Urinary tract infections: uncommon solutions for a common problem

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Have you had a UTI?

It's very likely that you or someone you know has experienced a urinary tract infection (UTI) in the past. They are one of the most common bacterial infections worldwide with 150 million people diagnosed every year [1]. Women make up the majority of those diagnosed and the statistics are shocking; over 50% of women will have a UTI during their life, and 1 in 3 women will contract a UTI by the age of 24 [2]. These infections cause painful symptoms, but most will simply take a course of antibiotics and move on. It's for this reason that UTIs are often regarded as nothing more than an inconvenience. However, for some women it can have a massive impact on their lives, with 25% of women who contract UTIs also having a recurrence. Some women have to live with UTIs for decades as they continue to reappear even after treatment. A 74 year old female patient in the United States experienced recurrent UTIs for 45 years, and the longest period she was free of a UTI was only 9 months [3]. For women like this they only experience a short break from symptoms after taking antibiotics, as bacteria quickly develop resistance. There is currently a lot of effort being put towards understanding the development of antibiotic resistance, but we aim to come at this problem from a different angle. By understanding these uropathogenic bacteria and characterising their behaviour during infections we can develop new ways to effectively treat those suffering from UTIs.

Understanding how the body copes with UTIs is especially important because women can face serious complications if they can't clear the infection. Complications include permanent kidney damage, increased risk of preeclampsia, birth of premature infants, and spreading of the infection to the reproductive tract causing pelvic inflammatory disease and infertility [4]. On top of this, women cannot change many of the risk factors associated with UTIs. They have shorter urethras which makes it easier for bacteria to reach the bladder and there's a shorter distance between the anus and the opening of the urethra leading to easy colonisation for bacteria. Menopause can also make women more vulnerable to infection. For women with recurrent UTIs the only treatment is prophylaxis, continuously dosing with lowered concentrations of antibiotics, and this can be a lifelong treatment. However, prophylaxis has negative impacts such as antibiotic resistance in bacteria leading to resistant UTIs, and can have detrimental effects on the body's natural

balance of good and bad bacteria [5, 6]. UTIs are becoming increasingly problematic for many women, especially when you consider they must cope with a chronic, painful infection while living their daily routine.

What causes recurrent UTIs?

The bacteria *Escherichia coli* is the main uropathogen responsible for UTIs. It normally lives in our gut and rarely causes issues there. However, it can infect the urinary tract if the bacteria are transferred from the anus to the urethra. This can occur through situations such as incorrect wiping after going to the toilet or during sexual intercourse. *E.coli* will travel up the urethra and get into the bladder where they invade bladder cells (Figure 1A). Our immune system will sense the infection and generate immune cells such as macrophages to eat the bacteria and clear them from our system. However, bacteria are very good at adapting to hostile environments and have developed ways to avoid our immune system. By avoiding being engulfed and killed by our immune cells it's thought that bacteria can remain in the urinary tract and cause recurrent infections.

It's commonly accepted that bacteria can change their shape from short rod forms into very long 'spaghetti-like' cells called filaments to help them adapt to an environment (Figure 1B and 1C).These filaments have been isolated from patients suffering from UTIs, and the importance of this shape change to survival of bacteria inside bladder cells has been studied [7]. However, filamentation is extremely complex as bacteria will also undergo this shape change when exposed to other conditions such as antibiotics, including those used to treat UTIs. So we don't fully understand the importance of this shape change in the context of current treatment regimens, particularly for recurrent infections. Based on research so far, it's assumed that becoming long (physically changing size) helps bacteria avoid engulfment by immune cells. But we know that immune cells such as macrophages can engulf things larger than filaments such as pollen or other dying cells [8], so there must be more to the story. We propose that filaments have physiological differences, such as changes to the bacterial cell surface, which allow them to avoid engulfment. This hasn't been examined previously because studying filaments is extremely challenging as they are a temporary shape and there are many different ways to

produce them. However, despite these challenges it's extremely important that we study filaments as they are an adaption bacteria use to survive during infections.

