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BENIGN PROSTATIC HYPERPLASIA (K MCVARY, SECTION EDITOR)

Implications of the Genitourinary Microbiota in Prostatic Disease

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Abstract

Purpose of Review To summarize recent investigation into associations between the genitourinary microbiota and prostatic disease.

Recent Findings The genitourinary tract is not sterile. There are microbial communities (microbiota) in each niche of the genitourinary tract including the bladder, prostate, and urethra, which have been the subject of increasing scientific interest. Investigators have utilized several unique methods to study them, resulting in a highly heterogeneous body of literature. To characterize these genitourinary microbiota, diverse clinical specimens have been analyzed, including urine obtained by various techniques, seminal fluid, expressed prostatic secretions, and prostatic tissue. Recent studies have attempted to associate the microbiota detected from these samples with urologic disease and have implicated the genitourinary microbiota in many common conditions, including benign prostatic hyperplasia (BPH), prostate cancer, and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS).

Summary In this review, we summarize the recent literature pertaining to the genitourinary microbiota and its relationship to the pathophysiology and management of three common prostatic conditions: BPH, prostate cancer, and CP/CPPS.

Keywords Microbiota · Microbiome · Prostate · BPH · Prostate cancer · Chronic prostatitis

Introduction

Diseases of the prostate make up a large proportion of male urologic disease, with benign prostatic hyperplasia (BPH) being the fifth most prevalent non-cancer-related disorder among men 60 years or greater, and prostate cancer being the most commonly diagnosed cancer in men [1–3]. Chronic bacterial prostatitis (CBP) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) are also common conditions, affecting up to 9% of men aged 40–79 [4]. Our understanding of the pathophysiology of these conditions contains knowledge gaps and relies on the assumption that urine is sterile in the absence of clinical infection. The discovery of communities of bacteria (microbiota) in the genitourinary tract and investigation of their roles in urologic disease have begun to shed light on novel factors that may have implications in pathophysiology and management of these common conditions.

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Despite their high incidences, the pathophysiologic mechanisms of prostatic diseases remain incompletely characterized. Prostatic inflammation has been implicated as a possible common factor in BPH, prostate cancer, and CP/CPPS, while the source of that inflammation has been subject to debate. For example, a high prevalence of chronic prostatic inflammation has been associated with BPH progression [5, 6]. Similarly, chronic inflammation has been implicated in the pathophysiology and progression of prostate cancer [7••, 8–14] and CP/CPPS [15, 16]. These inflammatory processes may relate to specific characteristics of the genitourinary microbiota and present a potential new target for diagnosis and therapy. Aside from the microbiota of the prostate itself, the urinary microbiota is of particular interest with regard to prostatic disease given the anatomical proximity, shared mucosal epithelium (urothelium) and the potential for the urinary tract to serve as a route of prostatic exposure to microorganisms contained in (or passing through) the urethra [17]. In this review, we summarize the literature relating the genitourinary microbiota, specifically the urinary and prostatic microbiota, to these three common prostatic diseases: BPH, prostate cancer, and CP/CPPS.

Discovery and Characterization of the Urinary Microbiota

Many internal surfaces, including the gastrointestinal or vaginal epithelium, possess resident microbial communities, collectively known as microbiota. The microbial constituents of these microbiota are believed to benefit human health; for example, by facilitating efficient removal of improperly functioning immune cells and protecting against infection [18–20]. Historically, the bladder had been considered "sterile" based primarily on culture-dependent methods of bacterial detection. Recently, however, numerous studies have revealed irrefutable evidence of microbes in the bladders of adult men and women without clinical infection [21–25, 26••, 27, 28].

16S ribosomal RNA (rRNA) gene sequencing and expanded quantitative urine culture (EQUC) are the techniques primarily utilized to reveal bacterial DNA and live bacteria in standard culture-negative urine samples [7••, 21–25, 27, 29–32, 33•, 34–39, 40•, 41]. Much research of the human microbiota have relied on sequencing portions of the highly conserved 16S rRNA gene, yielding the first glimpse of the bacterial communities present in diverse niches and between different disease states. A highly sensitive test that can distinguish bacterial species, 16S rRNA gene sequencing provided early evidence that bacterial DNA was present in the bladder but could not determine if the bacteria were alive. 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 common uropathogens [42], this test does not reproducibly detect most microbes of the urinary microbiota. Instead, simple refinements to the standard urine culture protocol (e.g., increased volume, various growth conditions, increased duration of incubation) are required to obtain more complete description of the urinary microbiota [21, 27, 43].

