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The Attending Physician

A 5-year-old girl has come to you a week after completing a course of antibiotics for a febrile urinary tract infection (UTI). She now seems well and energetic. A urinalysis is now clear without traces of inflammation, including an absence of protein, blood, leukocyte esterase, and nitrites. Her urine is submitted for a test of cure and comes back positive, with over 100,000 colonies per milliliter of *E. coli*, the same kind of bacteria that was cultured from her urine when she was symptomatic with the UTI. Perplexed, her mother asks how her child can have bacteria once again in her bladder but not be symptomatic and asks if antibiotics are again necessary.

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Anger management: bacteria soothe the savage host

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A 5-year-old girl has come to you a week after completing a course of antibiotics for a febrile urinary tract infection (UTI). She now seems well and energetic. A urinalysis is now clear without traces of inflammation, including an absence of protein, blood, leukocyte esterase, and nitrites. Her urine is submitted for a test of cure and comes back positive, with over 100,000 colonies per milliliter of *E. coli*, the same kind of bacteria that was cultured from her urine when she was symptomatic with the UTI. Perplexed, her mother asks how her child can have bacteria once again in her bladder but not be symptomatic and asks if antibiotics are again necessary.

Current therapy

Urinary tract infection (UTI) is one of the most common infections in humans, accounting for over 10 million infections per year with an estimated \$3 billion in costs (1). While the urinary tract is typically regarded as sterile, the diagnosis of UTI is complicated by a sizable minority group of 1% to 5% of women and children who are colonized with bacteria in the urinary bladder, but who do not have the symptoms and signs of UTI, so-called asymptomatic bacteriuria (ASB) (2). ASB yet further increases in prevalence among individuals with neurogenic bladders, the elderly, and those in nursing facilities, particularly those with some type of bladder catheterization, in whom the frequency may exceed 50% of the population (3). A hallmark of ASB is the absence of inflammation in the urinary tract, suggesting that the bacteria involved in ASB are able to colonize without inducing a host response. It is the inflammatory response of the host that produces the characteristic features of UTI, such as burning and pain with urination, urinary urgency, and sometimes fever.

Although tempting, treatment is not warranted in most individuals with ASB, with few exceptions such as pregnancy and anatomic or immunological defects. In general, the treatment of ASB with antibiotics has been shown to result in the emer-

gence of antibiotic-resistant bacteria without the clinical benefit of reduced future episodes of UTI (4, 5). For this reason, routine screening of urine for asymptomatic colonization is generally not indicated.

Knowledge gap

A major clinical problem, particularly in an era of rapidly rising antimicrobial resistance, is to distinguish between UTI and ASB, sparing antibiotics when not needed. Interestingly, the rise of antibiotic resistance, combined with benign behavior of ASB bacteria in the urinary tract, have fueled interest in turning ASB strains into therapeutics, thus capitalizing on the capacity of ASB bacteria to colonize without aggravating the host and to outcompete more pathogenic strains. Thus, the mechanisms by which ASB bacteria are so uniquely adapted to a commensal lifestyle have been of great interest.

ASB bacteria, which are predominantly strains of *E. coli*, have robust growth characteristics, even in nutrient-deficient conditions such as in urine (6, 7). Furthermore, ASB *E. coli* are known to have the capacity to outcompete uropathogenic *E. coli* in growth and adherence to abiotic surfaces such as catheters, as well as biotic surfaces such as epithelial cells (8). Taking advantage of these characteristics, a number of investigators have pioneered the use of specific ASB strains in high-risk patient populations, such as those with neurogenic bladders and indwelling catheters. Prior work using *E. coli* 83972, an ASB strain that was isolated from a young child with over 3 years

of persistent colonization without renal deterioration, demonstrated that slightly over 60% of adults with spinal cord injury and neurogenic bladder could be persistently colonized with the strain (9). Of those colonized, 60% were UTI-free by 1 year after colonization, while 10% of the controls were UTI-free at 1 year.

While past studies suggest that ASB *E. coli* do, in fact, outcompete uropathogenic *E. coli* strains, providing an explanation for why they prevent UTI by uropathogenic isolates, it has been less clear why the ASB strains do not themselves cause inflammation like the uropathogenic strains. Comparative genomic studies suggest that ASB *E. coli* strains have evolved from more archetypal uropathogenic strains, with genome reduction resulting in the attrition of loci that encode virulence determinants. However, this alone does not explain why factors such as lipopolysaccharides, shared by ASB and pathogenic strains alike, do not equally stimulate host inflammatory cascades.

Research advances

In this issue of the *JCI*, Lutay et al. (10) provide an exciting and novel explanation. The authors demonstrate that in the course of human inoculation with ASB *E. coli*, the bacteria block the phosphorylation of RNA polymerase II (RNA Pol II), which is typically phosphorylated following uropathogenic *E. coli* interaction with urinary tract epithelial cells. By doing so, the ASB strains broadly reprogram the target host cell's response to the bacteria-host interaction with the suppression of transcriptional regulatory pathways, cellular proliferation and remodeling pathways, and innate immune pathways such as IRF3, IRF7, and AP1 originating from the Toll-like receptor 4 (TLR4). These ASB strains further demonstrate that the RNA Pol II mechanism of suppression holds true for a wide variety of ASB and fecal commensal *E. coli*, while uropathogenic strains generally do not possess this capacity.

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Recommendations

The immediate impact of this work lies within the concept of using ASB strains as therapeutics in difficult patient populations that have a lifetime of recurrent UTIs and thus high antibiotic exposure. These include individuals with spinal cord injury and other forms of neurogenic bladder. Because these individuals may develop renal and bladder fibrosis with deterioration in function over time, the UTI-blocking capacity of ASB strains as well as their antiinflammatory properties remain intriguing. ASB strains may also have the ability to attenuate UTI-associated pain, as suggested by recent work (11).

In the broader view, the fundamental mechanisms of bacterial inhibition of RNA Pol II activation may provide one explanation for how bacteria densely inhabit our mucosal surfaces without driving inflammation and how a loss of this suppression may tilt the balance toward mucosal inflammatory diseases, which in turn may have long-term immune and allergic consequences. Conditions such as inflammatory bowel disease (12, 13), irritable bowel syndrome (14), necrotizing enterocolitis (15), and recurrent bacterial vaginitis (16) are among a number of examples in which commensal bacteria with strong RNA Pol II suppression phenotypes may be beneficial as adjunctive medical therapy. Current medically used

probiotics such as lactobacilli and *E. coli* Nissle 1917 may already have robust RNA Pol II suppression activity, which may be further optimized through the selection of natural derivatives or intentional genetic modifications. Future work will certainly determine the extent to which this mechanism applies and whether it can be harnessed therapeutically as an adjunct in treating inflammatory conditions.

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