Urinary Tract Infection and Neuropathic Bladder

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KEYWORDS

• Urinary tract infection • Neurogenic bladder • Urobiome

KEY POINTS

- Urinary tract infections (UTIs) are the most common infection in patients with neurogenic bladder (NGB).
- Diagnostic criteria for UTI in patients with NGB variers.
- UTIs can result in major morbidity for patients with NGB so prompt diagnosis and treatment is important.

INTRODUCTION

Patients with insults to the central and peripheral nervous system are likely to have an impact on normal bladder function with resulting neurogenic bladder (NGB). Etiology varies and includes spinal cord injury (SCI), multiple sclerosis (MS), spina bifida (SB), cerebral palsy, and Parkinson disease.[1] Urinary tract infection (UTI) is the most common infection in people with NGB with an estimated overall rate of 2.5 UTI episodes per patient year.[2] As a result, UTIs result in a tremendous burden on the health care system.

PATHOGENESIS

The pathogenesis of the increased risk of UTI in people with NGB is complex and multifactorial (**Fig. 1**). Abnormal bladder function can result in increased post-void residuals, urinary stasis, and secondary vesicoureteral reflux (VUR), decreased bladder compliance with high bladder pressures and a potential dysfunctional immune response.[3] Normal bladder emptying is important in eliminating bacteria, which suggest that incomplete bladder emptying with high post-void residuals may increase risk of UTI.[4] Elevated intravesical pressures may impact perfusion of the bladder and decrease movement of inflammatory cells and antibiotics to the bladder, and result in secondary VUR, increasing the risk of pyelonephritis.[5] High pressure bladders may alter bladder anatomy, impacting urine flow and increase the risk of UTI.[4] The glycosaminoglycan (GAG layer) acts as a protective barrier to bacterial invasions and may be disrupted in the NGB.[6] Immunoglobulin A, which is responsible for agglutinating bacteria and preventing bacterial adherence, may be reduced in the setting of NGB.[4] Finally, there are studies that suggest immunity in the NGB differs from the normally functioning bladder: Animal studies have shown the immune response in the SCI rat model is dysregulated with elevations of proinflammatory markers prior to infection, which decrease after infection introduction.[3,7] Research is needed to better understand the correlation of these factors and the increased risk of UTI in the NGB populations.

DIAGNOSIS

Defining Urinary Tract Infection

Prompt diagnosis of a UTI has been shown to both improve outcomes and prevent UTI-associated

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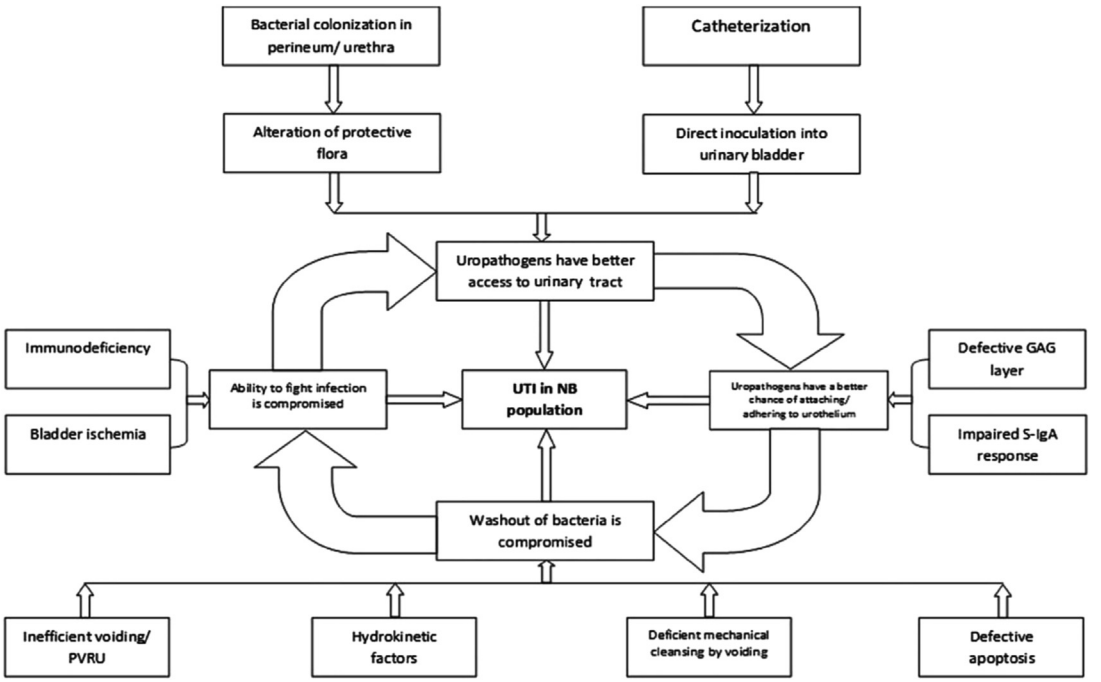