Characterization of relationships between the urinary microbiota and clinical factors relies on an appropriate sampling of specific anatomic sites. Urine sample collection has been the most clinically feasible methodology, with little deviation from standard clinical care needed to acquire samples for analysis. Numerous studies have attempted to validate various urine collection techniques as accurate sampling methods for the microbiota of respective anatomical sites within the urinary tract. One early study from our group indicated that voided urine in female patients does not faithfully represent the bladder microbiota, as the bacterial DNA detected in midstream voided urine often diverged substantially from the DNA detected in urine obtained by the transurethral catheter. The authors concluded that catheterized urine sampled the bladder because DNA detected from catheterized urine closely resembled that of suprapubic aspirate, which bypasses external contamination [24]. Another early study in male patients showed that the microbial communities of first catch urine were highly similar to those in paired urethral swab specimens [36]. A more recent study compared paired voided and catheterized urine obtained from males and found that these paired samples often did not match, providing evidence that voided urine does not faithfully characterize the male bladder microbiota [26••]. Like bacteria that comprise the female bladder microbiota, those that form the microbiota of males are distinct from bacteria that cause overt clinical UTI [26••, 36]. Recent investigation has indicated that the male urinary microbiota are overall more diverse between samples than the female urinary microbiota [44].

The early studies attempting to associate urologic disease with the urinary microbiota predominantly focused on female patients, revealing associations between the female bladder microbiota and post-instrumentation UTIs [40•], urgency urinary incontinence [22, 23, 29, 32], and response to overactive bladder treatment [34]. Some *Lactobacillus* species have even been associated with lack of symptoms and protection against UTI [23, 40•]. These results support the notion that microbes may have protective capabilities and that disruption (dysbiosis) of this microbial community can result in urinary disorders.

The Male Genitourinary Microbiota and Benign Prostatic Hyperplasia

Investigation into the female urinary microbiota and the relationships to different urologic disease states paved the way to

Table 1 Overview of select studies investigating the microbiota of prostatic disease

Subject	Sample size (n)	Sample type	Analysis method	Primary finding
Benign prostatic hyperplasia (BPH)				
Lewis et al. [39]	6	Midstream voided urine	16S rRNA gene sequencing	Total bacteria in distal urethra decrease with age, while number of genera increase.
Bajic et al. [26••]	49	Midstream voided urine, Catheterized urine	EQUC, 16S rRNA gene sequencing	Increased symptom score severity associated with detectable bacteria on catheterized urine, voided urine is inadequate to sample the bladder microbiome.
Yu et al. [45•]	21 BPH, 13 prostate cancer	Voided urine, expressed prostatic secretions/seminal fluid	16S rRNA gene sequencing with PCR-DGGE analysis	Bacterial flora in expressed prostatic secretions of patients with BPH differ from those with prostate cancer.
Prostate cancer				
Shrestha et al. [7••]	130 (65 biopsy negative, 65 biopsy positive)	Voided urine (following digital rectal exam)	16S rRNA gene sequencing	Increased presence of pro-inflammatory bacteria and uropathogens in the urinary tract of men with prostate cancer.
Alanee et al. [46]	30	Voided urine (after prostatic massage), Fecal swab	16S rRNA gene sequencing	No difference in fecal microbiome between in patients with and without prostate cancer, urinary communities were similar among prostate cancer patients and clustered separately from patients without prostate cancer.
Cavarretta et al. [47•]	16	Radical prostatectomy specimen: Tumor, peritumor, and non-tumor tissue	16S rRNA gene sequencing	Differences in the microbial niche within the prostate gland of patients with prostate cancer based on pathology.
Miyake et al. [48]	45 prostate cancer, 40 BPH	Prostatectomy specimen: Transurethral resection (BPH) or radical prostatectomy (Prostate Cancer)	PCR screening primers	Increase rate of *Mycoplasma genitalium* in prostate cancer patients compared to BPH.
Feng et al. [49•]	65	Radical prostatectomy tissue	Shotgun metagenomic sequencing	Prostatic tissue in prostate cancer patients is non-sterile. No difference in biodiversity among benign and malignant areas.
Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS)				
Nickel et al. [15]	110 CP/CPPS, 115 controls	First void urine (VB1), midstream void urine (VB2), post-prostatic massage urine (VB3)	T-5000 Universal Biosensor Mass Spectrometry	VB1 differed in bacterial composition between CP/CPPS and controls. No other differences were identified.
Mandar et al. [50••]	21 CP/CPPS, 46 controls	Semen	16S rRNA gene sequencing	Higher species diversity in men with CP/CPPS with lower relative abundance of *Lactobacillus* compared to controls.
Shoskes et al. [51•]	25 CP/CPPS, 25 controls	Midstream voided urine	16S rRNA gene sequencing	Higher phylogenetic alpha diversity with increased *Clostridia* and *Bacteroidia* in CP/CPPS patients compared to controls.

