Microbiologist in the Clinic:
Coitally Related Symptoms with Negative Urine Cultures

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Abstract:

In this first episode of the Microbiologist in the Clinic series, clinicians and laboratory scientists share their perspectives about a 30 y/o woman, who is seeking specialty consultation for frequent episodes of urinary urgency, frequency, and dysuria, which respond to short courses of antibiotics. Although her home dipsticks suggest that she has a UTI, and her urinalysis typically has a moderate number of white blood cells, her urine cultures are always negative. The challenges of this clinical presentation are discussed with evidence for evaluation and treatment.

Keywords:

UTI, Urobiome, Lower Urinary Tract Symptoms, Women's Health, Microbiome, Pyuria, Antibiotics

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In the Microbiologist in the Clinic series, clinicians, and laboratory scientists from two sides of “the pond” share their perspectives about adult women with lower urinary symptoms related to known or suspected microbial etiologies. Rajvinder Khasriya MD, PhD contributes her experience as a Consultant Urogynecologist and Principal Clinical Investigator for the Bladder Infection & Immunology Group at the University College London. Her colleague, microbiologist and cell biologist Harry Horsley PhD, Senior Research Fellow and Principal Scientific Investigator for the Bladder Infection & Immunity Group at University College London will outline how in office assessment of fresh urine may provide useful insights. Professor Linda Brubaker MD MS provides insights from her experience providing care for adult women with recurrent urinary tract infection. Professor Alan Wolfe PhD adds his perspectives based on his knowledge of microbial physiology and more than a decade of study into the urobiome, the microbial community of the urinary bladder.

This conversation will focus on a 30 y/o woman who is seeking specialty consultation for frequent urinary tract infections (UTIs). She is generally healthy. She became sexually active 5 years ago with her current male sexual partner. Since becoming sexually active, she has experienced frequent episodes of urinary urgency, frequency, and dysuria. Her GP (primary doctor) reports that her examination is unremarkable and the patient is prescribed short courses of antibiotics that resolve her symptoms completely. However, the events are occurring **nearly every month**. She reports that her home dipsticks suggest that she has a UTI, and her urinalysis typically has a moderate number of white blood cells; however, her standard urine cultures are always negative.

Let’s get the conversation started.

Linda: I’d like to be very practical here. Patients like this often receive very poor, fragmented care. Because her urine cultures are negative, her concerns may simply be dismissed because her clinician believes that there is no important health concern. In my experience, antibiotic-seeking behavior is rare. Increasingly, patients hope to avoid antibiotic use, if at all possible. The resolution of this patient’s symptoms resolution following antibiotics is important evidence – but evidence of what? Clarification on the relationship between symptoms onset and sexual activity is also important. The symptoms do not occur in the absence of sexual activity; this suggests a physical phenomenon. Infrequently, barrier contraceptive products, including latex condoms, contribute to these symptoms through allergic or irritative mechanisms.

Reliance on an antibiotic without a strategic therapeutic goal is problematic. It is clearly abnormal to have moderate white cells in the urine. This sign of inflammation should be further evaluated. Rare things occur and it is our duty to reasonably exclude unusual physical findings, such as concerning skin lesions, masses (pelvic vaginal or suburethral), urethral diverticulum, and endometriosis. Baseline imaging is not

necessary unless the physical examination is limited by body habitus. It is also essential to appropriately screen for past or current sexual trauma. As part of her physical examination, I would check her for pelvic floor myofascial pain. Even if there are other etiologies, I suspect that this patient has a component of myofascial pain disorder, as evidenced by trigger points within her pelvic muscles. These can be relatively quiescent until an activity, such as sexual activity or a pelvic examination, occurs. If myofascial pain is present, a prompt referral to a qualified pelvic floor physical therapist is essential, as myofascial pain is highly treatable. Assuming there are no “alarm” findings on the physical examination, and regardless of the finding of myofascial pain, I would also initiate a comfort measure strategy complemented with a different testing approach.

Comfort measures can include the liberal use of over-the-counter products, such as non-steroidals, to reduce inflammation, local anesthetic patches that can be placed in the supra-pubic location and bladder analgesics, such as phenazopyridine. I would also encourage the patient to adopt a different testing strategy, with avoidance of home test strips, which increase anxiety without providing rigorous evidence for/against the presence of a UTI.

