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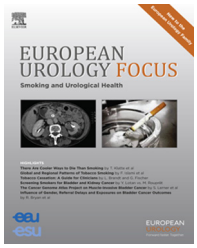

Review – Infections

The Urinary Tract Microbiome: The Answer to All Our Open Questions?

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Abstract

Context: The dogma of a sterile urinary tract persisted for over a century. With the advances in new high-throughput sequencing technologies and modified culture protocols for microbiome research, we have discovered a variable microbial spectrum in the urinary tract. Its relevance for health and disease is now under investigation.
Objective: To present the latest insights into the role of the urinary tract microbiome in functional disorders.
Evidence acquisition: Medline, PubMed, the Cochrane database, and Embase were screened for randomised controlled trials, clinical trials, and reviews on the urinary tract microbiome.
Evidence synthesis: The urinary tract is not sterile. Every individual harbours a complex microbial network in the urinary tract that is exposed to internal and external factors. Any imbalance in this network is likely to contribute to the development of lower urinary tract symptoms. Functional disorders such as interstitial cystitis, urinary urge incontinence, and chronic prostatitis/chronic pelvic pain syndrome, none of which include a bacterial origin for diagnosis, show features of an altered microbiome with specific dominating urotypes in contrast to urine from asymptomatic healthy individuals. The growing insights into the impact of the urinary microbiome on these entities may help in gaining a deeper understanding of the condition and may provide guidance for optimised management.
Conclusions: The urinary tract is not sterile. The discovery of the urinary microbiome suggests that any imbalance may have a relevant role in the development of symptoms in functional disorders.
Patient summary: The urinary tract is naturally colonised with a specific microbial spectrum for which impairment may cause bothersome symptoms.

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1. Introduction

In 2008 the Human Microbiome Project was established for a comprehensive characterisation of the microbiota of healthy adults. Initially, samples were collected from 242 participants at 18 body sites and were analysed using approaches that included 16S rRNA sequencing and metagenomic profiling. The outcomes from this extensive mapping allowed greater insight into the complex ecosystems that vary considerably across different body sites and

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between individuals [1,2]. One primary goal was to use this source of data as a reference to better understand the impact of an imbalanced microbiome on the development of disorders in the human host. A first picture was drawn of the structure, function, and diversity of the microbiota of five body sites: the gastrointestinal tract, the oral cavity, the airway, the skin, and the vagina. The urinary tract was not part of this agenda owing to concerns about sampling techniques, microbiological methods, and primarily the concept of the urinary tract as a sterile niche. However, with the introduction of advanced molecular techniques for urinalysis, the dogma that "urine is sterile" was disproved. The urinary tract is not a sterile environment. With the knowledge that there is a complex and distinct urinary microbiome, first results began to shed new light on functional urological disorders, believed to have no microbiological aetiology. This article presents our novel insights into the urinary microbiome in health and disease.

2. Evidence acquisition

Medline, PubMed, the Cochrane database, and Embase were screened for randomised controlled trials, clinical trials, and reviews on the urinary tract microbiome using the following single keywords or their combination: microbiome; microbiota; urinary tract; and urinary microbiome.

3. Evidence synthesis

A urine culture is still considered the gold standard for urinalysis [3] as it identifies fast-growing, aerobic prototypic uropathogens with good diagnostic accuracy. However, routine culture techniques do not support the detection of most atypical slow-growing, anaerobic and fastidious pathogens such as *Corynebacterium* and *Ureaplasma.* Advances in 16S rRNA sequencing technology made it possible to discover the presence of a rich and diverse urinary microbiota in every individual [4]. In addition, enhanced quantitative urine culture protocols demonstrated that previously undetected bacteria could be isolated, thereby confirming the sequencing results. Up to 80% of bacteria can be isolated using modified culture techniques for a sample that has been classified as having no growth according to the standard method [5]. These novel technical approaches were used to investigate the composition of the urinary microbiota in patients diagnosed with functional disorders such as interstitial cystitis (IC), urgency urinary incontinence (UUI), and chronic prostatitis/chronic pelvic pain (CP/CPP) syndrome (NIH type 3), none of which include a bacterial infection for diagnosis.

