Microbiomeâs Function in Urinary Bladder Disorders

Subjects: Urology & Nephrology

Contributor: Young Ho Kim

The beneficial role of the microbiota in preserving the human body’s homeostasis is expected to provide a protective role against infections by forming a physical barrier, and adds to the immune system’s development . However, the detailed physiological impact of the urinary microbiome remains unknown. The changes in the urinary microbiota have been linked to the development of a variety of urinary diseases. These transitions will guide the management of a variety of common urinary diseases associated with changes in the urobiome.

urinary bladder
microbiome
disease

1. Introduction

The Human Microbiome Project has examined the makeup of bacterial communities in a variety of human body niches, including the mouth cavity, skin, gastrointestinal system, and vagina, as well as their function in health and illness [1][2]. The urinary bladder was initially excluded from the research since urine was historically deemed sterile due to the notion that all microorganisms were harmful [2][3]. Microbial communities in the urinary tract were first discovered less than a decade ago. Numerous scientists have now verified the existence of a urinary microbiota [4][5]. Technological advancements will offer physicians better knowledge of the status of the urinary microbiome.

Recent research has shifted its emphasis to defining the microbiome and its relationship to human health. Thus, understanding the human urinary microbial makeup and how it changes under pathological situations may facilitate the creation of novel preventive, diagnostic, and therapeutic methods. The current level of knowledge about the urine microbiome is given in this review, with an emphasis on its relevance for health maintenance and its involvement in disease development.

2. The Functional Role of the Urinary Microbiome

Although the unique roles of the urine microbiome have not been fully identified, it is believed that, similar to other mucosal areas such as the gastrointestinal and female reproductive tract, the microbiota inside this location are essential for urinary tract homeostasis [6]. Few studies are examining the unique function of the urine microbiota in homeostasis maintenance and the underlying processes [7]. The urine microbiota, like other human microbial communities, may play a role in regulating the immune response [7]. Indeed, it has been shown that some bacteria metabolites may have a role in regulating the immune response and inflammation associated with bladder disorders [8]. The abundance of certain resident macrophages in the urinary tract may indicate the critical role of host cellâmicrobial interaction in preparing the immune response to infection [9][10]. However, additional investigation of microbial-mediated processes of urinary tract homeostasis is required.

The microbiota has a significant impact on the creatures it inhabits. A recent study revealed some

interesting findings by comparing germ-free (GF) mice to mice with a normal microbiota (i.e., specific pathogen-free, SPF) animals [11]. This study can examine the effect of microbiota on the bladder transcriptome. In general, GF mice have lower body fat and slower metabolic rates, smaller livers, a lower total surface area of the small intestine, and a bigger caecum [11][12] in comparison to other mice. This study reported that GF urinary bladders were 25% lighter than bladders from mice maintained under conventional SPF settings [11]. Additionally, there were differences in the expression of the uncharacterized immunoglobulin genes (Igkv1-122, Igkv4-68), but interestingly, the lack of microbiota had no effect on the expression of genes involved in microbe recognition and their products [11]. Some of the alterations in gene expression, such as circadian rhythm, extracellular matrix, and neuromuscular synaptic transmission support the notion that the microbiota has an effect on gene expression in the urinary bladder. The functional study of the urinary microbiome in the health and illness of the bladder can be enhanced by using GF mice. Numerous studies demonstrate a link between the urinary microbiome and bladder health. Assessing the impact of individual microbial strains requires the establishment of gnotobiotic mice, which can be generated by microbial reconstitution of GF mice with single organisms and defined mouse- or human-derived microbial consortia [13].

3. UTI and Urinary Microbiome

The study of the urine microbiome is becoming increasingly important due to the fact that changes in its composition have been linked to the development of many illnesses, mainly UTIs. UTIs are the bodyâs second most frequent bacterial infection, accounting for around 8.1 million medical visits each year [14]. UTIs are prevalent in women and commonly reoccur. According to the National Health and Nutrition Examination Survey III data, UTIs occur in 53,067 cases per 100,000 women throughout their lifetime, compared to 13,689 cases per 100,000 males [15]. The greatest gender disparity comes between the ages of 16 and 35, when women are about 35 times more likely to be impacted [15]. Women have a greater incidence of urinary colonization than men. Anatomically, the vaginal cavity and rectal opening are located in close proximity to the urethral opening. Additionally, women have more wet periurethral regions, which are suitable growing grounds for bacteria [16]. Due to the shorter urethral length, the bacteria entering the urethra are more likely to ascend to the female bladder than the male bladder [16]. Uropathogenic E. coli (UPEC) is responsible for about 80% of infections. Although virulence characteristics like sticky fimbriae play a role in UPEC pathogenesis, predisposing host variables also play a role in UTIs, especially in people who have repeated episodes [17]. UTI is defined as an infection of the urethral cavity followed by an infection of the lower urinary tract up to the bladder, resulting in urethritis and cystitis, respectively [18]. When infections cause pyelonephritis in the kidneys they can even spread via the bloodstream, resulting in systemic infection (urosepsis) [19].