Harry: Over my past 15 years studying UTI, I have had significant exposure to individuals suffering from chronic / recurrent UTI and debilitating lower urinary tract symptoms. The scenario described in this case study is far from uncommon. Our lack of a clear understanding of infective disease and pain disorders of the pelvis and urinary tract appears to push patients into self-diagnosis and self-care. Biochemical dipsticks are used almost ubiquitously in primary care as a point of care test to diagnose UTI and, in the UK at least, are freely available to purchase online and in high street chemists. More recently, ‘smart’ home test kits have become available, which use smart phone photographs of dipsticks to diagnose UTI. Unfortunately, dipsticks perform poorly, with numerous studies finding them to be of little diagnostic value. Their ability to detect the presence of pyuria (via leukocyte esterase) as a surrogate for infection is poor. Furthermore, the sensitivity and specificity of nitrite as a diagnostic aid is similar to flipping a coin, as only some uropathogens convert nitrates to nitrite. There is evidence that diagnosing UTI when leukocyte esterase, nitrites, and blood are present improves matters. However, these predictive values were calibrated against the ‘gold standard’ method, which involves a midstream voided urine sample analyzed by the standard urine culture used by most clinical microbiology laboratories. Considering the problems associated with this method, which I am sure Alan will speak about, then it would seem that dipsticks serve little purpose in these patients.

Raj: I would echo Linda’s comment that antibiotic-seeking behavior is rare. We know that over half of women will suffer with a UTI in their lifetime and, of those, approximately 40% will have recurrence. One of the problems for this group is that they are prescribed repeated short courses of antibiotics for 3-5 days and often the antibiotics are changed. Guidelines for recommendations on surveillance for those that do not respond to these short course protocols are lacking. Randomized control trials (RCTs) on treatment of acute UTI, using 3 to 14-day treatment courses, consistently demonstrate 25%-35% microbiological and symptomatic failure rates. Treatment failure

is often assumed to be the result of antibiotic resistance although the culture-derived evidence is weak. Other plausible explanations include guideline-driven inadequate or prophylactic dosing and short treatment durations. It is very stressful for patients to not only have persistent symptoms but also to then need to repeatedly seek help and additional short courses. Although it may be difficult in a busy general practice, patients should be assessed at the end of their treatment for symptom resolution. The treatment course can be potentially extended if there is efficacy but not complete resolution. We should move away from the 'one size fits all' approach, which inevitably leads to more prescriptions and wider and wider spectrum antibiotics or rotations of antibiotics. In female patients, there are many assumptions about the symptom spectrum of acute or recurrent UTI. We often ask about dysuria, frequency, and urgency but voiding symptoms, which are indicative of UTI, are missed in this population.[1] Asking about straining, stream and emptying is important.

Alan: I am suspicious when the standard urine culture results are always negative but antibiotic treatment resolves symptoms. Antibiotics do one thing very well; they kill bacteria. If there is a response to the antibiotic, then there must be something wrong with the urine culture results. Many do not know that the standard urine culture was designed about 70 years ago to detect the most common causes of pyelonephritis, which are typically bacteria that can grow quickly in air. The most common of these bacteria is *Escherichia coli*. But we now know that most of the bacteria species present in the urinary tract do not grow under the standard conditions. I suspect that the symptoms experienced by this young woman are caused by a bacterial species or a group of species that are not detected by the standard culture method.

Raj: I'd like to comment on the significance of the white blood cells in the urine. As mentioned by my colleagues, the landscape of diagnostics in UTI is confusing and we are now understanding that the standard cultures and dipsticks are unreliable. The immediate microscopy of a fresh urine sample to count white cells is now understood to be the best surrogate marker of UTI. This is conducted in the clinic at the time of seeing the patient. Unfortunately, this is not standard care in most clinical settings. Most laboratories screen urine using microscopy to look for white cells, but this may not be done immediately. White cells are lost in the urine over time. It is well established that 40% of cells will be lost by 4 hours. Thus, immediate microscopy is ideal if it can be achieved in a laboratory. There is a widespread assumption that pyuria has to be >10wbc/ µl to be significant and this has been set as a threshold in most studies. Our experimental series, though, have shown that any white cells in the urine, provided that it is collected properly and analyzed immediately, are significant in symptomatic patients.

