Implications of Bacteriuria in Myelomeningocele Patients at Time of Urodynamic Testing

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Objective: To identify those myelomeningocele (MMC) patients at risk for post-urodynamic study (UDS) complications. We hypothesized that patients who manage their bladder with clean intermittent catheterization (CIC) would have a greater risk of post-instrumentation complications due to higher rates of bacteriuria compared to those who freely void (FV). **Design/Methods:** Urine was collected from patients with MMC without augmentation cystoplasty undergoing routine renal ultrasound or urodynamic study (UDS). Samples were divided into those with bacteriuria (urine culture ≥10,000 colony-forming units) and those without. Post-UDS complications were evaluated and compared between CIC and FV patients. **Results:** A total of 91 urine samples from 82 total MMC patients were included for evaluation. Significantly more patients on CIC than those who FV had bacteriuria (67% vs 33%, $p = .0457$). From these urine samples, 54 were obtained at time of UDS of which 45 were from patients on CIC and 9 from FV patients. More patients on CIC had bacteriuria at the time of UDS than those who FV (60% vs 33%, respectively), but this did not reach significance ($p = .1416$). No patient with bacteriuria on CIC had a complication after UDS while one FV patient with bacteriuria developed post-UDS pyelonephritis. **Conclusion:** MMC patients with bacteriuria on CIC did not have post-UDS complications. Patients with bacteriuria who FV may be at particular risk for post-instrumentation UTI, providing guidance as to which MMC patients should undergo urine testing prior to UDS in order to prevent post-instrumentation pyelonephritis. **Key words:** *clean intermittent catheterization, myelomeningocele, spina bifida, urinary bacterial colonization, urinary tract infection, urodynamics*

Myelomeningocele (MMC) is a birth defect resulting in incomplete closure of the neural tube during development. It occurs in 3.1 of every 10,000 births in the United States and can be responsible for an array of neurologic symptoms depending on the location and severity of the lesion.[1] These patients often have abnormal bladder function, known as neurogenic bladder (NGB), which poses multiple risks to the urinary tract. NGB can cause impaired bladder cycling resulting in high intravesical pressures and incomplete bladder emptying. This can result in renal damage as high bladder pressures transmit to the upper urinary tract leading to renal injury or even renal failure.[2,3] In addition, NGB can predispose this patient population to urinary tract infections (UTI).[4]

Clean intermittent catheterization (CIC) was introduced in 1972 to prevent such complications and is now commonplace in the management of NGB.[5] The concept is to promote bladder emptying, preventing bacterial growth caused by urinary stasis and preventing elevated bladder pressures.[2,3] In the adult spinal cord injury population, CIC has been found to be comparable to suprapubic catheterization and spontaneous voiding for bladder management in regard to preventing complications such as infection, stone disease, urethral injury, and radiologic abnormalities; it is safer than chronic indwelling urethral catheterization.[6]

Yet, CIC can introduce bacteria into the bladder and potentially contribute to the risk of UTI.[7,8] While the benefits of different catheterization techniques or types of catheters have long been debated in an effort to reduce infectious inoculation,[9,10] CIC itself remains a potential

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source for the introduction of bacteria into the urinary system. As a result, patients with NGB on CIC have high rates of bacteria in their urine.[4,11] The implications of this finding, however, is unclear. There is concern that bacteriuria could predispose this patient population to complications related to urinary tract instrumentation such as during routine urodynamic study (UDS).

The present study sought to investigate the impact of bacteriuria on post-instrumentation complications from UDS in a large academic hospital's MMC population presenting for routine urologic evaluation. We hypothesized that the form of normal bladder management, and thus risk of bacteriuria, may predict those at risk for infectious complications. In particular, we thought patients on CIC may have a higher risk of post-instrumentation pyelonephritis.

Material and Methods

Patients with a history of MMC presenting to a single pediatric urban tertiary care institution between December 2015 and December 2016 were considered for study inclusion after approval by the Institutional Review Board. Patients or legal guardians of patients younger than 18 years old were approached for consent if the patients were undergoing urologic studies (renal ultrasound [RUS] or UDS) as part of routine clinical care through the hospital multidisciplinary MMC clinic. Assent was obtained in patients over 8 years of age. Consenting patients had their urine collected at time of study and were asked for UTI symptoms of fever >38°C, abdominal pain, new back pain, new or worsened incontinence, pain with catheterization or urination, and malodorous/cloudy urine. Normal bladder management, CIC versus freely voiding (FV), was also recorded. Only catheterized urine samples were collected. As is per protocol for these studies, bladder urine was obtained by catheterization during UDS regardless of normal patient bladder management and during RUS only in CIC patients. Urine was sent for formal microscopic urinalysis and urine culture by hospital laboratory core facilities. Patients with augmentation cystoplasty were purposefully excluded in order to eliminate bowel interposition in the urinary tract as a potential confounder for bacteriuria. Samples with incomplete urinalysis or culture data were also excluded.