PCR-DGGE polymerase chain reaction-denaturing gradient gel electrophoresis

explore similar relationships with the male urinary microbiome (Table 1—BPH). A study from Lewis and coworkers investigated the effect of aging on the microbiota of male midstream voided urine and observed an intriguing trend: while the total number of bacteria in the distal urethra substantially decreased with age, the number of genera increased [39]. Thus, with age, the microbiota of the urethra appeared to both diminish in numbers and increase in diversity. These changes to the urethral microbiota with aging correlate with the observation that older males report increasing lower urinary tract symptoms (LUTS), typically associated with benign prostatic hyperplasia (BPH) [52].

BPH is the most common urologic condition affecting men of advanced age [52]. Many, but not all, respond to oral therapies, the gold standard first-line treatment [53]. Combination therapy with an alpha-blocker and 5-alpha-reductase inhibitor has significantly reduced the risk of clinical progression, performing better than monotherapy or placebo. However, 12.6% of men on combination therapy show clinical progression after 4 years of treatment, with 5% requiring surgical intervention [54]. Although the prevalence of BPH is increasing, fewer men are receiving surgical treatment, and an increasing number are presenting with acute renal failure, a sign of advanced disease [55]. Together, the lack of response to medical therapy and progression of disease despite medical therapy suggest that the underlying pathophysiology of this disease is heterogeneous and not fully understood.

Several studies have suggested that prostatic inflammation may play a role in BPH pathogenesis and progression [5, 6, 56–58]. This inflammatory process is a potential new target for diagnosis and treatment; however, the etiology of the inflammation is poorly understood. One recent report hypothesized a link between the prostate and pro-inflammatory bacterial species [7••], including several previously associated with female UUI [23].

Using a combination of 16S rRNA sequencing and EQUC, a recent study from our group confirmed the existence of distinct microbiota in the distal (anterior urethral) portion of the male lower urinary tract and provided evidence of microbes in the proximal (bladder) portion of the male lower urinary tract [26••]. This study also indicated that the microbiota of the distal and proximal lower urinary tract microbiota are distinct. Finally, we observed distinct qualitative and quantitative differences between the microbiota of highly symptomatic men with BPH seeking surgical therapy and the microbiota of minimally symptomatic/asymptomatic controls [26••]. The presence of distinct proximal and distal lower urinary tract microbiota that differ between BPH/LUTS patients based on degree of symptoms suggests that a link exists between urinary microbiota and male LUTS. One limitation of this study was that it did not attempt to sample the microbiota within the prostate itself through analysis of prostatic tissue or secretions. Furthermore, the sample size was not large enough to detect statistically significant differences in the relative abundance of specific microbes in patients with BPH compared to controls.

Many voiding symptoms in BPH patients are likely a product of changes in the bladder rather than directly from the prostate. Thus, further investigation into the bladder microbiota may elucidate associations with degrees of certain LUTS. Notably, LUTS due to BPH, as measured by International Prostate Symptom Score (IPSS), are often broken down into voiding and storage domains [59, 60]. IPSS storage subscores have been compared with OAB-type symptom profiles in females [61]. While numerous studies have shown relationships between OAB-type symptoms in females [22, 23, 29, 41], no study to date has specifically attempted to associate the urinary microbiota with irritative symptoms in men. Unfortunately, our recent study on BPH/LUTS had too few patients to identify statistically significant differences in this subset of symptoms [26••]. This is a particularly interesting area for future investigation.

