	Conditions	Incubation(s) (h) for Microbial Identification
100	BAP[2] MacConkey CNA[3]	5% CO_2, 35°C	48

[1] In comparison, standard urine culture is 1 μl on BAP and MacConkey incubated aerobically at 35°C for 24 hours.

[2] Blood Agar Plate (5% sheep blood agar)

[3] Colistin-nalidixic acid agars