The microbiome in urological diseases

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Due to the rapid development of next-generation sequencing, it has become possible to obtain information on the sequences of all genes in a specific microbiome. The detection of bacteria in patients with no urinary tract infections indicated that the dogma that “urine is sterile” was false, leading to active research regarding the roles of the urinary microbiome in the human urinary tract. Here, we present a review of the current literature regarding the role of the microbiome in urology.

Keywords: Microbiota; Urine; Urologic diseases

INTRODUCTION

The term microbiome is a combination of “microbe,” or “living in the body” and “biome,” meaning ecosystem. The microbiome refers to the microorganisms living in the body and their genetic information, while the term microbiota refers to groups of microorganisms [1].

The human body is believed to contain 1.3 to 10 times as many microbes as human cells. Therefore, the human genome cannot be discussed without discussing microbes, which are sometimes referred to as a “second genome” [2].

Most bodily microorganisms are bacteria, but viruses, fungi, and protozoa are also found. The composition of the human microbiome varies between parts of the body, but a relatively balanced and stable community is maintained. There have been a number of investigations of the relationships of microorganisms with disease and metabolism. As recent studies have indicated that microbes have a significant impact on health, microbiomics has emerged as a growing research field in biology. Once the microbiome is completely interpreted as a map, the genes can be extracted from samples of blood, urine, stool, tissue, etc., and analyzed to predict, diagnose, and treat disease.

Identification of microorganisms is performed using the species specificity of 16S rRNA. To do this, the microorganisms are first isolated and then mass-cultured and confirmed through the 16S rRNA of the cultured colonies. However, the types of microorganisms present in nature that can be purely cultured in medium are limited. To overcome these limitations, many attempts have been made to study microorganisms without relying on culture. Next-generation sequencing (NGS) has made it possible to obtain information about the entire sequence of genes in a particular microbial community.

Urine culture is still regarded as the gold standard for urinalysis; the diagnostic accuracy is excellent [3]. However, commonly used culture techniques do not detect slowly growing or anaerobic pathogens, such as Corynebacterium or Ureaplasma species. Given the developments in 16S rRNA sequencing and enhanced quantitative urine culture (EQUC),
abundant and diverse urinary microbiomes can be identified in every individual. EQUC can isolate up to 80% of all bacteria from samples that do not grow bacteria on standard urine culture [4-8].

The Human Microbiome Project (HMP) was started in 2007 to characterize the human microbiome and analyze its role in human health and disease. Initially, the project focused on the gastrointestinal tract, nasal cavity, mouth, skin, and the vagina, and did not include the urinary tract because the bladder and urine were considered to be sterile [9-11]. However, there is now evidence that the healthy urinary tract has a urinary microbiome, with age- and sex-specific genera, that changes in urological disorders. Therefore, there is growing interest in the role of the urinary microbiome [12-14].

Here, we review the role of the microbiome in the field of urology, including studies of prostate cancer, bladder cancer, chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), interstitial cystitis/bladder pain syndrome (IC/BPS), urgency urinary incontinence/overactive bladder (UUI/OAB), stone disease, and urinary tract infection (UTI) (Table 1) [6,15-34].

THE MICROBIOME AND UROLOGICAL CANCER

Many infectious agents, which could act as cofactors in carcinogenesis, cause chronic inflammatory responses [35,36]. Certain commensal strains of bacteria may also control the outgrowth of pathogenic bacteria. This is consistent with other reports that the microbiome can control the immune response [37-39]. Therefore, the urinary microbiome may be involved in the regulation of pathogenic infection and cancer development.

1. Prostate cancer

Many pathogenic microorganisms are known to infect the prostate and induce symptomatic and asymptomatic inflammatory responses, including opportunistic endogenous Enterobacteriaceae, such as Escherichia coli and Pseudomonas spp, and sexually transmitted organisms (e.g., Neisseria gonorrhoeae, Chlamydia trachomatis, and Trichomonas vaginalis) [40,41]. Inflammation in the prostate plays an important role in the generation of prostate cancer, and cytokines such as interleukin (IL)-6 and IL-8 have been reported to be involved in prostate cancer [42]. Some reports have also suggested that a history of sexually transmitted disease increases the likelihood of prostate cancer [43-45].