Patients with culture-confirmed UTI should receive oral antibiotics, depending on their clinical status [20]. Sulphonamides or first-generation cephalosporins are the most often prescribed oral antibiotics. However, there is rising worry about urinary pathogen resistance to these antibiotics, as seen by the increasing frequency of therapeutic failures following empiric therapy [21]. Recent examination of the impact of antibiotic prophylaxis on urinary microbiota [22] showed that when the urinary microbiota of preventive trimethoprim-sulfamethoxazole therapy and a healthy control group were compared, the antibiotic group substantially increased the number of pathogenic species while decreasing microbial diversity relative to the healthy control group. These results emphasize the need to show sensitivity when choosing optimum preventive regimens and indicate that probiotic prophylaxis may be more successfully explored. [22][23]. The comparative genomic analyses were performed on E. coli isolates from adult female bladders without signs of lower UTI, with a clinical diagnosis of UTI, or with lower urinary tract symptoms (LUTS) [24]. The genetic compositions of the E. coli isolates or the makeup of the complete urobiome was unable to differentiate between the urinary microbiomes of persons with UTI and those without LUTS [24].

This study suggests that UTI symptoms linked with E. coli detection are more likely the result of microbiome composition. Recently, the study comparing urine next-generation sequencing (NGS) of patients with acute uncomplicated cystitis (AUC) and recurrent cystitis (RC) revealed differences in microbiome patterns [25]. Transurethrally obtained urine specimens from the RC group had substantially more microbiome diversity than the AUC group. Pseudomonas, Acinetobacter, and Enterobacteriaceae were identified in the urine NGS findings for the AUC group, while Sphingomonas, Staphylococcus, Streptococcus, and Rothia spp. were detected in the RC group [25]. Significant variations in bacterial diversity and patterning were seen between AUC and RC patients. This study suggests that AUC can be considered a transient infection produced by a single pathogenic organism, while dysbiosis seems to play a more significant role in the pathophysiology of RC [25][26]. RC may be linked with urinary tract dysbiosis, but more study is necessary [25][27].

Numerous UTIs go unreported and untreated, particularly in older individuals who frequently have polymicrobial UTI samples. The presence of significant uropathogenic species in mixed culture urine samples from older individuals, as well as resistance to first-line antibiotics with potentially enhanced resistance to ciprofloxacin and trimethoprim, was described [28][29]. Most notably, the study demonstrates that E. coli isolated from polymicrobial UTI samples is statistically more invasive than E. coli recovered from monomicrobial culture samples in in vitro epithelial cell infection tests [30]. E. coli contamination in polymicrobial UTI samples may offer an elevated danger to human health [30]. Furthermore, the function of enterococci in the pathogenesis of polymicrobial infections provides insight into the bacterial cooperation process. When virulent enterococci were evaluated in the presence or absence of E. coli strains in the in vivo Caenorhabditis elegans model, a synergistic impact on virulence was seen when enterococci and E. coli were compared to enterococci alone or E. coli alone [31]. Enterococcus faecalis has the ability to modify its immediate environment via signaling, therefore promoting the growth of other coinfecting organisms [31]. Increasing reports support that a single external pathogenic bacterial invasion is insufficient to account for UTI-associated disease in humans. Both an imbalance in the urine microbiota repertoire and polymicrobial pathogenic causes should be correlated.