Fig. 1. Multifactorial causes of urinary tract infection in neurogenic bladder. (*From* Vasudeva P, Madersbacher H. Factors implicated in pathogenesis of urinary tract infections in neurogenic bladders: Some revered, few forgotten, others ignored. Neurourol Urodyn 2014;33(1):95 to 100; with permission.)

sequela.[8] However, accurate diagnosis of UTI is challenging since there is no global consensus on the definition of UTI. A 2013 systematic review of UTI in pediatric SB patients found that only one-third of studies reported a definition for UTI, most of which were variable.[9] A 2021 follow-up study found some improvement in UTI definition, although with notable continued variation.[10] Both the National Institute on Disability and Rehabilitation Research (NIDRR) Consensus Statement and the Infectious Disease Society of America (IDSA) have provided guidelines for diagnosis of UTI in complex patients. The NIDDR defines UTI in indwelling catheterization (IC), clean intermittent catheterization (CIC) and condom-catheter patients as any detectable concentration of bacteria greater than 10 ˆ2 and 10ˆ4, respectively (NIDDR 1992). The IDSA definition is based on catheter-associated UTI (CA-UTI), which is then extrapolated to patients with NGB. In patients, who perform CIC or have an indwelling urethral or suprapubic catheter, an UTI is diagnosed when there are signs or symptoms of UTI with 10ˆ3 colony forming units (CFU) of 1 or more bacteria cultured from urine collected via a mid-stream void or a single catherized urine specimen, assuming the catheter source has been removed within 48 hours.[11,12] The United States (US) Centers for Disease Control and Prevention: National Health Safety Network defines CA-UTI as the presence of a fever, suprapubic tenderness, or costovertebral angle pain, along with a colony count greater than 100000 CFU/mL with no more than 2 different organisms.[13] Finally, guidelines for the Care of People with SB defines a UTI as a positive urine analysis (>10 white blood cells per high-powered field (wbc/hfp) in uncentrifuged urine or greater than 5 wbc/hpf centrifuged urine) and positive urine culture (>50,000 CFUs/mL in a urine specimen obtained by catheterization or suprapubic aspirate or >100000 CFUs/mL in a clean voided specimen) with symptoms such as fever (100.4 F/38C), new leakage with CIC, and back or pelvic pain.[14] There remains no gold standard definition of UTI in patients with NGB and additional research is desperately needed.

Symptoms of Urinary Tract Infection

In the NGB population, usual UTI symptoms are often absent due to impairment of sensation, which can complicate the decision to evaluate for infection. While symptoms may also vary based on the diagnosis resulting in NGB, in general fever, back or pelvic pain, pain with catheterization, or changes in continence should prompt UTI

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evaluation. For patients with SCI, dysuria, spasticity, lethargy or uneasy feeling, malaise, cloudy or malodorous urine, or autonomic dysreflexia (AD) are also important symptoms.[15] When considering UTI, patient symptoms should be included in the decision tree.

