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PERSPECTIVES

From Awareness to Action: Pioneering Solutions for Women's UTI Challenges in the Era of Precision Medicine

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Abstract: This article aims to bring clinicians' awareness to the widespread impact of urinary tract infection (UTI) on the lives of women and to the advances that offer hope for future improvements in the diagnosis and management of UTI. Thanks to physiological, anatomical, and lifestyle factor differences, women face heightened vulnerability to UTIs compared to men. In fact, women are four times more likely than men to develop a UTI and around half of these women encounter UTI recurrence, which is a significant source of both physical and psychosocial burdens. Despite the current shortcomings in diagnosis and management, emerging diagnostic technologies promise to identify UTIs more accurately and rapidly, offering women hope for a revolution in UTI management. Meanwhile, clinicians have the opportunity to reduce the psychosocial burden by recognizing the value of patients' lived experiences and ensuring their care plan is in alignment with their patients' goals and expectations for medical care.

Keywords: women's health, urinary tract infection, urine culture, multiplex-polymerase chain reaction, metagenomic next-generation sequencing, mass spectrometry

UTI and the Ambiguity of the Clinical Diagnostic Spectrum

UTIs occur anywhere from the urethra to the kidneys, manifesting as cystitis or pyelonephritis based on the infection's location.[1] The symptoms vary between individuals, but commonly cause physical discomfort and pose substantial psychosocial challenges, impacting women's daily lives. UTIs can be conceptualized as falling into a diagnostic spectrum, with varying clinical signs and symptoms.[2] Signs and symptoms of UTI may overlap with other urologic diagnoses, such as incontinence, overactive bladder (OAB), or interstitial cystitis (IC), a.k.a. bladder pain syndrome (BPS).[3,4] Furthermore, distinguishing UTI symptoms can be a significant challenge, especially in long-term care facilities, where residents experience high rates of both asymptomatic bacteriuria (ASB) (up to 80%)[5,6] and cognitive impairment.[7] For example, individuals with Alzheimer's disease, dementia, or other forms of cognitive impairments may be unable to clearly communicate their symptoms. In addition, many older individuals do not experience typical UTI symptoms, including urinary frequency, urinary urgency, and dysuria. In fact, atypical symptoms of UTI, which include nonspecific declines in cognitive or physical function, are frequently the only symptoms in elderly individuals.[8–10] Young children and individuals with disabilities, such as paralysis, are also likely to face diagnostic challenges due to difficulties in recognizing UTI symptoms. Therefore, advanced methods to distinguish infection and inflammation from healthy eubiosis are desperately needed to avoid unnecessary and potentially detrimental treatment resulting from confusing ASB with UTI in these vulnerable populations.

The diagnosis of a clinical UTI requires both the presence of symptoms and the confirmation of uropathogenic microorganisms in the urine. The term ASB has been used to describe the presence of bacteria in the urinary tract in the absence of any clinical urinary symptoms.[5] The prevalence of ASB in non-catheterized individuals has been reported to range from < 1–50% depending on sex and age.[11] Historically, because healthy urine was presumed to be sterile, ASB

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was thought to require treatment.[5] However, evidence that antibiotic treatment of ASB fails to produce a clinical benefit suggests that the presence of bacteriuria in the absence of symptoms should not be treated.[11–13] One exception relevant to women is during pregnancy, when treatment of ASB may be recommended to reduce risks of maternal pyelonephritis, pre-term labor, and/or low birth weight.[14]

Limitations in standard urine culture (SUC) have upheld the misconception that urine is sterile. SUC methodology is biased toward detecting classical gram-negative uropathogens, such as *Escherichia coli* (*E. coli*). Culture-independent, molecular-based methods have now revealed that SUC fails to reproducibly detect the majority of the urobiome.[15–18]Advances in the analysis of microbial communities over the last decade have demonstrated that the urinary tract, particularly the bladder, is home to a resident microbiota, referred to as the urobiome.[13,19–22] The use of next-generation sequencing has revealed that the urobiome, while distinct, exhibits similarities to the microbiomes of the genital skin and/or vaginal mucosa.[23–25] The urobiome has also been shown to change in response to aging, hormonal changes, and antibiotic use.[26–28] Therefore, the pathogenesis of UTI may involve dysbiosis of the urobiome.[29] Further research toward an improved understanding of the role of dysbiosis in the pathogenesis of urologic conditions and how to restore eubiosis as part of treating these conditions is, therefore, essential.