Lactobacilli species such as L. crispatus, L. iners, and so on are commensal bacteria that reside in healthy females [32]. These Lactobacilli deficits have been linked to the colonization of UTI-causing uropathogens [2][33]. Predisposition to get UTI is linked with a decline of Lactobacillus iners in the patients who develop postoperative UTI [34][35]. The change in the urine microbiota, in conjunction with other risk factors (age and estrogen levels) contributes to the development of postoperative UTI with uropathogens such as E. coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa [34][35]. The vaginal microbiome can influence the hostâs susceptibility to UTI. According to the clinical study on young women with a history of recurrent UTIs, women with recurrent UTIs become more resistant when their vaginal microbiome is modified with probiotics such as Lactobacillus crispatus [36]. Intravaginal probiotic treatment with L. crispatus showed significant reduction in recurrent UTI associated with high-level vaginal colonization with L. crispatus [36]. The regulatory effect of the vaginal microbiome on UTI was further supported by the report that women who have bacterial vaginosis as a result of anaerobic Gardnerella vaginalis overgrowth experience more UTI than women who have healthy microbial communities consisting primarily of Lactobacillus [37]. Clinical studies indicate that the makeup of a womanâs vaginal microbiome has an effect on her susceptibility to recurrent UTI [38]. Bladder exposure to G. vaginalis induces E. coli egress from latent intracellular E. coli reservoirs in the bladder and increases the risk of life-threatening E. coli [38]. G. vaginalis exposures were sufficient to induce bladder epithelial apoptosis and exfoliation, as well as interleukin-1 receptor-mediated kidney damage that persisted after G. vaginalis clearance from the urinary system [38]. This study provides the etiology of recurrent UTI, in which illness may be triggered by brief but potent urinary tract exposures to vaginal bacteria. Altogether, increasing evidence support the notion that single invasion by an

external pathogenic bacterium fails to explain UTI-associated pathology in humans. The complete understanding of UTI needs to consider both an imbalance in the urine microbiota repertoire and polymicrobial pathogenic sources [2][39].

4. Bladder Cancer and Urinary Microbiome

Limited research has been conducted on the bladder microbiome involvement in urological cancers. Recent studies indicate that the human microbiome can affect cancer formation, however the function of microbes in bladder cancer pathogenesis has not been investigated. According to a study comparing urine samples from healthy people to bladder cancer patients using 16S rRNA sequencing, an abundance of the genus Streptococcus in bladder cancer patients was detected [40]. Bladder urothelial carcinoma (UBC) is the sixth most common kind of cancer globally [41]. UBC can be categorized as non-muscle invasive, muscle invasive, or locally advanced/metastatic [42]. UBC is characterized by a heterogeneous tumor cell population and surrounding tumor microenvironment (TME). Given that the microbiota has been linked to the formation of cancer in a variety of tissues, urinary microbiome is also implicated in UBC. Only a few studies have examined the relevance of the microbiome in urologic malignancy.

Several studies were performed to define and compare the bladder cancer patientsâ urine microbiota to that of healthy controls. The potential changes in the extracellular matrix caused by the microbiota and the subsequent inflammation may play a role in carcinogenesis [43]. This study recruiting male bladder cancer patients and non-neoplastic controls collected midstream urine. Cancer patientsâ urine samples were enriched with some bacterial genera (e.g., Acinetobacter, Anaerococcus, and Sphingobacterium), but showed a decrease in others (e.g., Serratia, Proteus, and Roseomonas) [43]. Enrichment of Herbaspirillum, Porphyrobacter, and Bacteroides was identified in cancer patients with a high risk of recurrence and progression, suggesting that these genera might serve as risk stratification biomarkers [43]. Another study was performed to analyze bacterial populations using 16S sequencing in mid-stream urine specimens obtained from male patients diagnosed with bladder cancer and healthy, age-matched males [44]. Although microbial diversity and overall microbiome composition did not change substantially between groups, the study detected more abundant operational taxonomic units (OTUs) belonging to the genus Fusobacterium as a potential protumorigenic pathogen enriched in the bladder cancer group. OTUs from the genera Veillonella, Streptococcus, and Corynebacterium were less prevalent in the bladder cancer group [44]. An additional study reported that the midstream urine samples from bladder cancer patients exhibited a higher abundance of Actinomyces than the control group. The study suggested that the increased prevalence of Actinomyces europaeus in bladder cancer patient samples may be diagnostic of bladder cancer [45]. More recently, bladder cancer patientsâ urine microbiota was compared to that of healthy controls by utilizing 16S rRNA sequencing of voided urine samples. Bacterial populations were analyzed using 16S sequencing in urine specimens taken from bladder cancer patients and healthy, age-matched controls [44]. While microbial diversity and overall microbiome composition did not vary substantially across groups, the genus Fusobacterium was substantially enriched in the bladder cancer group and can be considered as a potential protumorigenic pathogen [44]. In healthy urines, the genera Veillonella, Streptococcus, and Corynebacterium were more prevalent [44]. However, owing to the small sample size, more research is required to establish if the urine microbiota is linked with bladder cancer.