In the gut microbiota of prostate cancer patients, the level of Bacteroides massiliensis was found to be elevated and those of Faecalibacterium prausnitzii and Eubacterium rectale were reduced in the gut microbiota, compared with levels in healthy controls [15]. Bacteroides species possess β-glucuronidase genes that remove sugars when the glycated substrate in the liver reaches the large intestine. Increased circulating levels of sugar-free xenobiotics or mutagens are considered to cause prostate cancer [46]. In addition, F. prausnitzii and E. rectale produce butyrate using acetate. This is one of the most abundant short-chain fatty acids in the colon and has anti-inflammatory properties, suggesting that it is one of the pathways for preventing prostate cancer [15]. Liss et al. [16] reported that bacteria associated with carbohydrate metabolism are abundant, and those producing B-vitamins are lacking, in patients with prostate cancer, suggesting that micronutrients might play roles in the prevention of such cancer.

In addition to the gut microbiome, a number of studies on prostate tissue microbiomes have been reported. No significant differences were reported in the compositions of microbiomes between prostate cancer and benign tissues [17,18]. Cavarretta et al. [17] evaluated the microbiome profiles of tumor, peri-tumor, and nontumor tissue and reported that Propionibacterium spp. were the most abundant species. The high abundance of Propionibacterium spp., predominantly composed of Propionibacterium acnes, is consistent with the proinflammatory role of P. acnes and supports reports of its association with prostate cancer and reports that the level of staphylococci was higher, whereas that of streptococci was significantly lower, in tumor/peri-tumor tissue than in nontumor tissue. Feng et al. [18] analyzed tumor tissues and adjacent benign tissues using shotgun-based integrated metagenomic and metatranscriptomic analysis in radical prostatectomy specimens. Escherichia, Propionibacterium, Acinetobacter, and Pseudomonas were the most abundant genera. As Pseudomonas infection has a negative association with metastasis, it was suggested that Pseudomonas could serve as a biomarker for active surveillance. Any such association requires validation in a large-scale study, but further work on the prostate bacterial microbiome would facilitate diagnosis and inform treatment decisions.

2. Bladder cancer

Bacteria modulate cancer risks via both catabolism and anabolism of carcinogenic chemicals such as nitrosamine and acetaldehyde. It remains unclear whether the urinary microbiome affects the development or progression of bladder cancer, or whether bladder cancer affects the composition, diversity, and abundance of the urinary microbiome.
| Disease          | Study                        | Year | Patients                              | Sample                  | Analysis technique       | Relevant microbiota                                                                 |
|------------------|------------------------------|------|---------------------------------------|-------------------------|--------------------------|-------------------------------------------------------------------------------------|
| Prostate cancer  | Golombos et al. [15]         | 2018 | Men with prostate cancer              | Fecal swab              | Whole-genome sequencing   | Prostate cancer group: *more Bacteroides massiliensis*  
Control group: *more Faecalbacterium prausnitzii, Eubacterium rectale* |
|                  | Liss et al. [16]             | 2018 | Men with prostate cancer              | Rectal swab             | 16S rRNA sequencing       | Prostate cancer group: *more Bacteroides, Streptococcus*  
Control group: *Tumor/peri-tumor tissue: *more Staphylococcus,  
*less Streptococcus* |
|                  | Cavarretta et al. [17]       | 2017 | Men who underwent radical prostatectomy | Prostate tissue         | 16S rRNA sequencing       | Tumor/peri-tumor tissue: *more Staphylococcus,  
*less Streptococcus* |
|                  | Feng et al. [18]             | 2019 | Men who underwent radical prostatectomy | Prostate tissue         | Whole-genome sequencing   | *Escherichia, Propionibacterium, Acinetobacter, Pseudomonas* |
| Bladder cancer   | Xu et al. [19]               | 2014 | Urothelial carcinoma patients         | Midstream urine         | Not available             | Bladder cancer group: *more Streptococcus, Pseudomonas, Anaerococcus* |
|                  | Wu et al. [20]               | 2018 | Men with bladder cancer               | Midstream urine         | 16S rRNA sequencing       | Bladder cancer group: *more Acinetobacter, Anaerococcus, Rubrobacter, Sphingobacterium,  
Atopostipes, Geobacillus*  
Control group: *more Serratia, Proteus, Roseomonas, Ruminiclostridium-6, Eubacterium-  
xylanophilum* |
|                  | Bučević Popović et al. [21] | 2018 | Men with non-muscle-invasive bladder cancer | Midstream urine         | 16S rRNA sequencing       | Bladder cancer group: *more Fusobacterium, Actinobaculum, Facklamia, Campylobacter*  
Control group: *more Veillonella, Streptococcus, Corynebacterium* |
| CP/CPPS          | Shoskes et al. [22]          | 2016 | Men with CP/CPPS                      | Midstream urine         | 16S rRNA sequencing       | CP/CPPS group: *more Clostridia, Bacteroides*  
Control group: *more bacilli* |
|                  | Mândar et al. [23]           | 2017 | Men with CP/CPPS                      | Semen                   | 16S rRNA sequencing       | CP/CPPS group: *more Proteobacteria*  
Control group: *more Lactobacilli (especially Lactobacillus iners)*  
CP/CPPS group: *less Prevotella* |
|                  | Shoskes et al. [24]          | 2016 | Men with CP/CPPS                      | Immersing soiled glove tip after rectal examination in sterile saline | 16S rRNA sequencing       | CP/CPPS group: *less Prevotella* |
| IC/BPS           | Siddiqui et al. [25]         | 2012 | Women with IC                         | Midstream urine         | 16S rDNA sequencing       | IC group: *more Lactobacillus* |
|                  | Nickel et al. [26]           | 2019 | Women with IC/BPS                     | Midstream urine         | Electrospray ionization—time-of-flight—mass spectrometry | IC/BPS group: *more Lactobacillus gasseri  
*less Corynebacterium* |
|                  | Abernethy et al. [27]        | 2017 | Women with IC/BPS                     | Catheterized urine      | rRNA sequencing           | IC group: *less Lactobacillus acidophilus* |
|                  | Braundmeier-Fleming et al. [28] | 2016 | Women with IC/BPS                     | Stool and vaginal swab  | 16S rRNA sequencing       | IC/BPS group: *less Eggerthella sinus, Collinsella aerofaciens, F. prausnitzii, Odoribacter splanchicus, Lactonifactor longiformis* |
### Table 1. Continued