Bladder Colonization

The diagnosis of UTI is also complicated by bladder colonization or asymptomatic bacteriuria (ASB). The use of CIC and IC results in colonization of the urine, which can result in an abnormal urinalysis. Studies in both SCI patients and patients with SB report elevated WBCs, positive nitrites, and cultures without symptoms of UTI.[16,17] In the absence of urinary symptoms, no treatment for ASB is recommended.[2,12] The only exception is select populations such as those on immunosuppression, pregnant women, or patients undergoing urologic procedures.[12,18]

Urine Collection

The collection of a urine specimen should always precede the initiation of antibiotic treatment. The method of urine collection is important to ensure an accurate interpretation of the results. Bagged urine specimens are only helpful if urinalysis and urine culture is negative. For patients who can void, urine should be collected by voiding into a sterile container. For people who are unable to void, sterile catheterization and suprapubic aspiration remain the optimal urine collection technique. If patients have an IC present for more than 2 weeks, the ISDA recommends removal of the old catheter and placement of a clean catheter with urine specimen obtained with catheter exchange. Specimens should be sent for urine microanalysis and urine culture. Laboratories suggestive of UTI include elevated serum inflammatory markers, urinalysis with elevated WBCs, plus/minus nitrite positivity with guideline-based colony forming unit positivity. Treatment should be initiated when UTI is suspected, with consideration of hospitalization for ill or unstable patients (**Fig. 2**).

TREATMENT

Treatment of UTI in patients with NGB requires additional considerations relative to the general population. Studies have shown variations in bacterial species and resistance. *Escherichia coli* (*E. coli*), the most common uropathogen in non-NGB UTI, accounts for only 18% of symptomatic UTIs.[19] One study of patients with SB reported that *E. coli* accounted for 41% of UTIs, followed by *Klebsiella* (17%), *Proteus* (6%), and *Enterococcus* (6%) with multi-drug resistant (MDR) bacteria comprising 21% of UTI episodes.[20] Studies in the SCI population have reported high levels of resistant bacteria with up to 50% of strains resistant to multiple antibiotics.[21,22] In the MS population studies report the most common organisms are *E.coli* (23%) followed by *Pseudomonas* (22%) and *Klebsiella* (12%), with increased antibiotic resistance especially in patients with a history of multiple infections.[23]

There is a lack of data to support optimal route or duration of antibiotics for patients with NGB and UTI. Antibiotic treatment should be based on previous cultures if available, or local antibiograms. Broad spectrum antibiotics should be initiated for ill-appearing patients, with addition of anti-pseudomonal antibiotics for patients with ICs. Antibiotic treatment should be narrowed and implemented for the shortest duration of treatment that is clinically safe.[2] Overall, a 7 to 10 day treatment is recommended for UTI without a fever and 14 days if a fever is present.[24] If the patient has developed urosepsis, treatment duration may be extended.

SEQUELA OF URINARY TRACT INFECTION

Urosepsis

Urosepsis is defined as sepsis causes by an infection in the urogenital tract and accounts for 20% to 30% of all sepsis cases. Urosepsis has a high mortality rate ranging from 20% to 40% with severe infections.[25] Patients infected with MDR organisms have worse outcomes and a higher mortality when compared to patients infected with a more susceptible organism.[26] Given the challenges with accurate diagnosis of UTI coupled with a higher rate of MDR organisms, urosepsis is more common and often more lethal in the NGB population. Ortiz and colleagues reported a 10-fold increase in urosepsis in children with SB with 57% of events caused by MDR organisms.[20] In one study of 147 veterans with SCI, death due to urosepsis was second only to pneumonia.[27] Given the complexity of UTI in this population, pre-antibiotic urine cultures, prompt treatment and careful monitoring is important in preventing urosepsis, septic shock, and death.

Renal Scarring

Patients with NGB are at high risk for renal injury due to poor bladder function resulting in high pressure uninhibited bladder contractions and detrusor-sphincter dyssynergia, which may lead to VUR, hydronephrosis, and urinary stasis, thus, increasing the risk of pyelonephritis and renal

