Diagnosis of Urinary Tract Infection in the Neuropathic Bladder: Changing the Paradigm to Include the Microbiome

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Bacteriuria, a non-specific term that refers to the presence of bacteria in the urine, is common in people with neuropathic bladders. However, accurately determining when bacteriuria represents a urinary tract infection (UTI) as opposed to asymptomatic bacteriuria is difficult. There is currently no widely accepted definition of what constitutes a UTI in people with neuropathic bladders. As a result, there is significant variation in care, which likely leads to unnecessary use of antibiotics for bacteriuria. To improve the clinical management of people with neuropathic bladders, it is important to be able to accurately diagnose and treat UTIs. In this article, we review the difficulties associated with accurately diagnosing UTIs and then review proposed definitions. Finally, we discuss the emerging literature of the urinary microbiome and how this may assist in accurately diagnosing UTIs in people with neuropathic bladders. **Key words:** *neuropathic bladders, urinary microbiome, urinary tract infection*

Bacteriuria, a non-specific term that refers to the presence of bacteria in the urine, is common in people with neuropathic bladders. Between 50% and 75% of urine cultures in people with neuropathic bladders will be positive, regardless of the presence or absence of symptoms.[1,2] Despite this high frequency of bacteriuria, determining when a positive urine culture is due to a urinary tract infection (UTI) as opposed to asymptomatic bacteriuria (ABU) is challenging. Classically, the diagnosis of UTI is based on the combination of urinary symptoms (ie, dysuria, urinary frequency, urgency, etc), markers of inflammation, such as pyuria, and a positive urine culture. However, there are several problems with the application of this definition to people with neuropathic bladders, most of which are based on the differing physiologies of this heterogenous patient population. In this commentary, we will review the difficulty in developing an accurate definition of UTI in people with neuropathic bladders and discuss the potential role of the urinary microbiome in this diagnostic dilemma.

The Problem With Overdiagnosis

The broad and inclusive definition of UTI that is used in people with normally functioning bladders is problematic when applied to people with neuropathic bladders, as it can lead to overdiagnosis of UTI and the associated unnecessary use of antibiotics. Indeed, a review of catheter-dependent nursing home patients found that only 50% of patients who were diagnosed with a catheter-associated UTI (CAUTI) met a standardized definition of CAUTI.[3] While the unnecessary use of antibiotics decreases the risk of systemic infection and associated renal damage, there are also risks associated with antibiotic exposure, including antimicrobial resistance and adverse drug events.[4] This risk of increased rates of antibiotic resistance is illustrated in the geriatric population, where there is a direct correlation between antimicrobial treatment of ABU and the presence of multidrug-resistant organisms in the urine.[5] This is also reflected in the increasing rates of infections with antibiotic-resistant organisms cultured from urine from people

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with neuropathic bladders.[6–8] These trends are concerning, as infections with antibiotic-resistant organisms are associated with increased hospital admissions and health care costs,[9] longer lengths of stay,[10] and higher mortality rates.[11] In order to mitigate the rise in antibiotic resistance, but also ensure adequate treatment of infection, a more accurate way of diagnosing UTIs in people with neuropathic bladders is needed. This, however, is a challenging task.

Why Are Special Definitions Needed?

Different definitions exist for UTIs in both children and adults. The American Academy of Pediatrics (AAP) defines a UTI as the presence of bacteriuria, at a cut-off of 50,000 colony-forming units/mL (CFU/mL), in combination with pyuria, defined as more than five urinary white blood cells per high-power field, in the general pediatrics population.[12] There is a similar definition for adults. The Infectious Disease Society of America (IDSA) refers to cystitis in adults as the presence of dysuria, urinary frequency and/or urgency in combination with bacteriuria in the absence of signs of pyelonephritis, such as fever or flank pain.[13] Whereas the IDSA definition relies on the combination of symptoms in the presence of bacteriuria, the AAP requires pyuria in addition to bacteriuria. However, neither of these definitions are sufficient for the diagnosis of UTI in people with neuropathic bladders.

The AAP's definition for UTIs in children is reliant on pyuria, which is a common finding in people with neuropathic bladders. However, pyuria was found in 45% of asymptomatic adults[14] and 50% of asymptomatic children[1] with neuropathic bladders, underscoring the lack of specificity of pyuria. Indeed, the IDSA's guidelines on UTIs for people with neuropathic bladders state that the presence of pyuria along with bacteriuria in the absence of symptoms is not an indication for treatment.[15] Despite the lack of specificity of pyuria for UTIs in patients with neurogenic bladders, clinicians still frequently consider it to be a proxy for infection. A survey of spina bifida clinics found that 56% of practioners would treat an asymptomatic patient with pyuria and bacteriuria for a UTI.[16] However, the lack of pyuria is useful in identifying patients at low risk for UTI. The combination of more than 10 urinary white blood cells with moderate to large leukocyte esterase has a high negative predictive value for UTI,[17] suggesting that the greatest utility of pyuria may be in identifying patients without a UTI.