Although these studies performed on the bladder cancer patients suggest the potential relationship between the bladder microbiome and bladder cancer, these studies collected voided urine specimens (midstream urine samples) which mischaracterized the urinary bladder microbiome for the urogenital microbiota [22][33]. A further comparative study of microbial communities in urine obtained via suprapubic aspiration or transurethral catheter should be performed in order to examine the contribution of the urinary bladder microbiome in bladder

cancer. A recent study evaluated the need to carefully compare the microbiome profiles linked with the urine and bladder mucosa in bladder cancer patients. Tissue samples were obtained from patients after transurethral excision of cancer tissue [46]. Simultaneously, urine samples were collected from the same individuals by transurethral resectoscopy. As âfive suspicious genera,â Akkermansia, Bacteroides, Clostridium sensustricto, Enterobacter, and Klebsiella were overrepresented in tissue samples compared to urine [46]. This study discovered significant differences in some taxa, suggesting that the bladder tissue microbiota and the urine microbiota may differ to some extent [2][46]. Greater knowledge of the microbiomeâs function in the development and progression of bladder cancer may open the way for novel treatment approaches. The urine microbiota may serve as a biomarker for bladder cancer and as a therapeutic target. Finally, **Table 1** contains a description of the major bacterial genera found in individuals with urinary diseases.

Table 1. A summary of the bacterial genera reported in individuals with urinary disease.

Disorder	Subjects	Specimens	More Abundant Microbiome than Control Group	References
UI/OAB	Women with MUI	Catheterized urine	No difference in Lactobacilli, but six bacterial community types identified	[47]
	Women undergoing POP/ SUI surgery	Catheterized urine	OAB group: Atopobium vaginae, Finegoldia magna	[48]
	Women with OAB	Midstream urine and vaginal swab	OAB group: Proteus (Less: Lactobacillus)	[49]
	Women undergoing SUI surgery	Voided or catheterized urine	Hormone-negative women: (Less Lactobacillus, Gardnerella)	[45]
	Women with OAB	Catheterized urine	OAB group: Sneathia, Staphylococcus, Proteus, Helcococcus, Gemella, Mycoplasma, Aerococcus	[50]
	Women with daily UUI	Catheterized urine	UUI group: Sphingomonadales, Chitinophaga, Brevundimonas, Cadidatus Planktoluna, Alteromonadaceae, Elizabethkingia, Methylobacterium, Caldicellulosiruptor, Stenotrophomonas(less: Prevotella, Comamonadaceae, Nocardioides, Mycobacterium)	[51]
	Women seeking UUI treatment	Catheterized urine	UUI group: Actinobaculum, Actinomyces, Aerococcus, Arthrobacter, Corynebacterium, Gardnerella, Oligella, Staphylococcus, Streptococcus	[52]
	Women with IC/BPS	Midstream urine	IC/BPS group: Lactobacillus gasseri (less Corynebacterium)	[53]
	Women with IC/BPS	Midstream urine	No difference in genus	[54]
	Women with IC/BPS	Midstream urine and vaginal swab	No difference in genus	[55]

Disorder	Subjects	Specimens	More Abundant Microbiome than Control Group	References
IC/BPS	Women with IC/BPS	Catheterized urine	IC group: (less Lactobacillus acidophilus)	[56]
	Women with IC/BPS	Stool and vaginalswab	IC/BPS group: (less Eggerthella sinensis, Colinsella aerofaciens, F. prausnitzii, Odoribacter splanchnicus, Lactonifactor longoviformis)	[57]
	Women with IC/BPS	Midstream urine	No difference in genus	[58]
	Women with IC	Midstream urine	IC group: -more Lactobacillus	[59]
UTI	Women with acute cystitis or recurrent cystitis	Catheterized urine	Acute cystitis group: Pseudomonas, Acinetobacter, Enterobacteriaceae Recurrent cystitis group: Sphingomonas, Staphylococcus, Streptococcus, Rothia spp	[25]
	postoperative urinary tract infection patients	Catheterized urine and vaginal swab	Patient group: Escherichia coli, Klebsiella pneumoniae, P. aeruginosa (Less Lactobacillus iners)	[60]
Bladder cancer	Bladder cancer patients	Midstream urine	Bladder cancer group: Actinomyces europaeus	[61]
	Men with non-muscle invasive bladder cancer	Midstream urine	Bladder cancer group: Fusobacterium, Actinobaculum, Facklamia, Campylobacter	[44]
	Men with bladder cancer	Midstream urine	Bladder cancer group: Acinetobacter, Anaerococcus, Sphingobacterium (Less: Serratia, Proteus, Roseomonas)	[43]
	Urothelial carcinoma patients	Midstream urine	Bladder cancer group: Streptococcus, Pseudomonas, Anaerococcus	[40]