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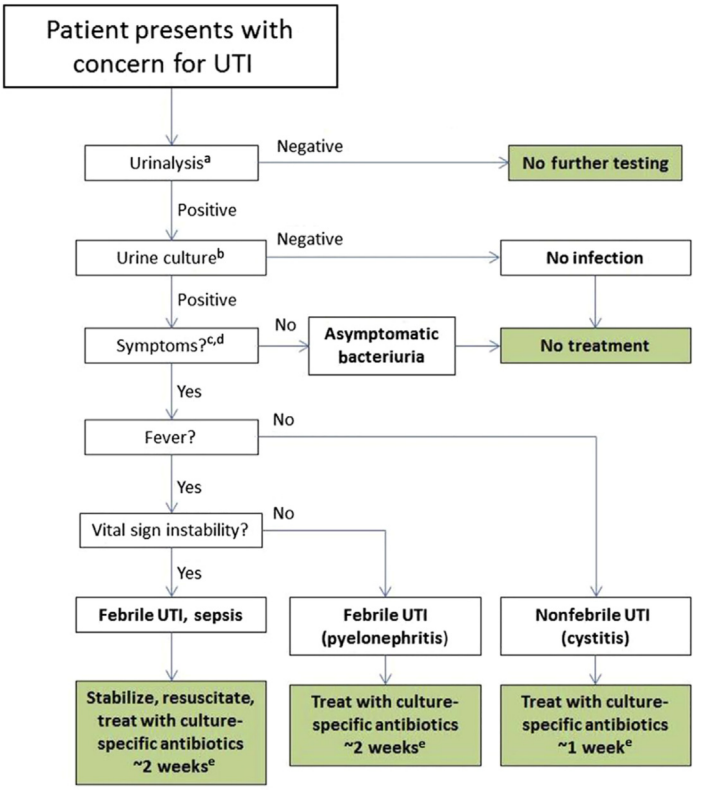

Fig. 2. Management algorithm for patients with neurogenic bladder and suspected urinary tract infection. [a] Positive urinalysis: greater than 10 WBC/HPF on microscopy (not validated end point). [b] Positive urine culture: greater than 10^2 CFU/mL from intermittent catheterized specimen, greater than 10^4 CFU/mL from condom catheter, and any value from indwelling and suprapubic catheters (not validated). [c] Symptoms include 2 or more of: fever greater than 38C, abdominal pain, new back pain, new or worse incontinence, pain with catheterization or urination, and malodorous or cloudy urine. [d] Urine culture should not be performed in the absence of symptoms, but often is, thus, is included in this algorithm. [e] Treatment duration may vary based on other considerations. (*Data from* Madden-Fuentes RJ, Ross SS. Urinary tract infections in the spina bifida population. Novel Insights into Urinary Tract Infections and Their Management 2014:61; and Everaert K, Lumen N, Kerckhaert W, et al. Urinary tract infections in spinal cord injury: prevention and treatment guidelines. Acta Clin Belg 2009;64(4): 335–40.)

scarring. In one study, renal scarring was present in 32% of SB patient with higher rates of hypertension (46%) and chronic renal disease (18%).[28] In a similar study of patients with SCI, 59% of patients had renal scarring.[29] Since UTIs can accelerate renal damage, it is important to promptly diagnose and treat UTIs effectively.

Co-morbidity Exacerbation

Patients with NGB often have medical issues that may be exacerbated in the presence of infection. MS patients may be immunocompromized so there is pressing need for prompt diagnosis and treatment of UTI to prevent progression of infection.[30] Further, any infection in patients with MS may increase the risk of relapse of their MS symptoms, which can be more severe and sustained after infection.[31,32]

Patients with SCI above T6 are susceptible to AD. UTIs are a common inciting event for AD. Since there is a 300% to 400% increased risk of stroke in the setting of AD, it is important to recognize the signs of impending onset, which include severe headache, hypertension, diaphoresis, flushing, and piloerection above the level of injury, cool and pale skin, visual changes, nasal stuffiness, anxiety, nausea, vomiting, and dizziness.[33]

URINARY TRACT INFECTION PREVENTION IN THE NEUROGENIC BLADDER

Catheter Management

Management of the NGB with some form of bladder drainage is a key to prevent UTI and renal failure. While there are no randomized studies comparing drainage options, one prospective study, which compared various methods of bladder management in patients with SCI and reported the lowest incidence of UTI was in the CIC group, which is the preferred method of bladder management if patients have the dexterity, mobility, and body habitus to catheterize on regular intervals.[5] Condom catheters are appropriate NGB patients if bladder storage pressures are low and bladder emptying is possible. UTI rates appear to be similar to CIC.[2] For patients with intraurethral catheter or suprapubic catheter, a closed drainage system is the most important measure against UTI. Drainage bag and tubing should be placed below the level of the bladder to allow urine to drain from the bladder to the bag and prevent bagged urine backflow.[12] Catheter change intervals may vary by provider

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but generally are changed on a monthly basis to prevent biofilms and encrustation. A recent Cochran review reported insufficient evidence to support one catheter technique, strategy, or design over another interms of UTI prevention.[34]

Overnight Bladder Drainage

Overnight bladder drainage allows the bladder to drain continuously overnight via an IC, which is removed in the morning with resumption of CIC during the day. This allows the bladder to remain decompressed while the patient is sleeping. Studies have reported fewer UTIs in children with NGB after implementing overnight bladder drainage.[35,36] Larger, controlled studies are needed to determine the efficacy of this intervention.