| Disease          | Study                                    | Year | Patients | Sample                                      | Analysis technique | Relevant microbiota                                                                 |
|------------------|------------------------------------------|------|----------|---------------------------------------------|--------------------|-------------------------------------------------------------------------------------|
| UUI/OAB          | Fok et al. [29]                          | 2018 | Women undergoing POP/SUI surgery            | Vaginal and perineal swab, catheterized urine | 16S rRNA sequencing | Higher OABq symptom severity score: more **Atopobium vaginae, Finegoldia magna**     |
| Wu et al. [30]   |                                          | 2017 | Women with OAB                             | Catheterized urine | 16S rRNA sequencing | OAB group: more **Sneathia, Staphylococcus, Proteus, Helcococcus, Gemella, Mycoplasma, Aerococcus**  |
| Pearce et al. [6]|                                          | 2014 | Women seeking UUI treatment                | Catheterized urine | 16S rRNA sequencing and EQUC | UUI group: more **Actinobaculum, Actinomyces, Aerococcus, Arthrobacter, Corynebacterium, Gardnerella, Oligella, Staphylococcus, Streptococcus** |
| Karstens et al.  |                                          | 2016 | Women with daily UUI                       | Catheterized urine | 16S rRNA sequencing | UUI group: more **Sphingomonadales, Chitinophaga, Bravundimonas, Cadidatus Planktoluna, Alteromonadaceae, Elizabethkingia, Methylobacterium, Caldicellulosiruptor, Stenotrophomonas** less **Prevotella, Comamonadaceae, Nocardioides, Mycobacterium** |
| Thomas-White et al. [32] |                               | 2017 | Women undergoing SUI surgery              | Voided or catheterized urine | 16S rRNA sequencing | Hormone-negative women: less **Lactobacillus, Gardnerella** |
| Urinary stone    | Stern et al. [33]                         | 2016 | Kidney stone patients                      | Fecal sample       | 16S rRNA sequencing | Kidney stone patients: more **Bacteroides** CONTROL GROUP: more **Prevotella** |
| Tang et al. [34] |                                          | 2018 | Kidney stone patients                      | Fecal sample       | 16S rRNA sequencing | Kidney stone patients: more **Alloprevotella, Erysipelotactostridium, unidentified Lachnospiraceae, Phascolarctobacterium, Megamonas, Actinobacter, Escherichia-Shigella, Sutterella** |

CP/CPPS, chronic prostatitis/chronic pelvic pain syndrome; IC/BPS, interstitial cystitis/bladder pain syndrome; UUI/OAB, urgency urinary incontinence/overactive bladder; POP/SUI, pelvic organ prolapse/stress urinary incontinence; EQUC, enhanced quantitative urine culture.
Schistosoma haematobium bladder infection and bladder Fusobacterium, Sphingobacterium, and Enterococcus species were considered to be potential markers of infection, and Trabulsiella and Weissella were considered to be markers of Treponema bovis) has long been used to treat urothelial bladder cancer, including bladder cancer [48,49].

