The microbial syndicate: dysbiosis and origins of recurrent UTIs

BY MOHAMED ALI RIDHA

Traditional dogma held that urine was sterile. However, recent molecular studies have revealed an underground microbial community, known as the urinary microbiome or 'urobiome' [1]. Far from being harmful, this community of microorganisms helps modulate immune responses, regulate inflammation, and protect against invading pathogens. Disruption or imbalance within this microbial ecosystem, termed microbial dysbiosis, can significantly influence susceptibility to disease, especially urinary tract infections (UTIs).

To understand how microbial dysbiosis affects the pathogenesis of UTIs, it is useful to revisit historical context. Since Robert Koch formulated his postulates in 1884, our understanding of microbial disease has advanced considerably. Landmark contributions by Pasteur and Semmelweis established germ theory, fundamentally altering infection control practices. Despite this, diagnostic standards for UTIs, one of the most common bacterial infections, were only formally established in 1957 by Edward Kass and colleagues [2]. Their seminal study involved approximately 2000 hospitalised patients and introduced a quantitative threshold, identifying bacterial counts of 100,000CFU/mL or greater as indicative of true bacteriuria, while counts below 10,000CFU/mL suggested contamination. The intermediate range between these thresholds remained uncertain. Although influential, Kass's work was limited methodologically, being conducted at a single centre without formal controls and relying on arbitrary criteria. Importantly, Kass's diagnostic framework did not adequately consider the complex interactions between host factors and pathogens, now understood to be crucial in recurrent UTIs.

It was not until 40 years later that the first bacterial genome was sequenced, and another decade passed before the Human Microbiome Project transformed our understanding of microbial ecosystems. Since then, studies employing direct bladder aspiration have definitively refuted the long-held belief that urine is sterile [1]. Paradoxically, it may be this very lack of sterility – the presence of a resident microbial community – that serves as a protective factor against uropathogen colonisation and invasion.

With this background, we should clarify some essential terms. A complicated UTI refers to an infection occurring in patients with structural or functional abnormalities of the urinary tract that increase susceptibility to infection or reduce treatment effectiveness [3]. Such abnormalities often predispose individuals to recurrent UTIs, defined as two or more acute infections within six months or at least three within a year [3,4]. Recognising these connections is vital, as recurrent infections frequently indicate deeper underlying disturbances in the urinary tract associated with microbial dysbiosis.

This article explores the interaction between host vulnerabilities and microbial dysbiosis, demonstrating how bacteria exploit changes in the urinary microbiome to establish persistent or recurrent infections.

Urinary tract infections typically occur when pathogens exploit host vulnerabilities to colonise the urinary tract. Uropathogenic bacteria such as *Escherichia coli, Staphylococcus saprophyticus, Enterococcus faecalis, Staphylococcus aureus*, and *Staphylococcus epidermidis* share several common strategies [5,6]. These include producing adhesins for strong attachment to urothelial surfaces, forming protective biofilms to persist within the urinary tract, evading immune defences, and releasing toxins or enzymes (such as urease) that damage host tissues and create a favourable environment for infection [5,6].

Despite extensive research into bacterial virulence and host immunity, we may have fundamentally misunderstood the true battleground of urinary tract infections: the integrity of the urinary microbiome itself. Although challenging to define precisely, Shafquat et al. argue that a healthy microbiome should fulfil three key criteria: it must maintain sufficient resources to support stable microbial communities, remain resilient in the face of physiological changes within the host, and sustain a mutually beneficial relationship with its host [7]. By this definition, certain genera of bacteria are commonly found in the urinary tract. These include, but are not limited to, *Staphylococcus, Corynebacterium, Gardnerella, Lactobacillus,* and *Streptococcus*. Variations exist between sexes – for example, *Lactobacillus* tends to dominate the female urobiome, while *Corynebacterium* is more prevalent in the male urobiome. Age also influences microbial composition, with older individuals typically exhibiting reduced diversity and shifts in dominant genera. Notably, the male urobiome remains under-researched compared to the female, and much of our current understanding of urinary dysbiosis stems from studies focused on the female urinary microbiome.