Others have attempted to examine expressed prostatic secretions to establish direct relationships between prostate-specific microbiota and prostatic disease [45•, 47•]. In 2015, Yu and coauthors reported that the microbiota in expressed prostatic secretions, voided urine, and seminal fluid differed between patients with BPH and those with prostate cancer. Compared with prostate cancer patients, those with BPH had higher rates of the genera *Eubacterium* and *Defluviicoccus*, but lower rates of the phyla Bacteroidetes, Alphaproteobacteria, and Firmicutes, as well as the family Lachnospiraceae and the genera *Propionicimonas*, *Sphingomonas*, and *Ochrobactrum* [45•]. The authors postulated that certain bacteria might induce a chronic inflammatory state in the prostate that results in enhanced production of pro-inflammatory cytokines. These results suggest that ecological dysbiosis of the microbiota in prostatic fluid might play an important role in the pathophysiology of both BPH and prostate cancer.

Prostate Cancer and the Prostatic Microbiota

Prostate cancer is the second most common cancer and the third most common cause of cancer-related death in the USA [3]. Chronic prostatic inflammation has been hypothesized to contribute to prostate cancer development and/or progression, but the etiology of that inflammation has not been defined [8–10]. While attempts to associate this inflammation with prostatitis have yielded conflicting results [62, 63], Sfanos and coworkers recently proposed that multiple different types of microorganisms could be implicated [11]. Numerous recent studies have examined prostatic secretions, urine, and even prostatic tissue and attempted to establish relationships

between microbes and prostate cancer (Table 1—Prostate cancer).

In 2018, Shrestha and colleagues published a study that compared the microbiota of voided urine (obtained following digital rectal exam prior to transrectal prostate biopsy) from men with and without prostate cancer [7••]. A total of 135 patients were included and microbial analysis was performed using 16S rRNA gene sequencing. While there were no differences in diversity and no clear hierarchical clustering of benign or cancer samples, the authors did identify a group of pro-inflammatory bacterial species that were enriched in a subset of malignant samples. These species included *Streptococcus anginosus*, *Anaerococcus lactolyticus*, *Anaerococcus obesiensis*, *Varibaculum cambriense*, and *Propionimicrobium lymphophilum*, which have been previously linked to cancer and UTIs [64–68]. *Anaerococcus lactolyticus*, *Varibaculum cambriense*, and *Propionimicrobium lymphophilium* were also found in higher abundance in voided urine from men with prostate cancer as compared with control men. The specific bacteria found to be more abundant in benign samples included the species *Corynebacterium genitalium* and *Haemophilus haemolyticus*, as well as the family Enterobacteriaceae, which includes numerous uropathogenic species, such as *E. coli* and *Klebsiella pneumoniae* [7••]. Based on their findings, the authors propose that proinflammatory bacterial species may be a source of chronic prostatic inflammation in the prostate. A limitation of this study was the use of voided urine, which likely largely represents the distal urethral microbiota. It was not stated whether the urine was the first catch or midstream voided. Furthermore, it was unclear whether standard digital rectal exam or a more vigorous and systematic prostatic massage was performed (as with the collection of expressed prostatic secretions or EPS).

Another very recent study from Alanee and colleagues examined the association of the urinary and fecal microbiota with prostate cancer after transrectal prostate biopsy using 16S rRNA gene sequencing in 30 patients. The urine specimens were first voids following prostatic massage, and the fecal microbiota were sampled by rectal swab. The majority of prostate cancer patients had similar microbial communities that clustered separately compared with patients without cancer. The cluster of the species *Streptococcus anginosus*, *Anaerococus lactolyticus*, *Anaerococcus obesiensis*, *Actinobaculum schaalii*, *Varibaculum cambriense*, *and Propionimicrobium lymphophilum* was associated with more cancer samples than non-cancer samples (71%, compared with 47%, respectively). There were no differences noted between the fecal microbiota of patients with and without prostate cancer [46]. Limitations of this study included a small number of patients and the use of voided urine. Furthermore, while controls were performed to test for contaminant bacterial DNA in extraction kits and reagents, these samples were not sequenced.

In 2015, Yu and coworkers utilized 16S rRNA sequencing to compare the microbes of three different body fluid collection techniques in cancer patients: EPS, seminal fluid, and voided urine. *E. coli* detection was significantly greater in EPS and seminal fluid compared to urine, while *Enterococcus* detection was more common in seminal fluid [45•]. No studies to date have examined catheterized urine in prostate cancer patients, which has been shown to be distinct from the microbiota of voided urine and is more representative of the proximal lower urinary tract [26••]. In addition to catheterized urine, future studies examining expressed prostatic secretions should ideally utilize a more standardized protocol for specimen collection to enhance the ability of this minimally invasive specimen collection method to provide insight into the microbiota of the prostate gland.

