URINARY INCONTINENCE

Making sense of the urinary microbiota in clinical urology

Gregor Reid and Jeremy P. Burton

Some urologists might be surprised that the urinary tract is not sterile, and bacteria might have important roles in a number of urological conditions such as urge incontinence. This paradigm shift, which has been further illustrated by data from a recent study, has implications for how urologists diagnose disease and treat patients.

Refers to Thomas-White, K. J. *et al.* Evaluation of the urinary microbiota of women with uncomplicated stress urinary incontinence. *Am. J. Obstet. Gynecol.* http://dx.doi.org/10.1016/j.ajog.2016.07.049 (2016)

A recently published article by Thomas-White and colleagues[1] further demonstrates the importance of microbes in the urinary tract. For urologists, this observation has been somewhat of a revelation given the long history of regarding the bladder as being sterile in most individuals. Implementation of the concept of the urinary microbiota into general medical and specialist training might take some time, but the implications must be considered now.

For decades, the culture of bacteria in urine was only of concern to a urologist in order to diagnose a urinary tract infection. Even then, a cutoff value of 10^5 colony forming units per ml was generally deemed sufficient to warrant treatment when signs and symptoms were present. The advent of high-throughput sequencing that enables the detection of bacterial DNA and the identification of specific genera and species has dramatically changed our view of tissue sterility. In tissues such as the breast[2] and brain[3], the detection of microbes in low quantities, some of which clearly have the capacity to cause infection, raises many questions of relevance to patient care. Why do these microbes not multiply and induce classical inflammation and infection? What role do these microbes have in tissue viability and function? In the case of the Thomas-White study[1], why would bacteria with similar profiles somehow affect urge incontinence, but not stress incontinence?

The assumption that host immune factors keep the bacteria in check is overly simplistic, and while they almost certainly have a role, sufficient nutrients are available in the urinary tract for these organisms to proliferate. Attempts have been made to understand bacterial quiescence, and continual exposure to low-dose antibiotics is one reason for bacteria to persist in low numbers[4]. Perhaps survival, rather than widespread proliferation, is the key objective of bacteria in this urinary tract niche. Thus, bacteria retain a low level of metabolic activity, do not cause major cell death, and avoid alarming the host defence mechanisms in the various tissues. We propose that the differences in the relative patterns of abundance of bacterial species in health and disease reflects an alteration in equilibrium or homeostasis where bacterial species coexist to some extent symbiotically, but in which dynamics are altered by specific hormones, sexual practices, instrumentation such as catheters, exposure to antimicrobials and other factors, including stress signalling from the brain and from the gut. The so-called pathogenic organisms might then use some of their virulence and persistence factors to more effectively access nutrients via enzymatic damage to cells, thereby increasing their proportions relative to that of others in the ecosystem.

The vagus nerve can act as a conduit for bacterial messaging to the brain from the gut, thus enabling the gut to influence memory and anxiety[5], and we should now consider extending this function to the bladder (FIG. 1). Bacterial metabolites transfer signals via the vagus nerve and capillaries, to influence human behaviour and bodily function. Thus, identifying the specific metabolites that modulate urinary tract function, including those of sensory systems associated with micturition, will be of great interest in the near future. These factors might explain the link between the urinary microbiota and urge incontinence or overactive bladder. Whereas, stress incontinence is created by a weakness in the pelvic floor muscles that is, as Thomas-White *et al.*[1] discovered, not as easily influenced by the sparse urinary microbiota. The influence of excess weight, as observed by these investigators, further correlates with stress incontinence and potentially also an altered gut microbiota.