These commensal organisms play a protective role against urinary tract infections, employing a range of molecular mechanisms to maintain urinary tract health [8]. As previously noted, many uropathogens produce urease enzymes to alkalinise the urinary environment, creating conditions that favour their growth and persistence. In contrast, *Lactobacillus* species contribute to the maintenance of microbial equilibrium by producing lactic acid, which lowers urinary pH and creates an environment less hospitable to uropathogens such as *Escherichia coli* [8]. This acidification not only inhibits pathogen overgrowth but also supports the stability of the native microbial community. Additionally, some *Lactobacillus* strains produce hydrogen peroxide, which has been associated with reduced colonisation by uropathogenic *E. coli* in the urogenital tract [8]. However, the significance of this mechanism remains debated, and its precise contribution to host defence has yet to be fully established.

In addition, one mechanism by which uropathogens establish persistent or recurrent infection is through the formation of biofilms, which protect them from host defences and antibiotic treatment. In vitro studies have demonstrated that certain Lactobacillus species can inhibit the formation of uropathogenic biofilms and, in some cases, actively disrupt established biofilms [8]. This further supports the role of commensal bacteria in maintaining microbial equilibrium and preventing recurrent urinary tract infections [8].

These findings correlate strongly with epidemiological patterns observed in individuals with recurrent UTIs. Ackerman et al. identified several common traits among patients prone to recurrence, including women aged 18–27 and those over 70, individuals who are immunosuppressed, and those with recent or frequent antibiotic use [9]. These risk factors can be reliably linked

to their impact on the urinary microbiome, either through direct disruption of microbial balance or impaired resilience of the host-microbe interface.

There is growing evidence that gut dysbiosis is linked to recurrent urinary tract infections. Faecal microbiota transplantation (FMT), primarily used to treat *Clostridioides difficile* infection, works by restoring microbial diversity in the gut, thereby suppressing *C. difficile* overgrowth [1,8]. Interestingly, several studies have reported a secondary benefit of FMT: a reduction in the frequency of UTIs [1]. This suggests that modifying the gut microbiota may reduce the reservoir of uropathogens with enteric origins, particularly uropathogenic *Escherichia coli* (UPEC), *Klebsiella pneumoniae*, and *Enterobacter* species. These organisms – members of the *Enterobacteriaceae* family – are well-recognised causes of recurrent and antibiotic-resistant UTIs in urological practice. In kidney transplant recipients, the presence of specific commensal gut bacteria at higher relative abundance has been associated with a lower risk of bacteriuria due to these uropathogens, further supporting the role of gut–urinary tract cross-talk in infection susceptibility [1,10].

In this context, it becomes clearer why certain patient factors contribute to complicated urinary tract infections. These factors can directly alter the composition and stability of the urinary microbiome, facilitating colonisation by uropathogens and making eradication more difficult. As previously discussed, the gastrointestinal tract often serves as a reservoir for these pathogens, particularly members of the *Enterobacteriaceae* family. Once introduced into the urinary tract, uropathogens can form biofilms – structured microbial communities encased in a self-produced extracellular matrix [1,3,8]. Within these biofilms, bacteria communicate through a process known as quorum sensing, coordinating gene expression in response to population density. Upon reaching a critical threshold, bacterial cells can detach and revert to their planktonic (free-floating) state, resuming active infection. Biofilms offer robust protection against both host immune responses and antibiotic therapy, and they can adhere to both biological tissues and inert surfaces such as catheters, further complicating treatment [8].

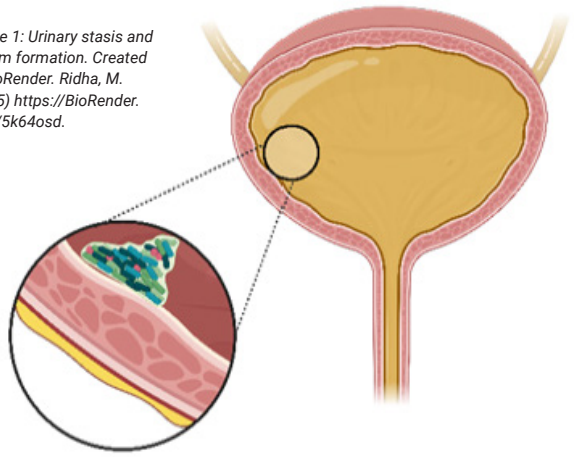

Figure 1: Urinary stasis and biofilm formation. Created in BioRender. Ridha, M. (2025) https://BioRender.com/5k64osd.

The urinary microbiome plays an active role in preventing infection, not only through direct inhibition of uropathogens but also by suppressing biofilm formation. However, host factors significantly influence this delicate balance. One of the most important of these is urinary stasis, which alters the local environment, impairs the clearance of pathogens, and disrupts conditions necessary for commensal survival.