Bacteria produce proteases that can act inside and outside of cells. These enzymes function as extracellular toxic factors that play an important role in host tissue degradation as well as evasion and destruction of host physical barriers. Among these factors, many bacterial enzymes capable of degrading ECM, including collagenases, elastases, and hyaluronidases, have been widely characterized [50-52]. In addition, bacterial invasion of tissues leads to inflammation, a reaction that further sustains ECM remodeling, and production of oxygen radicals, leading to mutations that cause DNA damage and both the development and progression of cancer [53].

There is a well-documented association between chronic Schistosoma haematobium bladder infection and bladder squamous cell carcinoma. However, the mechanism responsible for this association has not been clearly identified. Early studies suggested that bladder tumor development was caused by N-nitrosamines, polyaromatic hydrocarbons, free radicals, and microbes [54,55]. Adebayo et al. [56] investigated the urinary microbiomes of patients with urogenital schistosomiasis and found that certain urinary microbes including Fusobacterium, Sphingobacterium, and Enterococcus species (all of which are immunostimulatory) distinguished patients with urogenital schistosomiasis infections from healthy individuals. Of these microbes, Sphingobacterium and Aerococcus were considered to be potential markers of infection, and Trabulsiella and Weissella were considered to be markers of noninfection.

Bacille Calmette–Guérin (BCG, live attenuated Mycobacterium bovis) has long been used to treat urothelial bladder cancer. The mechanism by which the BCG vaccine prevents the recurrence and progression of bladder cancer remains poorly understood. However, BCG vaccine injection into the bladder induces inflammatory reactions that include antitumor immune responses [19,57].

Assuming that microbiota in the urinary tract could help to treat cancer if microorganisms are involved in the development and progression of cancer, it has been reported that oral administration of Lactobacillus casei strain Shirota afforded a more potent response and was safer than BCG vaccine when used to treat superficial bladder tumors [62].

Xu et al. [19] reported that streptococci were enriched in urine from bladder cancer patients, although the study was preliminary in nature and thus had a small sample size. Wu et al. [20] analyzed midstream urine from 31 patients with bladder cancer and 18 controls; Actinobacter, Anaerococcus, and Sphingobacterium species were abundant in bladder cancer patients. Herbaspirillum, Porphyrobacter, and Bacteroides species were detected in bladder cancer patients at high risk for recurrence and progression. However, another study found no significant differences in microbial diversity or the urinary microbiota between cancer patients and controls [21].

3. The Microbiome and CP/CPPS

The cause of CP/CPPS in men has not yet been clearly identified. The diagnosis is made by exclusion of diseases that show similar symptoms, such as UTIs, cancer, and IC/BPS with no anatomical abnormalities [63].

Several studies have compared the diversity of urine and intestinal microflora between CP/CPPS patients and controls. Shoskes et al. [22] analyzed the urinary microbiome in midstream urine from 25 CP/CPPS patients and 25 control subjects using 16S rRNA sequencing and found that bacterial diversity was higher in the CP/CPPS group than in the control group. Clostridia and Bacteroides species were over-represented, bacilli were under-represented, and the prevalence of anaerobic bacteria was significantly higher in the CP/CPPS group than in the controls. Mândar et al. [23] compared the seminal microbiome using 16S rRNA sequencing with semen from 21 CPPS patients and 46 control males. The species diversity was higher, and the numbers of lactobacilli (especially Lactobacillus iners) were lower, in the CPPS group.

CPPS is also known to be related to intestinal symptoms, which in turn are associated with gut dysbiosis [11] Shoskes et al. [24] showed that gut microbiome diversity was low in CP/CPPS patients, the distribution differed from that in the control group, and a decreased count of Prevotella with anti-inflammatory effects may serve as a biomarker for identifying patients with CP/CPPS.