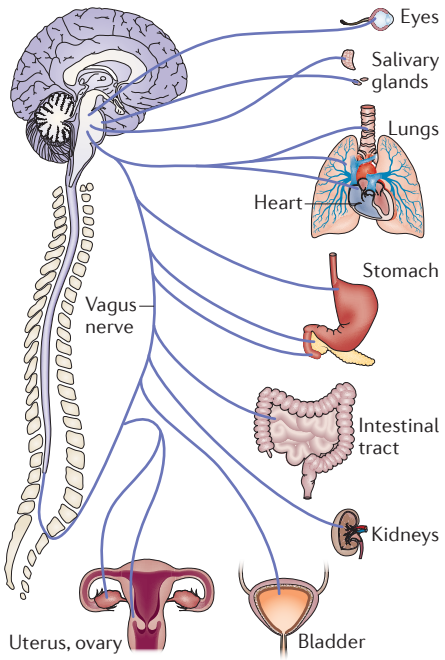

Figure 1 | **Anatomy of the vagus nerve.** The vagus nerve can carry bacterial signalling molecules, including neurochemicals, to the brain and other sites.

Glossary

Microbiota
The term microbiota describes all microorganisms present in a given niche. In many instances, studies only refer to bacteria in the microbiota, but fungi and viruses, for example, can also be included in this term.

For urologists, applying this knowledge to clinical practice might not simply be a matter of collecting urine and relying on a commercial enterprise to sequence the bacterial DNA and provide the abundance readouts. Many nuances exist in both the collection and processing of samples[6], not least the need for multiple longitudinal sampling. Analysis by commercial enterprises can miss, or overlook potentially important findings that dedicated scientists can pick up, especially the presence of metabolites that are associated with disease[7]. Nevertheless, this information will inevitably form part of a patient's medical review, and if a pattern associated with a urological disorder is detected, what next?

The study by Thomas-White *et al.*[1] illustrates, that not all patients' patterns of microbiota content fall into the categories that statisticians use to separate and compare the groups. Furthermore, their methodology did not identify bacteria at the species level, so a urologist would not know if, for example, *Escherichia coli* was the dominant organism and a potential aetiological agent. This makes a decision to treat with antibiotics, assuming such an approach is contemplated, more difficult. Another problem is that, currently, no studies have tested whether antibiotics can eradicate members of the urinary microbiota that colonize the tissues, or prevent their reappearance and subsequent dominance following cessation of antibiotics. Intuitively, such an approach seems unlikely to succeed and might worsen the situation by eradicating non-pathogenic members of the microbiota. Indeed, such is the widespread use of antibiotics, especially in early life, that this exposure might be the root cause of an aberrant microbiota[8]. The option of manipulating the urinary microbiota through dietary intake of compounds that are excreted in urine might be worth considering, given that the delivery of mannose seems to reduce the risk of recurrent UTI[9].

Thomas-White and colleagues[1] attempted to create phenotypes of patients based upon signs and symptoms aligned with their specific microbiota content, but more patients would need to be studied to truly verify this. Given the use of different sequencing methodologies, such patterns might not be easy to reproduce with appropriate cutoff values between each group. If a *Lactobacillus*-dominated urinary microbiota were to be preferred, owing to a consistent correlation with superior health compared with a microbiota dominated by other bacteria, use of probiotic lactobacilli therapy could be considered, with a view to some of the organisms ascending from the rectum and vagina into the bladder, and thereafter helping to out-compete pathogenic bacteria and restore homeostasis. However, this approach has not been investigated to date. The ultimate resetting of the bladder microbiota, by instilling a healthy donor's urinary microbiota (essentially someone else's urine), will one day be tested given the success of faecal microbiota transplant for patients with *Clostridium difficile* infections in the gut[10]. The ability of the donor urinary microbiota to effectively colonize the bladder of the host, in the long term, and to reset the microbiota to a healthy state will be challenging both ethically, as well as physiologically given previous efforts to do so with single species of *E. coli* and *Lactobacillus*.

In summary, the urinary tract is clearly not sterile, and studies are uncovering a wide range of bacteria in many patients with various urological dysfunctions. Associations are being made between patterns of bacteria content in the microbiota of the urinary tract and clinical presentation, and in due course these might help to guide changes in disease management.

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Competing interests statement
The authors declare no competing interests.