References

1. Human Microbiome Project, C. Structure, function and diversity of the healthy human microbiome. Nature 2012, 486, 207â214.
2. Perez-Carrasco, V.; Soriano-Lerma, A.; Soriano, M.; GutiÃ©rrez-FernÃ¡ndez, J.; Garcia-Salcedo, J.A. Urinary Microbiome: Yin and Yang of the Urinary Tract. Front. Cell. Infect. Microbiol. 2021, 11, 617002.
3. Zasloff, M. Antimicrobial Peptides, Innate Immunity, and the Normally Sterile Urinary Tract. J. Am. Soc. Nephrol. 2007, 18, 2810â2816.
4. Mueller, E.R.; Wolfe, A.J.; Brubaker, L. Female urinary microbiota. Curr. Opin. Urol. 2017, 27, 282â286.
5. Wolfe, A.J.; Brubaker, L. Urobiome updates: Advances in urinary microbiome research. Nat. Rev. Urol. 2018, 16, 73â74.

6. Whiteside, S.A.; Razvi, H.; Dave, S.; Reid, G.; Burton, J. The microbiome of the urinary tractâA role beyond infection. Nat. Rev. Urol. 2015, 12, 81â90.
7. Jones-Freeman, B.; Chonwerawong, M.; Marcelino, V.R.; Deshpande, A.V.; Forster, S.C.; Starkey, M.R. The microbiome and host mucosal interactions in urinary tract diseases. Mucosal Immunol. 2021, 1â14.
8. El-Deeb, O.S.; Atef, M.M.; Hafez, Y.M. The interplay between microbiota-dependent metabolite trimethylamine N -oxide, Transforming growth factor Î² /SMAD signaling and inflammasome activation in chronic kidney disease patients: A new mechanistic perspective. J. Cell. Biochem. 2019, 120, 14476â14485.
9. Mora-Bau, G.; Platt, A.M.; Van Rooijen, N.; Randolph, G.J.; Albert, M.L.; Ingersoll, M.A. Macrophages Subvert Adaptive Immunity to Urinary Tract Infection. PLOS Pathog. 2015, 11, e1005044.
10. Schiwon, M.; Weisheit, C.; Franken, L.; Gutweiler, S.; Dixit, A.; Meyer-Schwesinger, C.; Pohl, J.-M.; Maurice, N.; Thiebes, S.; Lorenz, K.; et al. Crosstalk between Sentinel and Helper Macrophages Permits Neutrophil Migration into Infected Uroepithelium. Cell 2014, 156, 456â468.
11. Roje, B.; Elek, A.; Palada, V.; Bom, J.; IljazoviÄ, A.; Å imiÄ, A.; SuÅ¡ak, L.; ViloviÄ, K.; Strowig, T.; VlahoviÄek, K.; et al. Microbiota Alters Urinary Bladder Weight and Gene Expression. Microorganisms 2020, 8, 421.
12. Smith, K.; McCoy, K.D.; Macpherson, A.J. Use of axenic animals in studying the adaptation of mammals to their commensal intestinal microbiota. Semin. Immunol. 2007, 19, 59â69.
13. McCoy, K.D.; Geuking, M.B.; Ronchi, F. Gut Microbiome Standardization in Control and Experimental Mice. Curr. Protoc. Immunol. 2017, 117, 1â23.
14. Patton, J.P.; Nash, D.B.; Abrutyn, E. Urinary Tract Infection: Economic Considerations. Med Clin. N. Am. 1991, 75, 495â513.
15. Dielubanza, E.J.; Schaeffer, A.J. Urinary tract infections in women. Med. Clin. North. Am. 2011, 95, 27â41.
16. Foxman, B. Urinary tract infection syndromes: Occurrence, recurrence, bacteriology, risk factors, and disease burden. Infect. Dis. Clin. North. Am. 2014, 28, 1â13.
17. Orndorff, P.E.; Falkow, S. Organization and expression of genes responsible for type 1 piliation in Escherichia coli. J. Bacteriol. 1984, 159, 736â744.
18. Hooton, T.M. Uncomplicated Urinary Tract Infection. N. Engl. J. Med. 2012, 366, 1028â1037.
19. Roberts, J.A. Management of pyelonephritis and upper urinary tract infections. Urol. Clin. N. Am. 1999, 26, 753â763.
20. Nicolle, L.E.; Bradley, S.; Colgan, R.; Rice, J.C.; Schaeffer, A.; Hooton, T.M. Infectious Diseases Society of America Guidelines for the Diagnosis and Treatment of Asymptomatic Bacteriuria in Adults. Clin. Infect. Dis. 2005, 40, 643â654.
21. GrÃ¼neberg, R.N. Changes in urinary pathogens and their antibiotic sensitivities, 1971â1992. J. Antimicrob. Chemother. 1994, 33, 1â8.
22. Modena, B.D.; Milam, R.; Harrison, F.; A Cheeseman, J.; Abecassis, M.M.; Friedewald, J.J.; Kirk, A.D.; Salomon, D.R. Changes in Urinary Microbiome Populations Correlate in Kidney Transplants With Interstitial Fibrosis and Tubular Atrophy Documented in Early Surveillance Biopsies. Arab. Archaeol. Epigr. 2016, 17, 712â723.
23. Akgul, T.; Karakan, T. The role of probiotics in women with recurrent urinary tract infections. Turk. J. Urol. 2018, 44, 377â383.
24. Garretto, A.; Miller-Ensminger, T.; Ene, A.; Merchant, Z.; Shah, A.; Gerodias, A.; Biancofiori, A.; Canchola, S.; Canchola, S.; Castillo, E.; et al. Genomic Survey of E. coli From the Bladders of Women With and Without Lower Urinary Tract Symptoms. Front. Microbiol. 2020, 11, 2094.