Bowel Management

Patients with NGB often have neurogenic bowel resulting in constipation and possible encopresis. While it is unclear how optimizing bowel management reduces the frequency of UTI, it appears to have some impact. In one study of children with NGB and bowel, reducing rectal diameter with aggressive treatment significantly reduced UTIs ($P<.00$).[37] In a study of SCI patients, bowel management resulted in a 29% reduction of UTIs.[38,39] Neurogenic bowel should be addressed in this population, especially if UTIs are recurrent.

Antibiotic Prophylaxis

Antibiotic prophylaxis in patients with NGB is a controversial subject, with ongoing debates that weigh long-term efficacy against concern for development of antibiotic resistance. A recent metanalysis evaluating continuous antibiotic prophylaxis in children with SB did not recommend prophylaxis for NGB.[40] For some patients who have frequent or severe infections, alternating antibiotic prophylaxis with antimicrobials targeting various bacterial mechanisms may challenge bacterial flora, thus, reducing resistance. In one study of patients with SCI, alternating 2 different antibiotics on a weekly basis reduced the rate of symptomatic UTIs from 9.4 per year to 1.8 per year.[41] While these methods may impact the rate of symptomatic UTI there are concerns about the long-term effectiveness of antibiotics coupled with selection pressure, and a global increase of MDR organisms.[42]

Bladder Irrigation or Instillation

Bladder irrigation has been considered as a potential method to prevent UTI in the NGB bladder population. The most frequently used irrigate are those with antimicrobial properties. In a recent study, gentamycin instillation was reportedly effective in both the treatment and prevention of UTIs in children with complex bladder abnormalities that included NGB, with no adverse reactions or increase in serum gentamycin levels.[43] However, other studies evaluating gentamycin irrigation have found no significant difference in the rate of symptomatic UTIs or UTIs requiring hospital admission.[44] A recent study looked at the use of povidone-iodine bladder irrigation and reported a greater than 99% reduction in recurrent UTI.[45] While these studies appear to suggest some benefit, they are all limited by a small number of patients.

Recently, studies have focused on repair of the bladder GAG layer with intravesical instillation of hyaluronic acid and chondroitin sulfate (HA/CS). Studies have reported reductions in UTI with HA/CS instillation.[46,47] More studies are needed to better understand the use of this option.

Cranberry and D-Mannose

D-Mannose and cranberry work to inhibit bacterial binding and invasion into uroepithelial cells. In one small study of patients with MS, D-Mannose demonstrated promising results regarding UTI prevention.[48] A 2008 Cochran Review concluded that routine use of cranberry in patients with NGB managed with CIC was not beneficial.[49] However, 2 different cross-over randomized control trials in children with NGB due to SB or SCI, reported significant decreases in recurrent UTIs with cranberry use.[50,51]

Probiotics

Probiotics have been studied as a potential non-antibiotic option to prevent UTIs in both non-complicated and complicated bladder populations. A randomized double-blind factorial-design placebo-controlled trial, which included 207 patients with SCI and stable NGB found a combination of oral *Lactobacillus* species or *Lactobacillus* + *Bifidobacterium* species had no impact on UTI prevention in this patient population.[52] A recent study that evaluated self-instillation of intravesical *Lactobacillus* species in both adults (N = 96) and children (N = 7) with SCI, SB, or MS found this approach may be effective at reducing urinary symptoms in adults.[53] More studies are needed to evaluate the efficacy of both oral and intravesical probiotics in reducing recurrent UTIs in people with NGB.[54]

Bacterial Interference

Bacterial interference utilizes inoculation and colonization of the bladder with benign microorganisms to limit the growth of uropathogenic bacteria. Three

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prospective blinded randomized control trials reported that interference with non-uropathogenic *E. coli* significantly decreased the rate of UTI in patients with NGB.[55,56] There are currently no commercially available therapies, limiting the use of the option.