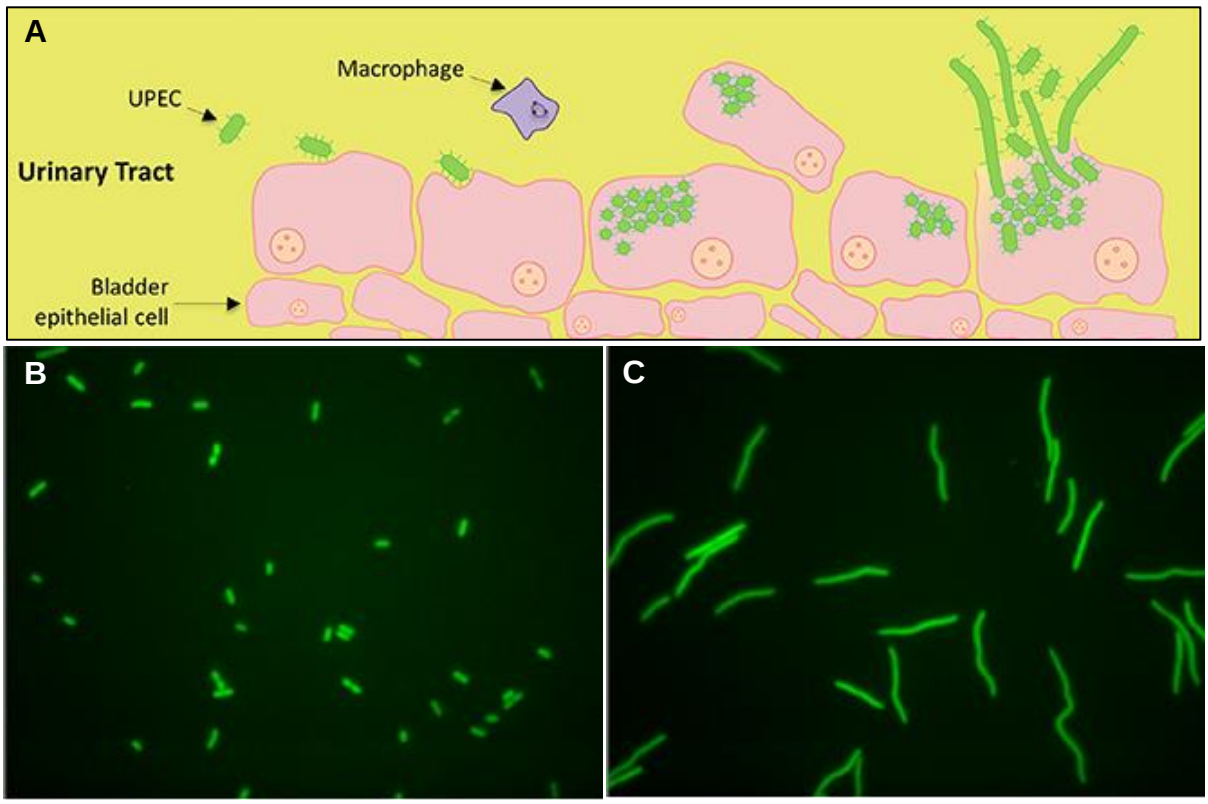

Figure 1. Uropathogenic *E.coli* (UPEC). A) UPEC infects the bladder forming various shapes before exploding from bladder cells to reinfect other nearby cells [9]. B) UPEC rods. C) UPEC filaments.

How can this research benefit UTI sufferers?

My research aims to provide an in-depth, comprehensive understanding of filaments and how they interact with immune cells, chiefly the differences between filaments themselves and what makes them special compared to other shapes. This is done by producing a variety of filaments through different stimuli, such as with antibiotics used in UTI treatment, 'artificial' filaments caused by protein disruption, and 'natural' filaments from UTI models and studying how they interact with macrophages in high resolution microscopy. We need to switch mindsets from regarding bacterial filaments as an interesting observation to considering them as a key virulence adaptation during infections. This can only be done by understanding why filaments avoid engulfment by macrophages. Using this understanding we can come up with innovative treatments to clear infections without the use of antibiotics. These treatments could include manipulating the length of bacteria, changing the way

macrophages interact with bacteria, or modulating our immune system to better fight infections. There is a strong need for these non-antibiotic based treatments as antibiotics are currently the only way to treat UTIs and they are becoming less and less effective as resistance increases worldwide. Our findings from this research and these potential new treatments will greatly help women with UTIs and ensure no one else has to suffer from a lifelong UTI.

References

1. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ: **Urinary tract infections: epidemiology, mechanisms of infection and treatment options**. *Nat Rev Microbiol* 2015, **13**(5):269-284.
2. Foxman B: **Epidemiology of urinary tract infections: incidence, morbidity, and economic costs**. *Disease-a-month : DM* 2003, **49**(2):53-70.
3. Forde BM, Roberts LW, Phan M-D, Peters KM, Fleming BA, Russell CW, Lenherr SM, Myers JB, Barker AP, Fisher MA *et al*: **Population dynamics of an *Escherichia coli* ST131 lineage during recurrent urinary tract infection**. *Nature Communications* 2019, **10**(1):3643.
4. Matuszkiewicz-Rowińska J, Małyszko J, Wieliczko M: **Urinary tract infections in pregnancy: old and new unresolved diagnostic and therapeutic problems**. *Arch Med Sci* 2015, **11**(1):67-77.
5. Yoon MY, Yoon SS: **Disruption of the Gut Ecosystem by Antibiotics**. *Yonsei Med J* 2018, **59**(1):4-12.
6. Beerepoot M, Geerlings S: **Non-Antibiotic Prophylaxis for Urinary Tract Infections**. *Pathogens* 2016, **5**(2).
7. Rosen DA, Hooton TM, Stamm WE, Humphrey PA, Hultgren SJ: **Detection of intracellular bacterial communities in human urinary tract infection**. *PLoS Med* 2007, **4**(12):e329-e329.
8. Paul D, Achouri S, Yoon Y-Z, Herre J, Bryant Clare E, Cicuta P: **Phagocytosis Dynamics Depends on Target Shape**. *Biophysical Journal* 2013, **105**(5):1143-1150.
9. Mann R, Mediati DG, Duggin IG, Harry EJ, Bottomley AL: **Metabolic Adaptations of Uropathogenic *E. coli* in the Urinary Tract**. *Frontiers in Cellular and Infection Microbiology* 2017, **7**(241).