25. Yoo, J.-J.; Shin, H.; Song, J.; Kim, M.; Yun, J.; Kim, Z.; Lee, Y.; Lee, S.; Lee, K.; Kim, W.; et al. Urinary Microbiome Characteristics in Female Patients with Acute Uncomplicated Cystitis and Recurrent Cystitis. J. Clin. Med. 2021, 10, 1097.
26. Gasiorek, M.; Hsieh, M.H.; Forster, C.S. Utility of DNA Next-Generation Sequencing and Expanded Quantitative Urine Culture in Diagnosis and Management of Chronic or Persistent Lower Urinary Tract Symptoms. J. Clin. Microbiol. 2019, 58.
27. Finucane, T.E. âUrinary Tract Infectionâ-Requiem for a Heavyweight. J. Am. Geriatr. Soc. 2017, 65, 1650â1655.
28. Zhanel, G.G.; Hisanaga, T.L.; Laing, N.M.; DeCorby, M.R.; Nichol, K.A.; Weshnoweski, B.; Johnson, J.; Noreddin, A.; Low, D.E.; Karlowsky, J.A. Antibiotic resistance in Escherichia coli outpatient urinary isolates: Final results from the North American Urinary Tract Infection Collaborative Alliance (NAUTICA). Int. J. Antimicrob. Agents 2006, 27, 468â475.
29. Nicolle, L.E. Urinary Tract Pathogens in Complicated Infection and in Elderly Individuals. J. Infect. Dis. 2001, 183, S5âS8.
30. Croxall, G.; Weston, V.; Joseph, S.; Manning, G.; Cheetham, P.; McNally, A. Increased human pathogenic potential of Escherichia coli from polymicrobial urinary tract infections in comparison to isolates from monomicrobial culture samples. J. Med. Microbiol. 2011, 60, 102â109.
31. Lavigne, J.-P.; Nicolas-Chanoine, M.-H.; Bourg, G.; Moreau, J.; Sotto, A. Virulent Synergistic Effect between Enterococcus faecalis and Escherichia coli Assayed by Using the Caenorhabditis elegans Model. PLOS ONE 2008, 3, e3370.
32. Gottschick, C.; Deng, Z.-L.; Vital, M.; Masur, C.; Abels, C.; Pieper, D.H.; Wagner-DÃ¶bler, I. The urinary microbiota of men and women and its changes in women during bacterial vaginosis and antibiotic treatment. Microbiome 2017, 5, 1â15.
33. Fouts, D.E.; Pieper, R.; Szpakowski, S.; Pohl, H.; Knoblach, S.; Suh, M.-J.; Huang, S.-T.; Ljungberg, I.; Sprague, B.M.; Lucas, S.K.; et al. Integrated next-generation sequencing of 16S rDNA and metaproteomics differentiate the healthy urine microbiome from asymptomatic bacteriuria in neuropathic bladder associated with spinal cord injury. J. Transl. Med. 2012, 10, 174.
34. Thomas-White, K.; Forster, S.C.; Kumar, N.; Van Kuiken, M.; Putonti, C.; Stares, M.D.; Hilt, E.E.; Price, T.K.; Wolfe, A.J.; Lawley, T.D. Culturing of female bladder bacteria reveals an interconnected urogenital microbiota. Nat. Commun. 2018, 9, 1â7.
35. Raz, R. Urinary Tract Infection in Postmenopausal Women. Korean J. Urol. 2011, 52, 801â808.
36. Stapleton, A.E.; Au-Yeung, M.; Hooton, T.M.; Fredricks, D.N.; Roberts, P.L.; Czaja, C.A.; Yarova-Yarovaya, Y.; Fiedler, T.; Cox, M.; Stamm, W.E. Randomized, Placebo-Controlled Phase 2 Trial of a Lactobacillus crispatus Probiotic Given Intravaginally for Prevention of Recurrent Urinary Tract Infection. Clin. Infect. Dis. 2011, 52, 1212â1217.
37. Sumati, A.; Saritha, N. Association of urinary tract infection in women with bacterial vaginosis. J. Glob. Infect. Dis. 2009, 1, 151â152.
38. Gilbert, N.M.; OâBrien, V.P.; Lewis, A.L. Transient microbiota exposures activate dormant Escherichia coli infection in the bladder and drive severe outcomes of recurrent disease. PLOS Pathog. 2017, 13, e1006238.
39. Domann, E.; Hong, G.; Imirzalioglu, C.; Turschner, S.; KÃ¼hle, J.; Watzel, C.; Hain, T.; Hossain, H.; Chakraborty, T. Culture-Independent Identification of Pathogenic Bacteria and Polymicrobial Infections in the Genitourinary Tract of Renal Transplant Recipients. J. Clin. Microbiol. 2003, 41, 5500â5510.
40. Xu, W.; Yang, L.; Lee, P.; Huang, W.; Nossa, C.; Ma, Y.; Deng, F.-M.; Zhou, M.; Melamed, J.; Pei, Z. Mini-review: Perspective of the microbiome in the pathogenesis of urothelial carcinoma. Am. J. Clin. Exp. Urol. 2014, 2, 57â61.