Examination of urine and prostatic secretions or seminal fluid must be interpreted with caution as none of these methods have been validated to directly sample the microbiota of the prostate gland itself, which is likely most pertinent to the development of prostatic malignancy. Surgically removed prostatic tissue has recently been studied in cancer patients to characterize the prostatic microbiome more directly. A study by Cavarretta and colleagues, published in 2017, examined 16 radical prostatectomy specimens and performed 16S rRNA gene sequencing of tumor, peri-tumor, and non-tumor prostatic tissue. Significant differences in specific microbial populations among tumor/peri-tumor and non-tumor prostate specimens were observed at certain taxonomic levels. Among the detected genera, *Propionibacterium* was the most abundant, whereas *Staphylococcus* was more represented in the tumor/peri-tumor tissues ($p < 0.05$). The authors concluded that there are spatial differences within the prostate glands of individuals with prostate cancer, with differences noted in areas based on pathology. They further concluded that there may be pathophysiological correlations between the composition of the local microbial niche and the prostatic pathology present [47•]. This study was limited by its small sample size but provides intriguing evidence of the heterogeneity of the prostatic microbiota, with possible associations between microbiota composition differences in areas of prostatic disease. Other limitations include a lack of negative controls and the use of formalin-fixed paraffin embedded prostate tissue, which carries a risk of bacterial DNA contamination. Furthermore, *Propionibacterium* is a known sequencing contaminant [7••, 17, 69, 70].

In 2017, Yow et al. utilized 16S rRNA gene and total RNA sequencing of tissue from cancerous and benign areas of ten cases of aggressive prostate cancer prostatectomy specimens. These authors identified the family Enterobacteriaceae and its member genus *Escherichia* in all samples from benign and malignant areas. Unfortunately, no negative controls were

included for DNA extraction and sequencing, making it difficult to interpret these findings [71]. However, many of the bacteria identified have been previously reported by prior studies [72–74].

More recently, Miyake and colleagues utilized PCR to determine if the species *N. gonorrhoeae*, *Chlamydia trachomatis*, *Mycoplasma genitalium*, and *Mycoplasma hyorhinis* were present in the prostate glands of 45 men with prostate cancer who underwent robotic prostatectomy, and in the prostate tissue of 40 men with BPH who underwent transurethral resection of prostate. Only the rate of *Mycoplasma genitalium* detected was significantly different between the prostate cancer (18/45, 40%) and BPH cohorts (6/33, 18%). The other bacterial species were not detected in either group [48]. This study was limited by its lack of statistical analysis of the difference between *M. genitalium* positivity in prostate cancer versus BPH and use of formalin-fixed paraffin embedded tissue samples.

Finally, Feng and coworkers examined 65 radical prostatectomy specimens using shotgun metagenomic and metatranscriptomic sequencing and noted that the genera *Escherichia*, *Propionibacterium*, *Acinetobacter*, and *Pseudomonas* were abundant. No differences in biodiversity were noted between benign and malignant areas. The expression profiles of several *Pseudomonas* genes were strongly correlated with that of host small RNA genes, with three having a potential negative association with metastasis. The authors conclude that the prostate microenvironment in prostate cancer patients is non-sterile and that relationships may exist between the presence of certain microbes and the propensity for metastasis [49•]. Limitations of this study include a lack of detail about whether or not formalin fixed paraffin embedded tissue was used and no mention of negative sequencing controls.

While numerous specimen types have been examined to establish relationships between lower urinary tract microbiota and prostate cancer, optimal techniques remain undefined. Whole prostate gland examination shows promise as a method for minimizing external contamination. However, the most common technique for diagnosing prostate cancer prior to prostate removal, transrectal prostate biopsy, likely translocates large numbers of bacteria, or at the least bacterial DNA, from the rectum to the prostatic stroma. Increasing use of transperineal biopsy may remove this potential confounding factor from future studies [75].