Physical and Psychosocial Burden of UTIs in Women

Approximately 60% of women will experience a UTI in their lifetime[30] with a recurrence risk[31] and a gender disparity that sees women four times more likely than men to develop a UTI.[32] This discrepancy underlines the physiological and anatomical differences, alongside lifestyle factors, that contribute to the heightened vulnerability among women.[30] The higher prevalence of UTI in females[33,34] is largely attributed to differences in urinary tract and genital anatomy, with women having a shorter urethra located closer to the rectum relative to men.[30] Many UTIs occur in young, otherwise healthy, sexually active, adult females, given that sexual activity and the use of intravaginal birth control and menstrual products are considered risk factors for UTI development.[30] However, UTI is also the second-most common infection in community-dwelling elderly women and the number one cause of infection in elderly women residing in long-term care facilities or hospitals.[35] This high prevalence is associated with hormonal changes that occur during menopause and increase the risk of developing UTIs.[30] Similarly, UTI is the most common infection during pregnancy, being diagnosed in up to 60% of pregnancies, where it poses unique risks and challenges.[36–39] In addition, up to half of women who experience one UTI will develop another within six months, and this is referred to as recurrent UTI.[31]

Due to being one of the most prevalent infections in women, UTIs are also a leading cause of prescribed antibiotics.[40] Furthermore, most antibiotics being prescribed for UTI are ordered empirically, rather than as guided therapy.[41] Many common uropathogens demonstrate clinically significant levels of resistance to first-line antibiotics, particularly internationally, and some have even been reported to be multidrug-resistant, which means that empirically prescribed antibiotics are increasingly likely to fail.[42–45] For example, while nitrofurantoin and fosfomycin are frontline choices for empiric treatment of UTIs, with low reported resistance rates in the USA, they have higher resistance rates in Norway and Asia, respectively.[44,45] Additionally, increasing antibiotic resistance to antibiotics used for UTI treatment, including trimethoprim/sulfamethoxazole[46] and fluoroquinolones, especially ciprofloxacin,[47] has been reported leading to escalating healthcare expenditures and demonstrably higher mortality.[42,43] Certain groups of women have additional difficulty with empiric antibiotic selections. For example, elderly women, experience both high rates of polypharmacy and comorbid conditions that alter pharmacodynamics.[48,49] Likely due to differences in lifetime antibiotic exposures, elderly individuals, particularly post-menopausal women,[50] have also been demonstrated to have significantly different antimicrobial susceptibility patterns than younger age groups.[51,52] Another group that faces additional challenges with antibiotic selection is pregnant women, in whom additional considerations must be made for placental permeability and the fetal safety profile of the selected antibiotic.[36,39] Lastly, women experiencing recurrent or persistent/chronic UTI often face challenges with empiric therapy due to multi-drug resistant organisms and repeated antibiotic exposure.[53]

The physical health consequences of UTI can be severe. UTI in pregnancy can result in premature rupture of membranes and low birth weight.[54] Pediatric UTIs can result in acute complications such as renal abscess, pyonephrosis, and pyelonephritis, as well as long-term health consequences, including renal scarring, hypertension, and renal insufficiency in adulthood.[33,55–61] When misdiagnosed or not effectively treated, UTIs can also result in severe health

complications in adults, including infectious urolithiasis[62] and urosepsis, which accounts for approximately 25% of all sepsis cases.[34] Complications from UTI also result in around 12,000 deaths annually in the US.[63] However, serious physical health complications of UTI are not the only factors that can have a significant impact on quality of life.