41. Bray, F.; Me, J.F.; Soerjomataram, I.; Siegel, R.L.; Torre, L.A.; Jemal, A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer J. Clin. 2018, 68, 394â424.
42. Crow, P.; Ritchie, A. National and international variation in the registration of bladder cancer. BJU Int. 2003, 92, 563â566.
43. Wu, P.; Zhang, G.; Zhao, J.; Chen, J.; Chen, Y.; Huang, W.; Zhong, J.; Zeng, J. Corrigendum: Profiling the Urinary Microbiota in Male Patients With Bladder Cancer in China. Front. Cell. Infect. Microbiol. 2018, 8, 429.
44. PopoviÄ, V.B.; Å itum, M.; Chow, C.-E.T.; Chan, L.S.; Roje, B.; TerziÄ, J. The urinary microbiome associated with bladder cancer. Sci. Rep. 2018, 8, 1â8.
45. Thomas-White, K.J.; Kliethermes, S.; Rickey, L.; Lukacz, E.S.; Richter, H.E.; Moalli, P.; Zimmern, P.; Norton, P.; Kusek, J.W.; Wolfe, A.J.; et al. Evaluation of the urinary microbiota of women with uncomplicated stress urinary incontinence. Am. J. Obstet. Gynecol. 2016, 216, 55-e1.
46. Mansour, B.; MonyÃ³k, Ã.; Makra, N.; GajdÃ¡cs, M.; Vadnay, I.; Ligeti, B.; JuhÃ¡sz, J.; SzabÃ³, D.; OstorhÃ¡zi, E. Bladder cancer-related microbiota: Examining differences in urine and tissue samples. Sci. Rep. 2020, 10, 1â10.
47. Komesu, Y.M.; Network, F.T.P.F.D.; E Richter, H.; Carper, B.; Dinwiddie, D.L.; Lukacz, E.S.; Siddiqui, N.Y.; Sung, V.W.; Zyczynski, H.M.; Ridgeway, B.; et al. The urinary microbiome in women with mixed urinary incontinence compared to similarly aged controls. Int. Urogynecol. J. 2018, 29, 1785â1795.
48. Fok, C.S.; Gao, X.; Lin, H.; Thomas-White, K.; Mueller, E.R.; Wolfe, A.J.; Dong, Q.; Brubaker, L. Urinary symptoms are associated with certain urinary microbes in urogynecologic surgical patients. Int. Urogynecol. J. 2018, 29, 1765â1771.
49. Curtiss, N.; Balachandran, A.; Krska, L.; Peppiatt-Wildman, C.; Wildman, S.; Duckett, J. A case controlled study examining the bladder microbiome in women with Overactive Bladder (OAB) and healthy controls. Eur. J. Obstet. Gynecol. Reprod. Biol. 2017, 214, 31â35.
50. Wu, P.; Chen, Y.; Zhao, J.; Zhang, G.; Chen, J.; Wang, J.; Zhang, H. Urinary Microbiome and Psychological Factors in Women with Overactive Bladder. Front. Cell. Infect. Microbiol. 2017, 7, 488.
51. Karstens, L.; Asquith, M.; Davin, S.; Stauffer, P.; Fair, D.; Gregory, W.T.; Rosenbaum, J.T.; McWeeney, S.K.; Nardos, R. Does the Urinary Microbiome Play a Role in Urgency Urinary Incontinence and Its Severity? Front. Cell. Infect. Microbiol. 2016, 6, 78.
52. Pearce, M.M.; Hilt, E.E.; Rosenfeld, A.B.; Zilliox, M.J.; Thomas-White, K.; Fok, C.; Kliethermes, S.; Schreckenberger, P.C.; Brubaker, L.; Gai, X.; et al. The Female Urinary Microbiome: A Comparison of Women with and without Urgency Urinary Incontinence. mBio 2014, 5, e01283-14.
53. Nickel, J.C.; Stephens-Shields, A.J.; Landis, J.R.; Mullins, C.; Van Bokhoven, A.; Lucia, M.S.; Henderson, J.P.; Sen, B.; Krol, J.E.; Ehrlich, G.D.; et al. A Culture-Independent Analysis of the Microbiota of Female Interstitial Cystitis/Bladder Pain Syndrome Participants in the MAPP Research Network. J. Clin. Med. 2019, 8, 415.
54. Bresler, L.; Price, T.K.; Hilt, E.E.; Joyce, C.; Fitzgerald, C.M.; Wolfe, A.J. Female lower urinary tract microbiota do not associate with IC/PBS symptoms: A case-controlled study. Int. Urogynecol. J. 2019, 30, 1835â1842.
55. Meriwether, K.V.; Lei, Z.; Singh, R.; Gaskins, J.; Hobson, D.T.G.; Jala, V. The Vaginal and Urinary Microbiomes in Premenopausal Women With Interstitial Cystitis/Bladder Pain Syndrome as Compared to Unaffected Controls: A Pilot Cross-Sectional Study. Front. Cell. Infect. Microbiol. 2019, 9, 92.
56. Abernethy, M.G.; Rosenfeld, A.; White, J.R.; Mueller, M.G.; Lewicky-Gaupp, C.; Kenton, K. Urinary