3.1. Interstitial cystitis

IC is a chronic condition defined by persistent or recurrent pain in concert with at least one additional symptom, such as worsening of pain with bladder filling or urinary frequency. For diagnosis, local pathologies and infection need to be ruled out. High-throughput sequencing techniques to characterise the microbiota of female patients with IC compared to asymptomatic healthy controls revealed differences in the composition of midstream urine between the groups [6]. In IC patients, the species richness and ecological diversity were significantly lower. A significantly higher abundance of the genus *Lactobacillus* (>90%) was found in IC samples, compared to 60% in controls. It has been suggested that this shift towards a *Lactobacillus* urotype impacts symptom severity. Some studies reported an improvement in bothersome symptoms after targeted treatment leading to eradication of *Lactobacillus* spp. in the urine of patients [7,8]. This first observation is intriguing, but the exact role of *Lactobacillus* in IC still needs to be determined.

3.2. Urgency urinary incontinence

UUI is a debilitating condition with a considerable effect on patients' quality of life, mostly in women and the elderly. It can be a component of overactive bladder syndrome or neurogenic detrusor hyperactivity, and thus urinary tract infection has to be excluded for diagnosis. First studies investigating the urinary microbiome in women suffering from UUI and healthy controls identified significant differences in the bacterial composition of urine, with relevant implications for management [9,10]. The UUI cohort was characterised by a higher number of bacterial species by culture and a sequence profile with higher abundance of *Gardnerella* and lower abundance of *Lactobacillus*. Interestingly, at the species level *Lactobacillus gasseri* was more frequently cultured from UUI urine, while *Lactobacillus crispatus* was detected most frequently in controls. This higher diversity found in UUI appears to correlate with the response to anticholinergic treatment [11]. The higher the diversity of cultivable bacteria, the more likely is the need for a higher dose and the risk of treatment failure. These first new insights into the complex bacterial networks underlying functional disorders such as UUI may help in optimising our current understanding and management, but more studies are needed to reveal the full picture.

3.3. Chronic prostatitis/chronic pelvic pain syndrome

CP/CPPS is defined as chronic pain or discomfort in the pelvic area for at least 3 mo in the previous 6 mo, variably associated with lower urinary tract symptoms (LUTS), sexual dysfunction, and psychosocial consequences. The main objective for diagnostic assessment is to rule out differential diagnoses of pelvic pain such as urinary tract infection. Culture-independent technology was applied to study the microbiome in CP/CPPS patients compared to healthy controls [12]. Of note, species and genus composition varied significantly between groups only in initial-stream urine, and not in midstream urine or urine after prostate massage. *Burkholderia cenocepacia* was more prevalent in CP/CPPS patients, whereas a minor under-representation was detected for *Propionibacterium acnes* and *Staphylococcus capitis/capare*. Again, high-throughput techniques proved

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to be powerful tools for detecting and profiling microbial communities for which standard culture methods failed. However, these first results warrant further studies to provide a comprehensive understanding of this condition.

4. Conclusions

With the first results provided by novel high-throughput culture-independent technologies for analysis of the urinary microbiome, the paradigm of a sterile urinary tract has to be dismissed. Every individual harbours a complex microbial network in the urinary tract that is exposed to internal and external factors. The first lesson we learned is that an imbalance in the urinary microbiome may contribute to the development of LUTS. Functional disorders, believed to have no underlying microbial origin, appear to involve significant differences in urinary bacterial composition. More studies are needed to gain a deeper understanding of how our observations can be used to improve current LUTS management.

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Study concept and design: Magistro, Stief.
Acquisition of data: Magistro.
Analysis and interpretation of data: Magistro.
Drafting of the manuscript: Magistro.
Critical revision of the manuscript for important intellectual content: Magistro, Stief.
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