Urine samples with ≥10,000 colony-forming units (CFU) on urine culture were classified as bacteriuria. This group was further divided into those who were infected and those colonized based on urinalysis results and symptoms. Those without bacteriuria (<10,000 CFU on urine culture) were subdivided into sterile urine without pyuria or sterile pyuria based on urinalysis results (**Table 1**). Classifications were based on previously published definitions,[12] although 50,000 CFU of bacteria was used as the minimum required culture growth for patients classified as infected.[13,14]

Patients were segregated by their routine method of bladder management into those who FV and those who perform CIC. Patients who do both were included in the CIC group. Patient demographics and urine study results were compared between groups. All samples were analyzed for rates of bacteriuria and evaluation of bacterial organisms isolated. Only those samples collected at UDS were analyzed for rate of post-UDS complications. Infections occurring within 1 week after evaluation were considered study related.

Statistical analysis was subsequently performed using chi-square test, Student's *t* test, or Mann-Whitney *U* test depending on the data involved and whether the distribution of data was parametric or non-parametric. Between-group correlation was calculated using Pearson correlation coefficients

Table 1. Classifications of collected urine samples

	Positive urinalysis[a]	Negative urinalysis
Positive urine culture[b] indicating bacteriuria	Infected[c] OR Colonized[d]	Colonized
Negative urine culture	Sterile pyuria	Sterile urine without pyuria

Note: WBC = white blood cell; CFU = colony-forming unit.

[a]Positive urinalysis: >10 WBC per high power field.

[b]Positive urine culture: ≥10,000 CFU of bacteria on culture

[c]Infected: Patient reports ≥2 concurrent symptoms AND has ≥50,000 CFU of bacteria on culture.

[d]Colonized: Patient reports <2 concurrent symptoms or has <50,000 CFU of bacteria on culture

or Spearman's rank depending on normality. A p value <.05 was considered significant.

Results

Eighty-two consecutive unique MMC patients met inclusion criteria, consented to be in the study, and provided samples. Of these, 9 patients (8 on CIC and 1 FV) provided samples at two different time-points for a total of 91 samples obtained at time of RUS and UDS. Median patient age was 7.9 years (mean, 10.7; range, 0.2 to 39.7 years). Thirty-four of the samples were from males (37.4%). Eighty-two samples were from patients on CIC while 9 were from patients who normally FV. Patients on CIC tended to be older than those who FV (p = .0605). There was no significant difference between groups in regard to gender. No FV patient was on antibiotics during the study. Eighteen patients in the CIC group were on antibiotics with one undergoing active treatment for presumed UTI diagnosed prior to presentation. The other 17 were on standing antibiotic prophylaxis; 10 of whom were performing intravesical antibacterial irrigations. The demographics of the patient groups are listed in **Table 2**.

Patients on CIC had significantly more bacteriuria than patients who FV (67% vs 33%, p = .0457), but this significance was lost when divided into infected and colonized urine samples (**Table 2**). There was no significant correlation between active antibiotic use and bacteriuria, colonized urine sample, or infected urine sample in the CIC group. There was a significant negative correlation between male patients on CIC and bacteriuria (r = -0.330, p = .002, nonparametric) that held true in colonized urine samples (r = -0.275, p = .013, nonparametric) but did not correlate with presence of infected urine (p = .433). There was no significant correlation between gender and bacteriuria in FV patients.

More of the infected CIC samples grew >1 organism when compared with the colonized CIC samples (60% vs 10%, respectively; p = .0025). Colonized FV patients all grew single organisms. Ten different organisms were found in patients on CIC compared with 3 in FV patients (**Table 3**). *Escherichia coli* was the most common organism found in both colonized and infected patients on CIC. Nine patients provided two samples. The bacterial carriage in each of these samples is shown in **Table 4**. Seven of these patients had bacteria on their first sample, one of whom had two strains of bacteria. Five patients with bacteria on initial sample demonstrated bacteria on repeat urine sample. Four of the five with repeat bacteria demonstrated the same bacteria in both samples (including the patient with two different strains of bacteria). The median time between samples was 176 days (mean, 181; range, 32-285 days).