Harry: Immediate urine microscopy to enumerate white blood cells in common practice in Scandinavian primary care. Unfortunately, in the UK and undoubtedly the USA, this skill appears to have been lost. In our hands, urine microscopy significantly outperforms both the dipstick and standard urine culture.[1] We have even found, using mathematical models, experiences of pain and voiding symptoms positively predict pyuria. However, as Raj has mentioned, it must be conducted immediately due to rapid

cell death. Much very elegant work has been conducted to further our understanding of the urobiome and to uncover the good, the bad, and the ugly bacteria that call the bladder home. Discovering causation, however, is going to take time. Until then, making use of the highly evolved immune receptors leading to white blood cell recruitment in the urine would appear to be a good option. I believe progress in our understanding of the human immune response in UTI to be an important consideration when developing future diagnostic tests.

Alan: A major problem with multiple antibiotic exposures, especially with no knowledge of the targeted bacteria, is the risk of problematic bacteria developing resistance to those antibiotics. Bacteria have all sorts of ways to defeat antibiotics and repeated exposures tend to select for those bacteria that do the best job at avoiding death by antibiotic. So, what happens is that a bacterium that just happens to be resistant to the prescribed antibiotic multiplies while the sensitive bacteria die. Over time, the resistant bacterium takes over and the antibiotics no longer work.

I would like to return to the apparent relationship between sexual activity and the occurrence of symptoms. I have a hypothesis that has yet to be rigorously tested. One of my former students used sensitive microbial detection methods to analyze urine samples obtained from 8 asymptomatic females of reproductive age who sampled themselves every day for 3 months. All were sexually active. Most had urobiomes predominated by members of the bacterial genus *Lactobacillus*, which is well known to inhibit or kill *E. coli* (and many other uropathogens). Intriguingly, he noticed that, in most cases, the *Lactobacillus* diminished for a day or two following vaginal intercourse (with or without condom usage). This was coupled with an increase in members of *Streptococcus*, a genus whose members are not noted for inhibiting or killing *E. coli*.[2] A follow-up study revealed that the Streptococcus was native to the female urogenital tract, evidence that this phenomenon was not due to microbial transfer between partners.[3] Now, none of these participants developed a UTI but these results suggest a possible mechanism for post-coital UTI. If the physical nature of vaginal intercourse causes the urogenital environment to change temporarily, causing the protective *Lactobacillus* to decrease and the non-protective *Streptococcus* to increase, this would create a window of opportunity for a uropathogen like *E. coli* to bloom and cause symptoms. Perhaps this woman or her partner carry a uropathogen not detected by the standard urine culture that blooms every time they have sex, causing symptoms.

Linda: Interesting! This is an area that needs dedicated research focus. This patient, and many like her, undoubtedly has experienced a decreased quality of life and a disruption to her sexual intimacy and relationship. Caring sexual partners don't want to cause pain or see their partners suffer; yet the desire for a physically intimate relationship is normal and healthy. Unfortunately, much of what clinicians (and the internet) tell this patient to do is not evidence-based and further disrupts their intimate comfort. Recommendations for use or avoidance of particular undergarments or "feminine" hygiene products are not evidence-based. And there is no evidence that voiding/showering/bathing immediately before or following coitus reduces symptoms such as these. Recommendations such as these further disrupt intimate moments and

detract from a health quality of life. This is especially taxing on couples attempting to conceive, particularly those who are using timed sexual activity with or without assisted reproductive technologies. In summary a short list of “things to do” should include: 1) Listen to the patient and don’t try to fit her story into the current algorithm of UTI dogma, 2) Compassionately examine the patient, making sure to include assessment of pelvic muscle tenderness, 3) Be aware of the limitations of common UTI tests, 4) Include the patient in planning further evaluation and treatment that is aligned with her goals and preferences.

Thank you all for joining this conversation. It is clear that clinicians can provide better care to patients, such as this example, by conducting a targeted history with attention to life-impact, considering voiding symptoms in women, physical examination that guides further evaluation and perhaps treatment, guidance for testing and clarity about the evidence for various treatment options. We should not consider UTI as a ‘mild’ or self-limiting disease as this is not the case in many patients and has a significant impact on quality of life. It is incumbent on the clinician to keep in mind the limitations of standard diagnostics, the need to improve microbial detection for less well known uropathogens, the importance of symptoms, a holistic approach, including non-antibiotic strategies, but also that individualized prescribing and follow up will minimize antibiotic misuse. Providing empathetic, effective clinical care for patients with these symptoms and test results is our responsibility – and as caring clinicians, we must do better.

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