In contrast to the AAP's definition of UTI in children, the IDSA's definition of cystitis does not rely on pyuria, but rather refers to the combination of symptoms suggestive of bladder irritation – dysuria, urinary frequency and urgency – in combination with bacteriuria. Similar to pyuria, bacteriuria is also not specific for UTIs in the neuropathic bladder population as demonstrated by the rate of positive urine cultures in this population, regardless of the presence or absence of symptoms.[1,14] The other half of the IDSA's definition relies on the presence of symptoms. The reliance on urinary symptoms to diagnose a UTI is problematic in the neuropathic bladder population. The etiology of neuropathic bladder, level of the lesion, method of bladder management, degree of sensation experienced by the patient, and the patient's neurological status (or developmental status in children) will affect the degree to which patients experience and report symptoms. Additionally, symptoms frequently attributed to UTIs in people with normally functioning bladders have other, often more likely, etiologies in people with neuropathic bladders. For example, urinary incontinence is a frequent symptom of UTI in otherwise healthy children. However, in a child with a neuropathic bladder, increased incontinence may be related to altered bladder dynamics. A recent patient-centered investigation highlighted these differences in urinary symptoms experienced by those with neuropathic bladders, identifying that urinary symptoms in this population are complex and distinct from those with normally functioning bladders.[18] Further, symptoms frequently lack good predictive accuracy for UTIs: In a series of patients with spinal cord injury (SCI), only 61% of patients were able to accurately predict when they had a UTI.[19]

The generalized definitions of UTI lack specificity in people with neuropathic bladders as they do not take into consideration the aspects of

bladder function and management that are unique to the neuropathic bladder population. There is a need for a definition of UTI that is applicable to people with neuropathic bladders.

Specific Definitions for Neuropathic Bladders

Multiple organizations have created definitions of UTI in patients with neuropathic bladders. However, none have been widely accepted, and there is currently significant variability in the way various clinicians diagnose UTIs.[17] One of the older definitions came out of the American Academy of Cerebral Palsy and Development Medicine's round table discussion of symptoms of UTI in neurogenic bladder in 1990, which defined a UTI as the combination of a positive urine culture with either fever, abdominal pain, change in continence, or change in color or odor of urine.[20] More recently, the IDSA published their definition of a catheter-associated UTI, which is the combination of signs or symptoms of an infection along with $\geq 10^3$ CFU of at least one bacterial species in a single catheterized urine sample.[21] Both of these definitions are relatively vague and essentially define a UTI as the combination of symptoms with a positive urine culture. However, given the rate of positive urine cultures in this patient population, and the lack of specificity of many symptoms of UTI, these definitions lead to an overdiagnosis of UTI and significant variation in care.[16] In response to this variation, a third definition was proposed, which was as follows: Growth of ≥100,000 CFU/mL of a known uropathogen on urine culture with at least 10 urinary white blood cells, as well as at least two of the following symptoms: fever, abdominal pain, new or worse incontinence, pain with catheterization, and malodorous or cloudy urine.[22] This definition, proposed for use in research, is the most specific of those listed, given the requirement for pyuria and more than one clinical symptom, and may have utility within the clinical realm as well.

A notable difference between these definitions is the chosen colony count. The choice of 100,000 CFU/mL as a standard cutoff for UTI is based on work completed in 1956 by Kass.[23] Kass reported that patients with large amounts of bacteria in their urine were more likely to have symptoms suggestive of a UTI and asymptomatic patients had fewer bacteria in their urine. The use of 100,000 CFU/mL quickly became accepted as the cutoff for UTIs. However, more recently, several authors have demonstrated that lowering the cutoff does not affect specificity of the urine culture in diagnosing UTI when used in combination with fever and pyuria.[24] This is reflected in the AAP UTI guidelines, in which the cutoff for a positive urine culture is 50,000 CFU/mL.[12] The variation in these definitions suggests that the utilization of colony counts to diagnose a UTI is much like pyuria in that the lack of growth on a urine culture may be useful in ruling out a UTI. However, even this may be inaccurate: A recent study found that almost 36% of children with DMSA results suggestive of pyelonephritis had negative urine cultures.[25] Taken together, these data suggest that interpretation of urine culture results should be made in combination with clinical symptoms and the results of other diagnostic tests and imaging.