Awareness of the detrimental impacts of UTI on women's quality of life has been gaining increasing appreciation since the turn of the millennium.[64,65] Understandably, quality-of-life outcomes are significantly poorer in women who experience failure of their initial antibiotic treatment.[66] Specifically, women with clinical treatment failure and/or UTI recurrence reported feelings of helplessness and dread.[67] Recurrent UTI, which occurs in up to half of women who experience one UTI,[31] is one of the biggest sources of psychological burden due to UTI.[68] An international web-based survey of women with recurrent UTIs found that women reported taking an average of three sick days off of work and an average of 3 days of limited social activity each year due to UTIs.[69] Additionally, despite nearly seventy-five percent of the women reporting that they tried prophylaxis, the prospect of recurrence was a significant source of stress.[69] Investigation into the sources of this stress of recurrence revealed that fear of negative side-effects of antibiotics used to prevent and treat UTI, as well as frustration with the medical profession for ineffective management, were the two major concerns.[70] Another survey found that recurrent UTIs were not only associated with physical impact on sleep and healthy lifestyle, but with mental health burdens, such as anxiety and depression, and also with damage to women's social relationships with colleagues, family, and friends.[71] Furthermore, lower urinary tract symptom-induced depression has been found to worsen the perception of physical symptoms, resulting in a vicious cycle.[72] A more recent study even found that self-esteem was significantly impacted and that social functions were more severely affected than physical functions in women with recurrent UTIs, emphasizing the need for future studies to include quality-of-life measures when determining the effectiveness of UTI management strategies.[73]

Very recently, the Recurrent UTI Impact Questionnaire (RUTIIQ), was validated and optimized for assessing the patient-reported psychosocial impact of living with recurrent UTI symptoms and pain as a unique tool to improve patient-centered care.[74,75] Physician and patient perspectives of recurrent UTI demonstrate a number of commonly recognized areas for improvement. First, many physicians report feeling that they have insufficient knowledge of guideline recommendations for recurrent UTI management, especially for peri- and post-menopausal women.[76] They also express a need for increased education on UTI pathophysiology.[77] Second, similar to patients, physicians also recognize that symptoms have a significant impact on patients' lives[78] and report feeling frustrated with the limited management options and recommendations for recurrent UTI.[77] However, physician and patient perspectives also had some areas of contrast. For example, patients report being more concerned with improving care for acute UTI episodes, while physicians report being primarily concerned with preventative measures and ongoing management of recurrent UTI as a chronic condition.[79] Physicians may also be inappropriately confident that recurrent UTI patients are satisfied with their medical care.[80] Indeed, clinicians should be aware that recurrent UTI is highly associated with healthcare disillusionment and should be prepared to not only offer creative prophylactic and treatment options but also emphasize the value of patients' lived experiences and communicate with thoroughness and empathy to help ensure patients remain active participants in their own care.[81]

Limitations of Current Diagnostic Methods

Because point-of-care tests do not require being sent to a lab for testing, they are generally cheaper, easier, and faster. As such, the quest for new and improved point-of-care tests is continuous. However, none are currently sufficient for UTI diagnosis when used as independent tests.[82] The most common in-office test used when a UTI is suspected is a dipstick urinalysis. These are moderately specific for UTIs but are significantly limited by low and highly variable sensitivity (10% to 80%).[83–86] The utility of dipsticks also varies with patients' clinical presentations, urine specimen collection method,[87] and the infecting pathogen(s).[88–92] Dipsticks are more accurate with classical symptoms than atypical symptoms,[93] and less accurate in very young children and elderly adults compared to young adults.[94–97] Importantly, they are also more accurate in men than women,[98] and can be impacted by menstrual status.[99] Therefore, it is essential for clinicians to consider the individual patient's age, sex, and clinical presentation when interpreting dipstick results.

Standard urine culture (SUC) has been regarded as the gold standard for UTI diagnostic testing for decades.[100] SUC methodology was optimized for the growth of gram-negative classically uropathogenic bacteria, especially *E. coli*, the most

commonly identified organism in acute UTIs.[101] However, several additional microbial species, such as gram-positive organisms, fastidious microbes, and fungi, have been demonstrated to contribute to urinary microbiome dysbiosis in symptomatic subjects diagnosed with UTI.[16] Thanks to the low sensitivity of SUC, a significant proportion of cases of suspected UTIs end up with negative or other inconclusive results, leaving a diagnostic gap for healthcare providers as they manage these cases.[101,102] Recent publications have shown poor outcomes for patients with negative SUC results, and that more sensitive expanded culture conditions did grow microorganisms that were missed in these cases.[103] In those studies, even many SUC-positive cases experienced poor outcomes, possibly due to limitations in recognition of polymicrobial infections and the inability to assess pooled antibiotic susceptibility within polymicrobial infections.[104] This is a significant limitation given that recent research in the field has demonstrated that polymicrobial UTIs (with two or more uropathogens present) are common.[104–110] In published guidelines for SUC, there also remains a pressing need for consensus regarding the minimum microbial threshold for diagnosing a UTI.[111–119] Published guidance on thresholds for midstream voided urine vary from ≥ 10,000 to ≥ 100,000 colony forming units per milliliter (CFU/mL) and from any microbial detection to ≥ 10,000 CFU/mL for urine collected by in-and-out catheter.[120] The commonly used diagnostic threshold of 100,000 CFU/mL has surprisingly scant and dated evidence to support it,[111–116] and the resulting confusion regarding a minimum threshold subsequently leads to uncertainty amongst clinicians, which can lead to increased use of empiric therapy or undertreatment of UTIs with lower microbial densities.[121] SUC is usually followed by a standard antibiotic susceptibility test (AST) which frequently requires ≥ 3 days to return results, longer than most clinicians and patients are willing to delay treatment. Standard AST typically measures the susceptibility of up to two species in which colonies are grown in the presence of antibiotics. Additionally, AST typically relies on testing just three isolates of a given species, and therefore may fail to capture different strain phenotypes.[122]