4. The Microbiome and IC/BPS

IC/BPS is defined as suprapubic pain related to bladder filling, accompanied by other symptoms, such as increased daytime and night-time urination frequency, in the absence
of proven urinary infection or other obvious causes. Therefore, diagnosis requires the exclusion of infection. However, high-throughput sequencing techniques for the characterization of microbiota in asymptomatic healthy controls and female IC patients show differences in urine composition between groups [25]. Reduced microbial diversity is evident in patients with IC, and the abundance of lactobacilli was significantly elevated in 90% of IC patients compared with 60% of controls. Another study showed low levels of Corynebacterium and high levels of Lactobacillus gasseri in the urine of BPS patients [26]. However, the above two studies used midstream urine samples, so the vaginal microbiome may have been contaminated. Abernethy et al. [27] reported that microbial diversity was decreased in catheterized urine samples, as in the above study, but Lactobacillus acidophilus was rather low.

The stool microbiome has also been studied for potential biomarkers and targeted therapies in patients with IC/BPS. One study showed that the level of some bacterial species, including Eggerthella lachnii, Clostridium negranum, F. prausnitzii, Odoribacter splanchnicus, and Lactobacillus johnsonii, was reduced in stool samples from patients with BPS [28].

5. The microbiome and UUI/OAB

UUI is a disease that significantly affects the quality of life of patients, mainly women and the elderly, and may be a symptom of OAB or neurogenic detrusor hyperactivity. Many studies of the urinary microbiome have been conducted in patients with OAB and UUI, because OAB syndrome is frequently associated with UUI.

Fok et al. [29] reported that two bacterial species, Atopobium vaginae and Finegoldia magna, are associated with preoperative urinary symptom severity in women with stress urinary incontinence/pelvic organ prolapse and are thought to be factors affecting OAB symptoms. Wu et al. [30] reported that urinary microbiome diversity was lower in OAB patients than in healthy controls, and that decreases in bacterial diversity and richness were more severe in OAB patients with depression. In addition, some bacterial genera showed differences according to the presence of anxiety or depression in OAB patients, suggesting the presence of a brain-bladder-microbiome axis.

Research on the urinary microbiome, perturbation of which may cause functional disorders such as UUI, may help to optimize diagnosis and treatment. Several studies that have compared the urinary microbiomes of female UUI patients and healthy controls have reported significant differences in bacterial urine compositions and have reported that the differences affect symptom severity and treatment responses [67,31] Compared with controls, UUI patients exhibit higher Gardnerella and fewer Lactobacillus sequence profiles. Additionally, in culture tests using EQUC, nine genera (Actinobaculum, Actinomyces, Aerococcus, Arthrobacter, Corynebacterium, Gardnerella, Oligella, Staphylococcus, and Streptococcus) were more frequently found in samples from UUI patients [6]. Lactobacillus was isolated from both groups, but notably, L gasseri was cultured more frequently from UUI urine and Lactobacillus crispatus more commonly from control urine.

Thomas-White et al. [32] reported that the urinary microbiome was more diverse in patients with a high body mass index and more UUI symptoms, and this diversity was associated with low levels of Lactobacillus in hormone-negative women (postmenopausal women not taking exogenous hormones). No correlation was evident between the urinary microbiome and stress urinary incontinence symptoms. In contrast, Karstens et al. [31] reported that UUI symptom severity was higher in patients with low microbial diversity. They attributed these contradictory results to the small numbers of patients, differences among those patients (primarily postmenopausal women not taking estrogen therapy), differences in urine sample volumes, and the different data preprocessing/filtering techniques used.

Because a high diversity in UUI patients correlates with the response to anticholinergic treatment, the response to oral UUI medication can be predicted if the urinary microbiome is analyzed. In one study, higher variety was associated with a reduced probability of a response to solifenacin; higher doses were needed by such patients [7].

This new view of the complex bacterial network underlying functional disorders, such as UUI, may help to optimize our understanding and treatment, but further research is needed to gain insight into the overall picture [64].

6. The microbiome and stone disease

The role of microorganisms in the formation of urinary stones is relatively well established. Urea-splitting organisms, such as Proteus mirabilis and Ureaplasma urealyticum, are known to raise urinary pH, resulting in crystallization of calcium, magnesium, and phosphate in urine and leading to the formation of struvite stones known as infection stones.

The gut microbiome is a regulator of diet-driven metabolism, and gut dysbiosis is associated with metabolic diseases, such as diabetes, obesity, and cardiovascular disease. Diet is one of the most important factors for stone formation; it is important to consider the relationship between gut dysbiosis and urinary stone formation. Stern et al. [33] studied the differences and characteristics of gut microbiomes in patients
with and without kidney stones. Kidney stone patients had higher levels of *Bacteroides* and less *Prevotella* than the control group. Tang et al. [34] recently analyzed the characteristics of gut microbiomes in kidney stone patients and found an abundance of proinflammatory bacteria and fewer anti-inflammatory bacteria in kidney stone patients than in healthy controls.