The use of a specific cutoff for positive urine cultures when used in isolation for the diagnosis of UTI is largely based on the presumption of urine sterility, where the growth of an organism in urine culture is an aberration from the norm. However, the presence of bacteriuria in an asymptomatic person, known as asymptomatic bacteriuria (ABU), is not a harmful state. Multiple studies demonstrate the safety of ABU in a wide variety of patient populations, including children,[26] women with diabetes,[27,28] and elderly patients.[29,30] This documented "safety" of asymptomatic bacteriuria is likely partially related to the lower innate immune response seen in patients colonized with nonvirulent strains of bacteria, such as *Escherichia coli*.[31] Further, there is some evidence to suggest that treatment of ABU is associated with increased risk of recurrent UTI compared to patients in whom bacteriuria was not treated.[32] Finally, and most relevant in people with neuropathic bladders, the paradigm of UTIs is changing. The traditional view of urine sterility has been challenged by the discovery of the urinary microbiome, the host of microbes within the urine that are not reproducibly cultivated using standard urine culture techniques.[33,34]

Urinary Microbiome

The advent of methods designed to identify all bacteria in the urine, such as sequencing-based techniques (ie, 16S rRNA sequencing or whole genome sequencing), or the cultivation-based technique of expanded quantitative urine culture (EQUC),[35,36] have demonstrated that a wide array of bacteria can be found in the urine of healthy, asymptomatic individuals.[14] This field of research is still young, as much is yet to be discovered about the urinary microbiome and its role in maintaining bladder homeostasis. However, emerging data suggest that the urinary microbiome may play a role in multiple pathologies of the urinary system, such as urge incontinence,[36] bladder cancer,[37] and overactive bladder,[38] indicating the important role of the urinary microbiome in urinary health and disease.

Evaluation of the urinary microbiome of people with neuropathic bladders demonstrates that different communities of organisms are present in a neuropathic bladder compared to people with normally functioning bladders. The urinary microbiome of patients with neuropathic bladders consists predominantly of bacteria classically considered to be uropathogens, such as *Klebsiella, Pseudomonas,* and *Enterococcus*, compared to the non-uropathogenic bacteria that predominant the urinary microbiome of people with normally functioning bladders, such as *Lactobacillus.*[14,39] The composition of the urinary microbiome of patients with neuropathic bladders explains the rate of positive urine cultures in this population. The standard urine culture was designed to detect a limited number of most common, aerobic uropathogens,[34] such as those that predominant the urinary microbiome in people with neuropathic bladders. Conversely, the standard urine culture identifies far fewer of the bacterial species either grown on EQUC or found with the use of sequencing technologies.[14,34,35] The majority of the components of the baseline microbiome in people with neuropathic bladders are those bacteria that optimally grow on the standard urine culture, while the components of the urinary microbiome from people with normally functioning bladders do not grow reproducibly or at all on the standard urine culture, thus explaining the seemingly disproportionate rate of ABU in people with neuropathic bladders.

The urinary microbiome has been implicated in UTI pathogenesis. One study demonstrated that patients who developed UTIs during a period of observation had lower diversity of the urinary microbiome compared to patients who did not develop UTIs.[40] Similarly, another series demonstrated that patients with decreased proportions of *Lactobacillus iners* and an increased number of uropathogens in their preoperative urinary microbiome had an increased risk of postoperative UTI.[41] One additional study demonstrated that a change in the urinary microbiome occurred preceding the development of a UTI and that the urine microbiome normalized following treatment,[42] suggesting that the urinary microbiome is relatively stable over time. Taken together, these data suggest that perturbations in the urinary microbiome, a state referred to as *dysbiosis*, may suggest the development of a UTI. Indeed, there has been the suggestion within the literature to change the term UTI to "urinary tract dysbiosis,"[43] thereby reflecting the perturbations seen within the urinary microbiome in the setting of a UTI. Although currently cost-prohibitive, longitudinal monitoring of the urinary microbiome analysis in patients with neuropathic bladder may help improve the accuracy of diagnosis when neuropathic bladder patients present with concern for UTI.

In addition to diagnosis, the urinary microbiome also has potential implications for the prevention and treatment of UTIs. Several authors have investigated whether probiotics, exogenous microbes that have potential to improve health,[44] have therapeutic potential for UTI.[45,46] Although data are mixed, a meta-analysis found that there was no overall benefit to the use of probiotics to prevent UTIs in patients with neuropathic bladder.[47] However, comparing these works is difficult due to limitation in sample size and significant heterogeneity in the strains of probiotic used. Further, while similarities exist, there is interperson variability in urinary microbiomes.[42] Therefore, it is unlikely that a single intervention will have the same effect on the microbiome in every person. Although mechanistically appealing, there is no current robust evidence to support the use of probiotics to prevent or treat UTIs in people with neuropathic bladders. Additional work is

needed to understand how various interventions affect the urinary microbiome and the implications for bladder health.

Conclusion

The discovery of the urinary microbiome has challenged the previously held views of the sterility of the urine and the paradigm of a single organism leading to a single infection. The improved ability to identify components of the microbiome has challenged these beliefs. We need to shift our concept of a UTI to encompass the ecological view of the microbiome and to consider the community of organisms as a whole, rather than focus on the individual components. Although much more work is needed, the urinary microbiome has promise to improve our understanding of the pathophysiology, as well as the accuracy of diagnosis, of UTI.

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