In summary, these studies identified the presence of numerous proinflammatory bacteria in the urinary microbiota of prostate cancer patients, and there are likely spatial differences in the prostate tissue microbiota between cancerous and noncancerous areas; however, the possibility of translocation of rectal bacteria to the prostate during biopsy has not been ruled out. While proinflammatory bacteria in the urinary microbiota may relate to prostate cancer, others have investigated inflammation in patients with chronic prostatitis/chronic pelvic pain syndrome.

Chronic Prostatitis/Chronic Pelvic Pain Syndrome and the Urinary Microbiota

Prostatitis is the most common urologic diagnosis in men under age 50 [76]. Several studies have investigated the role of the urinary microbiota in CP/CPPS (Table 1—CP/CPPS). The earliest study in this domain by Nickel and coworkers in the MAPP network. In 2015, they reported a study that utilized a robust specimen collection protocol based on the Meares-Stamey 4-vial test [38, 77]. This study examined first void (VB1), midstream void (VB2), and post-prostatic massage void (VB3) urines from 110 CP/CPPS patients and 115 controls (only 67 and 62 completed VB3, respectively) using the Ibis T-5000 Universal Biosensor Analysis (which relies on mass spectrometry for bacterial identification). Overall species and genus composition differed significantly for first void urine only (VB1), but not VB2 or VB3. The bacterial species *Burkholderia cenocepacia* (an opportunistic human pathogen) was overrepresented in the CP/CPPS population [38]. Others have described *B. cenocepacia* as a pathogen, possibly involved in the etiology of CP/CPPS [78–80]. However, this study was limited by poor adherence to the study protocol with respect to VB3 collection.

Building on this work, Mandar et al. in 2017 used 16S rRNA gene sequencing to study the semen samples of 21 men with CP/CPPS and 46 without. The authors noted a statistically significant difference with lower relative abundance of the genus *Lactobacillus* in prostatitis patients (median 20.2% [4.9–25.0%] vs 27% [quartiles 20.2–34.6%]; $p = 0.05$), specifically the species *L. iners* (9.8% [3.2–14.3%] vs 14.2% [8.8–19.4%]; $p = 0.013$). They also noted greater microbial diversity in prostatitis patients compared with controls [50••]. These findings are of particular interest as vaginal *Lactobacillus* species have been shown to have protective features [23, 81, 82].

In 2016, Shoskes and colleagues used 16S rRNA gene sequencing to compare midstream voided urine of 25 patients with CP/CPPS with 25 controls. These authors showed significantly that patients with CP/CPPS had higher α (phylogenetic) diversity and higher counts of the classes Clostridia and Bacteroidia compared with controls [51•]. These authors have also recently examined the role of the gut microbiome in CP/CPPS [83].

In 2017, Murphy and coworkers utilized a murine model to perform intraurethral instillation of a specific *S. epidermidis* strain isolated from the expressed prostatic secretions of a healthy human male. The instillation reduced tactile allodynia response and increased T cell markers associated with prostatitis. These results suggest a new potential therapeutic role for

commensal *S. epidermidis* and its cellular constituents in the treatment of prostatitis-associated pain [84].

The pathophysiology of CP/CPPS is very complex and poorly understood. Many authors have proposed it to be a complex disorder, with possible infectious, inflammatory, and psychoneuromuscular components [85–88]. It is feasible that the genitourinary microbiota may be harnessed to better understand the pathophysiology and improve the management of this disease. Unfortunately, no study to date has attempted to directly sample the prostatic microbiota in these patients. This is particularly difficult in this population as the standard management of these patients does not entail prostatic tissue sampling.

Conclusions

The genitourinary microbiota is an intriguing new area of clinical investigation. Our historical understanding of lower urinary tract pathology must be called into question given the discovery that the urinary tract is not sterile. While most investigations today have focused on bacteria in the urinary tract, investigation into the fungi [89], viruses [90, 91], and other microorganisms [92] are ongoing. Long-standing nomenclature for conditions such as asymptomatic bacteriuria and urinary tract infection will require modification [30]. Prostatic disease must also continue to be reevaluated and diseases previously thought to be unrelated to microbes should be thoroughly investigated. Preliminary investigations in the areas of BPH, prostate cancer, and CP/CPPS have identified intriguing new areas for harnessing the genitourinary microbiota to improve prostate health.

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Compliance with Ethical Standards

Conflict of Interest Petar Bajic and Chirag P. Doshi each declare no potential conflicts of interest.

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- • Of importance
- •• Of major importance

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