Immunotherapy

Immunotherapy to prevent UTI is based on the introduction of substances that stimulate an immune response that subsequently prevents infection. There is some evidence that oral immunotherapy may be beneficial in people with NGB.[57] Ongoing studies are important to better understand how immunotherapy may prevent UTIs in this population.

Future Strategies

Microbiome

The human microbiome is defined as the organisms that live on and in the human body, with variation in components of the respective microbiota based on anatomic location. Historically, the urine was considered sterile. However, studies have identified a urinary microbiome (urobiome) with increasing amounts of evidence to suggest the relevance of the urobiome in various pathologies of the urinary tract.[58,59] Perturbations in the urobiome (referred to as "dysbiosis") have been reported in multiple disease states.[60–62] The early data on the urobiome of people with NGB has shown that it is distinct from the urobiome of people without NGB.[63,64] Further, data from a cohort of children with SB suggests there are additional differences in the urobiome among people with NGB based on bladder management technique.[65]

The evidence base around the urobiome in people with NGB and UTI is mainly limited to cross-sectional studies, thus, limiting the applicability of this data. Early urobiome data in a cohort of adults with IC found that those who had recurrent UTIs had lower diversity of the urobiome compared to people without recurrent UTIs.[66] Other work, which did include longitudinal samples from a small number of people with SCI that had UTIs, reported changes in the urinary microbiome prior to UTI with return to microbiota after treatment.[67] The data in people without NGB has suggested that the urobiome may have utility in distinguishing between UTI and ASB.[68,69] While using the urobiome to distinguish UTIs from ASB in people with NGB is of great interest, there are limited published data demonstrating the role of the urobiome in this area.[65] The other application of the urobiome in the management of UTIs in people with NGB is within the realm of therapeutics. While the use of oral probiotics has not shown to prevent UTIs in people with SCI,[52] ongoing research is centered on using intravesical probiotics as a means to restore the urobiome and decrease symptom burden in people with NGB.[70–73] Using the urobiome to differentiate UTI from ASB in people with NGB, as well as restoring the urobiome to a non-dysbiotic state, remain areas of active research.

Surgery for prevention of urinary tract infection

Surgical intervention may alter NGB function thus, decreasing UTI risk. Botox is an effective treatment for NGB. Studies have reported that Botox may decrease symptomatic UTIs.[74] Sacral neuromodulation has been used to treat detrusor overactivity and neurogenic detrusor. There have been some studies that suggest use of sacral neuromodulation may prevent UTI in people with NGB.[75] Finally, augmentation cystoplasty increases bladder capacity, decreases bladder pressures and often resolves secondary VUR.[76] However, recurrent UTI remains a common problem but may be improved with aggressive bladder irrigation and irrigation with gentamycin.[77,78] More studies are needed to better understand how surgical intervention may impact symptomatic UTI in people with NGB.

SUMMARY

UTI in the NGB is complex. There are multiple potential etiologies for increased risk of UTI. The diagnosis of UTI remains complex, given variations in how to define UTI in this population. Prompt treatment is necessary, and given the increased in MDR bacteria, use of urinalysis and culture should drive antibiotic administration. Prevention of UTI is the best option to prevent morbidity and mortality. A better understanding of the urinary microbiome with likely is the key to future management of UTIs in people with NGB.

CLINIC CARE POINTS

- UTI in the NGB may result in renal injury and urosepsis. Providers should be suspicious of UTI if patients present with fever, back pain, pain with catheterization, new urinary incontinence, or other suspicious symptoms.
- UTI may exacerbate co-morbidities in patients with NGB. It is important to be aware of symptoms for problems such as automatic dysreflexia and promptly treat when symptoms arise.

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- Methods to prevent UTI vary but often include catheter management and bowel management at baseline. It is important to consider prevention techniques such as bladder irrigation or probiotics in patients with recurrent infection. Other techniques such as immunotherapy are currently being studies so familiarity with current literature is important for those caring for the NGB population.

DISCLOSURE

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