There have been a number of studies on the relationship between the generation of stones and *Oxalobacter formigenes*. Recent studies have demonstrated that *O. formigenes* reduces urinary oxalate by reducing intestinal absorption [65]. Some studies described *O. formigenes* as a probiotic with the potential to treat hyperoxaluria [66-69].

### 7. The microbiome and UTI

The microbiome is likely to play a role in UTIs as they are associated with bacteria. The pathogenesis of UTIs is often explained by the ascending of intestinal bacteria. Recent studies have reported the important roles of vaginal, urinary, and intestinal microbiota in the regulation of disease activity [70]. Commensal bacteria may surpass pathogens and act as barriers to uropathogens by releasing inhibitory or bactericidal molecules. A study of patients with indwelling urinary catheters suggested that microbial diversity plays a protective role in the development of UTIs and that UTIs can be caused by dysbiosis of commensals [71].

The most common treatment method for UTIs is antibacterial therapy. However, the use of broad-spectrum antibiotics may negatively affect beneficial bacterial populations of the host and, consequently, affect the selective growth of pathogenic bacteria. Prolonged use of antibiotics can cause unwanted side effects, such as bacterial resistance [72].

*Lactobacilli* can prevent the adherence, growth, and colonization of uropathogenic bacteria [73]. The antibacterial activity of *Lactobacillus* strains can be explained by acidification of mucosal surfaces, inhibition of adhesion of pathogens, production of substances, such as vitamins and immunomodulators, and synergistic activity with the host’s immune system [74].

In the glycosaminoglycan layer of the vaginal epithelium, lactic acid excreted into the environment during carbohydrate metabolism reduces the pH, creating a poor environment for most pathogenic bacteria [75]. *Lactobacillus* species also produce antibacterial metabolites, including hydrogen peroxide and bacteriocin [76,77]. Because of this characteristic, studies have been conducted with *Lactobacillus* strains, and there are reports that *Lactobacillus* strains such as *Lactobacillus rhamnosus* GR-1, *Lactobacillus fermentum* RC-14, and *Lactobacillus reuteri* B-54 are effective for the treatment and prevention of UTIs [78-83]. However, the dose, duration, and routes of administration have not been established, and the evidence for efficacy is weak.

Fecal microbiota transplantation has been attempted to modulate the effects of the intestinal microbiota on the pathogenesis of recurrent UTIs. Tariq et al. [84] reported decreases in recurrent UTIs and the antibiotic-resistance profile of urinary bacteria in patients with recurrent *Clostridium difficile* infections during the year following fecal microbiota transplantation. In addition, recurrent UTIs were reported to have been treated by fecal microbiota transplantation in kidney transplant recipients [85]. Clinical trials of the safety and tolerability of urine transfusion in patients with recurrent UTIs have been conducted, but no results have been reported.

NGS can be used to identify causative pathogens in UTIs and to identify patterns of resistance to antibiotics [86,87]. Because it is clear that the urinary microbiome changes during UTI and antibiotherapy, efforts to prevent or treat recurrent UTIs by delivery of single strains into the bladder [88,89] or vagina [83] or via fecal microbiota transplantation, will undoubtedly continue.

### CONCLUSIONS

The observation that the urinary tract is not a sterile environment and has a complex and distinct urinary microbiome has led to a new perspective on urological diseases, which had heretofore been considered to have no microbiological etiology.

Consensus on terminology, specimen collection, storage techniques, and analytic approaches is necessary, and further large-scale studies are required. Once the urinary microbiome has been well characterized and a database to understand how these microorganisms are involved in human health and disease is completed, the microbiome will play many important roles in the diagnosis, treatment, prognosis, and prevention of urinary disease.

### CONFLICTS OF INTEREST

The authors have nothing to disclose.

### AUTHORS’ CONTRIBUTIONS

Research conception and design: Young Ho Kim. Data acquisition: Kwang Woo Lee and Young Ho Kim. Data analysis and interpretation: Kwang Woo Lee. Drafting of the manuscript: Kwang Woo Lee. Critical revision of the manu-
script: Ho Yeon Song and Young Ho Kim. Administrative, technical, or material support: Young Ho Kim. Supervision: Ho Yeon Song and Young Ho Kim. Approval of the final manuscript: all authors.

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