Fifty-four samples were obtained at the time of UDS: 45 from patients on CIC and 9 from FV patients (**Table 5**). Of these, 27 (60%) patients on CIC demonstrated bacteriuria compared to 3 (33%) FV patients (p = .1416). Following UDS, there was only one post-instrumentation infectious complication. It occurred in a 4-month-old FV female patient whose urine collected at time of UDS met criteria for being colonized (90 white blood cells [WBC] on urinalysis and >100,000

Table 2. Demographics of patients on clean intermittent catheterization (CIC) and freely void (FV)

	Demographics	CIC (n = 82)	FV (n = 9)	p
Median age, years (mean; range)		8.2 (11.2; 0.7-39.7)	4.4 (6.3; 0.2-15.8)	.0605
Male sex (%)		30 (37)	4 (44)	.6436
Current antibiotic use (%)		18 (22)	0 (0)	.1960
No bacteriuria	Sterile urine without pyuria (%)	25 (30)	6 (67)	.4676
	Sterile pyuria (%)	2 (2)	0 (0)	>.999
Bacteriuria	Colonized urine (%)	50 (61)	3 (33)	.1104
	Infected urine (%)	5 (6)	0 (0)	>.999

Table 3. Potential uropathogens found in urine samples of patients on clean intermittent catheterization (CIC) and freely void (FV)

	CIC[a]		FV[a]	
Pathogen	**Colonized**	**Infected**	**Colonized**	**Infected**
Gram-negative				
Escherichia coli	30	4	1	0
*Klebsiella spp.***	9	1	1	0
Pseudomonas spp.	3	1	0	0
Enterobacter spp.	3	1	0	0
Enterococcus spp.	3	0	0	0
Providencia spp.	2	1	0	0
Proteus spp.	1	0	1	0
Stenotrophomonas spp.	1	0	0	0
Gram-positive				
Coagulase-negative Staphylococcus	3	0	0	0
Streptococcus viridans	1	0	0	0

Note: spp. = species plural.
[a]Expressed as number urine samples growing potential uropathogen.

CFU *Klebsiella pneumonia* on final culture, without symptoms at presentation to UDS), but who developed a fever 2 days after the study requiring hospital admission for intravenous antibiotics for pyelonephritis. For comparison, none of the patients on CIC had any post-instrumentation complications ($p = .0989$), including a patient who appeared infected at the time (grew >100,000 CFU *E. coli*).

Discussion

UTIs are a significant source of MMC patient morbidity and a strain on health care resources.[15] Half of MMC patients will have at least one UTI by 15 months of age, with 81% having at least one UTI by 15 years of age. In addition, a significant portion of these patients will have multiple infections.[16] As a complex patient population, they also risk other sequela as a result of UTIs due to associated MMC co-morbidities, such as seeding of ventriculoperitoneal shunts by UTI uropathogens.[17] MMC patients may in fact have altered systemic innate and adaptive immunity that increase their susceptibility to UTI dissemination.[18,19] One study found that children with MMC have a 10-fold increased risk of urosepsis.[8]

Yet, MMC patients are prone to the presence of bacteria in their urine even without developing signs of UTI given their NGB and increased requirement for regular instrumentation of their urinary tract. Schlager et al performed weekly urine cultures for 6 months on 14 children with NGB on CIC and found 70% of cultures grew ≥10,000 CFU.[11] Our study similarly found that the

Table 4. Bacterial carriage in samples from patients with more than one urine sample

Bladder management	Bacteria present in sample #1	Bacteria present in sample #2	Time between samples, days
CIC	*Enterococcus faecalis*	*Enterococcus faecalis*	161
CIC	*Escherichia coli*	*E. coli*	285
CIC	*Streptococcus viridans*	None	242
CIC	*E. coli*	*E. coli*	175
CIC	*Providencia rettgeri, Enterobacter cloacae*	*Providencia rettgeri, Enterobacter cloacae*	32
CIC	*E. coli*	*Klebsiella pneumoniae*	189
CIC	None	None	176
CIC	*E. coli*	None	200
FV	None	None	168

Note: CIC = clean intermittent catheterization; FV = freely void.

Table 5. Classification of urine samples from patients on clean intermittent catheterization (CIC) and freely void (FV) undergoing urodynamic study

Classification		CIC ($n = 45$)	FV ($n = 9$)	p
No bacteriuria	Sterile without pyuria (%)	17 (38)	6 (66.7)	.1096
	Sterile pyuria (%)	1 (2)	0 (0)	>.999
Bacteriuria	Colonized (%)	26 (58)	3 (33.3)	.1794
	Infected (%)	1 (2)	0 (0)	>0.999

majority of NGB urine samples collected at the time of routine urologic evaluation demonstrated bacteriuria. While it was present in significantly more patients on CIC than those who FV, bacteriuria was present in even 33% of our FV patients (2 females, 1 male).