In scenarios where urinary flow is impeded, the resulting stasis reduces the mechanical flushing action of urination – one of the most fundamental innate defences against infection. Without this clearance mechanism, bacteria are afforded more time to adhere to urothelial surfaces, initiate quorum sensing, and form biofilms. Moreover, the change in urinary composition due to stagnation – such as increased pH or altered nutrient availability – can favour the proliferation of uropathogens over protective commensals [11].

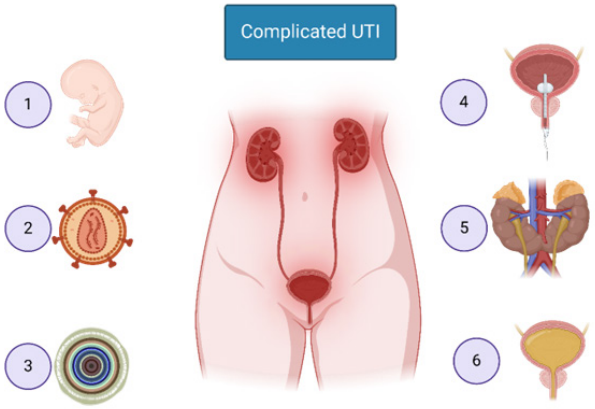

Figure 2: Factors which make UTI complicated: 1.) Pregnancy; 2.) HIV / immunosuppression; 3.) Stones; 4.) Instrumentation; 5.) Anatomical abnormalities; 6.) Enlarged prostate. Created in BioRender. Ridha, M. (2025) https://BioRender.com/fyj4nbj.

Pregnancy is a prime example of this phenomenon. As the uterus enlarges, it exerts mechanical pressure on the bladder and ureters, leading to voiding difficulties and increased residual urine. Concurrent hormonal changes, particularly elevated progesterone levels, further reduce ureteric peristalsis, compounding urinary stasis. Together, these factors create an environment highly conducive to microbial dysbiosis and infection persistence. In addition, hormonal fluctuations influence the composition of the urobiome itself – most notably through a reduction in *Lactobacillus* species [8]. The loss of these commensal organisms strips away a critical barrier against uropathogen overgrowth, rendering pregnant individuals more susceptible to recurrent or ascending urinary tract infections.

The presence of inert substances such as catheters provides a nidus for infection. By offering a surface for organisms like *Pseudomonas spp*. and *Staphylococcus epidermidis* to form biofilms, the urinary microbiome is significantly disrupted [6]. Indwelling devices also contribute to the continuous seeding of planktonic bacteria into the urinary tract, frequently resulting in persistent or recurrent infection. A similar process is observed in nephrolithiasis. Uropathogenic bacteria raise urinary pH through the production of urease, leading to the precipitation of ions and the formation of struvite stones. These stones then become colonised by the same urease-producing bacteria, establishing a self-sustaining cycle of infection and stone growth [11].

Antibiotic treatment often fails in these settings. Not only does it promote dysbiosis by depleting beneficial members of the urobiome, but it also fails to eradicate uropathogens residing within biofilms. These bacteria can return to their sessile state, shielded from both immune defences and antimicrobial agents, while the protective commensals needed to suppress their overgrowth are no longer present.

It should be noted, however, that much of the current understanding is based on in vitro studies, epidemiological correlations, and small case series. While these provide compelling support for the hypothesis that dysbiosis of the urobiome predisposes individuals to infection, the true extent of its influence remains uncertain. It is still unclear how much the microbiome

modulates host susceptibility versus how much host physiology shapes the microbial landscape.

Furthermore, this discussion has focused exclusively on bacterial communities. The roles of fungi and bacteriophages, both of which are known to inhabit the urinary tract, are largely unexplored and may contribute significantly to microbial dynamics and infection risk.

What does need to evolve is our approach to urinary tract infections. The current reductionist model, which emphasises pathogen eradication through increasingly broad-spectrum antibiotics, often perpetuates dysbiosis rather than addressing its root causes. A paradigm shift is needed – one that considers strategies to promote eubiosis rather than disrupt it. This may involve identifying and supporting the growth of beneficial urobiota, such as *Lactobacillus* species, or correcting underlying factors such as urinary stasis that compromise microbial balance.

This emerging field represents the next frontier in urology. By integrating microbiome science into our diagnostic and therapeutic frameworks, we may better prevent, manage, and perhaps even cure recurrent and complicated UTIs.

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