Innovative New Diagnostic Approaches

A growing number of sensitive diagnostic methods are being investigated, including metagenomic next-generation sequencing (mNGS), mass spectrometry, expanded quantitative urine culture (EQUC), and multiplex polymerase chain reaction (M-PCR) to improve testing accuracy.[123–125] These techniques can analyze a urine specimen for the presence of microbes that SUC cannot detect, thus providing a clinical picture different from the findings of SUC alone.[18,101,102,106,126–130]

EQUC is a culture-dependent method that employs a wide array of environmental conditions to encourage the growth of microorganisms for identification and quantification but does not provide antibiotic susceptibility data.[131] A prospective study comparing SUC and EQUC results from female patients with and without UTI symptoms showed that SUC missed 67% of identified uropathogens and 88% of non-*E. coli* uropathogens (including yeasts, gram-positive bacteria, anaerobic bacteria, and fastidious bacteria) with over half of subjects having uropathogens grown by EQUC but not SUC.[105] However, since the expanded conditions involve several different growth media with a variety of nutrients, both aerobic and anaerobic atmospheric conditions, longer incubation times, and other factors, EQUC is too laborious to be useful in routine clinical practice.

M-PCR based tests use extracted microbial DNA to rapidly identify infectious organisms with higher sensitivity and specificity than standard cultures.[132] In the context of UTI, the identification of uropathogens in under 24 hours provides an opportunity to make more informed decisions regarding choices for empiric antibiotic therapies if local resistance rates of specific organism-antibiotic combinations are known.[133,134] One inherent limitation of M-PCR is that it can only identify a pre-determined set of organisms for which probes and primers are present in the assay. However, when an assay is optimally designed to include a wide range of known and potential uropathogens, it can provide identification of more gram-positive and -negative bacteria than SUC, as well as fastidious microorganisms and viruses, which do not grow under SUC conditions.[127–129,135] The inherently high sensitivity of M-PCR-based methodologies and the technical reliance on detecting nucleic acids has also raised questions about whether microbes detected by M-PCR and missed by SUC reveal an active infection with living organisms. Positive M-PCR results have been reported to have high concordance with the identification of viable organisms cultured by EQUC methodology.[103] Organisms detected by M-PCR in the urine of UTI patients have also been associated with inflammation of the urinary tract, as would be expected of live, infectious organisms.[136–138] Furthermore, questions arose regarding how quantitative M-PCR reads

compare to the standard units for bacterial quantification by SUC, via CFU/mL. Fortunately, M-PCR has been confirmed to produce quantitative results in reads/mL that directly correspond to the microbial load in cells/mL and correlate linearly 1:1 with the CFU/mL units used in SUC.[139]

The second limitation of M-PCR-based diagnostic tests reliance on nucleic acid identification rather than culture is an inability to provide antibiotic susceptibility information. One approach to counter this limitation without resorting to performing SUC with AST in parallel is to design M-PCR assays to detect antibiotic resistance (ABR) genes. However, in UTI cases, a reported 40% discordance between ABR gene detection and susceptibility phenotypes demonstrates that the detection of an ABR gene may not translate into phenotypic resistance, nor can the absence of an ABR gene absence guarantee susceptibility.[140] Another approach taken by one company to address this limitation is to pair M-PCR with Pooled Antibiotic Susceptibility Testing (P-AST), which measures the susceptibility of the entire community of cultivable organisms from a urine specimen. The P-AST method has multiple advantages. In addition to accounting for any effects of multi-species interactions that may alter susceptibility in polymicrobial infections, the community culture approach of P-AST can account for the presence of multiple strains of a single species, which can co-occur in a UTI and have varying susceptibilities (heteroresistance).[141–143]