While asymptomatic bacteriuria is generally not treated,[20,21] concern arises in patients requiring urinary tract instrumentation. It is recommended that MMC patients undergo regular testing, including RUS and UDS,[22] of which UDS requires urinary tract manipulation. UDS requires bladder catheterization and artificial filling, with a resulting risk of post-instrumentation infection. Post-UDS UTI have been reported in up to 20% of all patients,[23,24] while UTI after UDS specific to patients with NGB has been reported in 9.7% to 15.8% of patients.[25,26] NGB patients with bacteriuria have been found to be especially prone to post-UDS UTI compared to those with sterile urine with an incidence of 32.5% versus 8.6%, respectively.[25]

As a result of these concerns, the Society of Urodynamics, Female Pelvic Medicine, and Urogenital Reconstruction (SUFU) published recommendations in 2017 to administer antibiotic prophylaxis prior to UDS in patients with neurogenic lower urinary tract dysfunction.[27] MMC patients were specifically included in this patient category. A randomized control trial found that antibiotic prophylaxis around the time of UDS was associated with fewer post-UDS infections compared to patients given placebo (0% vs 14%, respectively).[28]

Our institution does not routinely administer antibiotic prophylaxis specific to UDS in our MMC population. Although we found high rates of bacteriuria in our patients undergoing UDS, regardless if they regularly perform CIC or FV, only a single patient had a post-UDS infectious complication (overall rate of 1.1%). This single complication occurred in a FV patient who was initially colonized at the time of UDS, consistent with a prior study reporting a higher rate of post-UDS UTI in FV patients as compared to those who required catheterization.[25] One explanation for this may be that FV patients may be prone to harboring more virulent strains that can cause UTI during urologic manipulation. This may be a result of differing etiology for bacteriuria between CIC and FV patients. Bacteriuria in patients on CIC may be a result of self-inoculation with less virulent flora as compared to a result of incomplete bladder emptying in those who FV. Indeed, it has been suggested that colonization with less-virulent strains of bacteria may prevent symptomatic UTI.[29] CIC may prime innate mechanisms of defense for appropriate response during extraneous instrumentation and thus may be protective. Regardless, our finding suggests that bacteriuria in the setting of CIC does not increase the risk of post-instrumentation infectious complication. As a result, prior recommendations for antibiotic prophylaxis in this group do not appear to be indicated. In a FV patient with a history of bacteriuria, however, one may want to reconsider the recommendations by SUFU or consider rescheduling UDS if a FV patient has a positive urinalysis suggesting likely bacteriuria.

There are several limitations of our study. It is limited by low recruitment of FV patients due to only including urine samples obtained by catheterization. Thus, only FV patients undergoing UDS were included. Broadening the

study to allow urine collection by clean catch would increase recruitment but might increase rates of specimen contamination. Future studies within our institution targeting a larger and more inclusive number of patients or multi-institutional studies may solve this problem. Larger sample size would also enable a number needed to treat analysis if our finding of post-UDS infection in colonized FV patients holds true. Our study is also limited in that we did not incorporate bowel regimen or status of neurogenic bowel, which may impact rates of infection and bacteriuria. More CIC patients were on antibiotics at the time of UDS compared to FV. The overall number was low, however; as this was part of their routine bladder management, we did not think this significantly impacted our results.

Conclusion

Despite the majority of MMC patients on CIC having bacteriuria, there does not appear to be a high risk of developing a post-UDS UTI in this patient population. Thus, it appears prudent not to proceed with antibiotic prophylaxis around the time of UDS in this population contrary to recent recommendations. A subset of patients with MMC, such as colonized FV patients, may have an increased risk for post-UDS complication. This information could guide which patients should undergo pre-study urine testing and dictate which patients should be postponed pending treatment in order to prevent infectious complications following instrumentation.