Microbiome and Cytokine Levels in Women With Interstitial Cystitis. Obstet. Gynecol. 2017, 129, 500â506.

57. Braundmeier-Fleming, A.; Russell, N.T.; Yang, W.; Nas, M.Y.; Yaggie, R.E.; Berry, M.; Bachrach, L.; Flury, S.C.; Marko, D.S.; Bushell, C.B.; et al. Stool-based biomarkers of interstitial cystitis/bladder pain syndrome. Sci. Rep. 2016, 6, 26083.
58. Nickel, J.C.; Stephens, A.; Landis, J.R.; Mullins, C.; Van Bokhoven, A.; Lucia, M.S.; Ehrlich, G. MAPP Research Network Assessment of the Lower Urinary Tract Microbiota during Symptom Flare in Women with Urologic Chronic Pelvic Pain Syndrome: A MAPP Network Study. J. Urol. 2016, 195, 356â362.
59. Siddiqui, H.; Lagesen, K.; Nederbragt, A.J.; Jeansson, S.L.; Jakobsen, K.S. Alterations of microbiota in urine from women with interstitial cystitis. BMC Microbiol. 2012, 12, 205.
60. Thomas-White, K.; Gao, X.; Lin, H.; Fok, C.S.; Ghanayem, K.; Mueller, E.R.; Dong, Q.; Brubaker, L.; Wolfe, A.J. Urinary microbes and postoperative urinary tract infection risk in urogynecologic surgical patients. Int. Urogynecol. J. 2018, 29, 1797â1805.
61. Bi, H.; Tian, Y.; Song, C.; Li, J.; Liu, T.; Chen, Z.; Chen, C.; Huang, Y.; Zhang, Y. Urinary microbiota â a potential biomarker and therapeutic target for bladder cancer. J. Med Microbiol. 2019, 68, 1471â1478.