Metagenomic next-generation sequencing (mNGS) offers a culture-free pathogen detection based on 16S ribosomal RNA sequencing. In comparison to M-PCR, mNGS microorganism detections are not limited by a pre-determined set of probes and primers.[17] However, reliance on sequence reads results in an output of bacterial presence in terms of relative abundance (relative sequence reads) amongst detected species instead of quantitative values.[144] Sequencing results are also limited by the quality of the genomic reference libraries, which are publicly annotated and, therefore, difficult to trust for clinical accuracy.[145,146] To date, this technique has been primarily used in studies exploring the constituents of the urobiome; however, mNGS has also been studied for its utility in clinical UTI diagnostics.[144,147–149] The advantages and limitations of mNGS relative to SUC are similar to M-PCR, because commercial mNGS testing typically utilizes a PCR test for microbial identity/density and the presence of antibiotic resistance genes as the first phase of analysis.[123,150] The second phase then utilizes 16S ribosomal RNA to detect virtually all microbial organisms, offering extreme sensitivity, but with limited speed.[123,150]

Matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass-spectrometry delivers rapid and accurate identification of microorganisms and is available to clinical laboratories on two FDA-approved systems. The main disadvantage is that the method requires a pure culture of bacteria, meaning it is most commonly used as a supplemental method for identifying bacterial colonies isolated following SUC, and therefore, MALDI-TOF exhibits many of the same time and sensitivity limitations.[125] Furthermore, these systems do not generate antibiotic susceptibility results. Unlike M-PCR and mNGS, MALDI-TOF analysis is not currently performed directly on polymicrobial urine samples. However, recently developed proteomic libraries and the use of machine learning enabled mass-spectrometry to identify 15 of the most common uropathogens directly from urine in less than four hours, along with protein signatures for specific antibiotic resistances.[151–153] As such, direct-from-specimen mass-spectrometry holds potential promise for the future of clinical UTI diagnostics.

The immune response in the urinary tract involves pro-inflammatory cytokines, such as interleukins (ILs), as well as bacteriostatic agents, such as neutrophil gelatinase-associated lipocalin (NGAL).[154–160] Since these can be measured from the same non-invasive urine sample used for microbial detection, soluble inflammatory biomarkers can be useful as a supplement to urine culture or molecular detection and quantitation methods for the diagnosis of UTI.[137,138,161] Such biomarkers are essential to accurately differentiating ASB from UTI, when symptoms cannot be clearly recognized or communicated.[121] Biomarker testing can help avoid unnecessary and potentially harmful treatment of ASB in individuals with difficulty communicating symptoms, such as the very young and those suffering with mental disabilities, such as dementia. However, biomarker testing is not a replacement for microbial identification and quantification or for antimicrobial susceptibility testing.

The development of diagnostic tests with improved sensitivity and specificity combined with an increasing understanding of the urobiome is likely to lead to improved management of UTI and other dysbiosis-associated urologic conditions. Improved diagnostic speed and accuracy will reduce the prevalence of misdiagnoses, enabling better antibiotic stewardship and improving clinical outcomes.

Call to Action

Medical providers and researchers alike must recognize that women bear a disproportionate physical and psychosocial burden from UTIs, particularly due to missed diagnoses and failed treatments. Hope for a better future exists in advancements in understanding UTI pathogenesis and in the growing number of sensitive diagnostic methods being investigated, but we must be diligent in continuing to investigate and improve these methods. We must also strive to reduce the described discrepancies between patient and clinician perspectives, such as through shared decision-making or other communication improvement strategies. Together, advancements in diagnostic methodology and improving communication between clinicians and patients hold the potential to offer unprecedented relief to women suffering from UTIs.

Disclosure

Luke reports patents (11,053,532, 10/160,991, and 11,746,371) licensed to Pathnostics; patents (18,351,286, 18,351,385, 17,830,227, 18,451,748, 17,178,091) pending to Pathnostics and both Haley and Luke are employees of Pathnostics which offers the Guidance UTI test for diagnosis and the determination of treatment options for those with complicated or recurrent UTI's. The authors report no other conflicts of interest in this work.

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