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REFERENCES

1. Shin M, et al. Prevalence of spina bifida among children and adolescents in 10 regions in the United States. *Pediatrics*. 2010;126(2):274-279.
2. Dik P, et al. Early start to therapy preserves kidney function in spina bifida patients. *Eur Urol*. 2006;49(5):908-913.
3. Snodgrass WT, Gargollo PC. Urologic care of the neurogenic bladder in children. *Urol Clin North Am*. 2010;37(2):207-214.
4. Groah SL, et al. Redefining healthy urine: A cross-sectional exploratory metagenomic study of people with and without bladder dysfunction. *J Urol*. 2016;196(2):579-587.
5. Lapides J, et al. Clean, intermittent self-catheterization in the treatment of urinary tract disease. *J Urol*. 1972;107(3):458-461.
6. Weld KJ, Dmochowski RR. Effect of bladder management on urological complications in spinal cord injured patients. *J Urol*. 2000;163(3):768-772.
7. Armour BS, et al. Hospitalization for urinary tract infections and the quality of preventive health care received by people with spina bifida. *Disabil Health J*. 2009;2(3):145-152.
8. Ortiz TK, et al. Predominant bacteria and patterns of antibiotic susceptibility in urinary tract infection in children with spina bifida. *J Pediatr Urol*. 2018;14(5):444.e1-444.e8.
9. Schaeffer AJ, Schaeffer E. Infections of the urinary tract. In: McDougal WS, et al, eds. *Campbell-Walsh Urology*. Philadelphia: Saunders; 2012:257-325.
10. Lucas EJ, et al. Comparison of the microbiological milieu of patients randomized to either hydrophilic or conventional PVC catheters for clean intermittent catheterization. *J Pediatr Urol*. 2016;12(3):172 e1-8.
11. Schlager TA, et al. Bacteriuria in children with neurogenic bladder treated with intermittent catheterization: Natural history. *J Pediatr*. 1995;126(3):490-496.
12. Madden-Fuentes RJ, et al. Variation in definitions of urinary tract infections in spina bifida patients: A systematic review. *Pediatrics*. 2013;132(1):132-139.
13. Hoberman A, et al. Pyuria and bacteriuria in urine specimens obtained by catheter from young children with fever. *J Pediatr*. 1994;124(4):513-519.
14. Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management, Roberts KB. Urinary tract infection: Clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics*. 2011;128(3):595-610.

15. Spencer JD, et al. Pediatric urinary tract infections: An analysis of hospitalizations, charges, and costs in the USA. *Pediatr Nephrol.* 2010;25(12):2469-2475.
16. Filler G, et al. Prevention of chronic kidney disease in spina bifida. *Int Urol Nephrol.* 2012;44(3):817-827.
17. Caesar RE, et al. Cerebrospinal fluid shunt infection secondary to *Escherichia coli* bacteriuria. *Urology.* 1994;44(2):288-290.
18. Meisel C, et al. Central nervous system injury-induced immune deficiency syndrome. *Nat Rev Neurosci.* 2005;6(10):775-786.
19. Riegger T, et al. Immune depression syndrome following human spinal cord injury (SCI): A pilot study. *Neuroscience.* 2009;158(3):1194-1199.
20. Cai T, Bartoletti R. Asymptomatic bacteriuria in recurrent UTI - to treat or not to treat. *GMS Infect Dis.* 2017;5:doc09.
21. Koves B, et al. Benefits and harms of treatment of asymptomatic bacteriuria: A systematic review and meta-analysis by the European Association of Urology Urological Infection Guidelines Panel. *Eur Urol.* 2017;72(6):865-868.
22. Routh JC, et al. Design and methodological considerations of the Centers for Disease Control and Prevention urologic and renal protocol for the newborn and young child with spina bifida. *J Urol.* 2016;196(6):1728-1734.
23. Okorocha I, Cumming G, Gould I. Female urodynamics and lower urinary tract infection. *BJU Int.* 2002;89(9):863-867.
24. Onur R, et al. Incidence of bacteraemia after urodynamic study. *J Hosp Infect.* 2004;57(3):241-244.
25. Bothig R, et al. Morbidity of urinary tract infection after urodynamic examination of hospitalized SCI patients: The impact of bladder management. *Spinal Cord.* 2013;51(1): 70-73.
26. Pannek J, Nehiba M. Morbidity of urodynamic testing in patients with spinal cord injury: Is antibiotic prophylaxis necessary? *Spinal Cord.* 2007;45(12):771-774.
27. Cameron AP, et al. Best practice policy statement on urodynamic antibiotic prophylaxis in the non-index patient. *Neurourol Urodyn.* 2017;36(4):915-926.
28. Darouiche RO, Smith MS, Markowski J. Antibiotic prophylaxis for urodynamic testing in patients with spinal cord injury: A preliminary study. *J Hosp Infect.* 1994;28(1):57-61.
29. Prasad A, et al. A bacterial interference strategy for prevention of UTI in persons practicing intermittent catheterization. *Spinal Cord.* 2009;47(7):565-569.