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Number of urinary white blood cells is a poor identifier of symptomatic urinary tract infection among children with spina bifida evaluated in the emergency department

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Abstract

Background: Patients with spina bifida evaluated for possible urinary tract infection (UTI) often receive antibiotics inappropriately. One possible factor is the diagnostic value placed in a relatively low threshold for "significant" pyuria (typically >10 white blood cells [WBC] per high power field [HPF]), which is relatively common among these patients. Determination of a more optimal WBC/HPF threshold for "significant" pyuria in this population would improve the accuracy of UTI diagnosis for these patients.

Objective: To identify the association between urinary WBC/HPF and the presence symptomatic bacteriuria among children with spina bifida presenting to the emergency department (ED) and identify an optimal WBC/HPF threshold value for this association.

Study design: We retrospectively reviewed the charts of children (age < 21 years) with spina bifida who presented to the ED between January 2016 and January 2020. Patients reliant on intermittent catheterization or volitional voiding/permissive incontinence and had both urinalysis and urine culture were included. The primary outcome was symptomatic bacteriuria, defined as having ≥2 urologic symptoms with >100k CFU/mL urine culture, regardless of urinalysis results. The primary exposure was pyuria, defined as >10 WBC/HPF on urinalysis. Sensitivity analysis was performed to identify an optimal threshold value of urinary WBC/HPF to identify symptomatic bacteriuria, defined as one which maximized the area under the classification receiver-operator curve (AUC).

Results: A total of 84 patients across 256 ED encounters were included. The median urinary WBC/HPF value was 40 (range 0 - 3,607) with 68% of patients having >10 WBC/HPF. Symptomatic bacteriuria was identified in 17% of patients. Pyuria was associated with

symptomatic bacteriuria (p = 0.019), however with poor classification AUC (0.578). On sensitivity analysis, the threshold >45 WBC/HPF maximized the classification AUC for symptomatic bacteriuria (AUC = 0.602), however this did not differ significantly from the prior threshold (p = 0.24) and would still be characterized as a poor classifier. This result was similar when patients were stratified by catheterization status.

Discussion: Limitations of this study include its retrospective nature and the definition of symptomatic UTI that was utilized, which has not been validated. The study's findings contribute to the body of literature highlighting the poor performance of pyuria with respect to UTI diagnosis in the spina bifida population.

Conclusions: Urinary WBC/HPF at any threshold performed poorly at classifying symptomatic bacteriuria among children with spina bifida presenting to the ED. The importance of pyuria for UTI diagnosis for these patients should be rethought.

Key words: pyuria, spina bifida, urinary tract infection, emergency department, urinary white blood cells

Introduction

Urinary tract infection (UTI) diagnosis remains challenging among patients with spina bifida. This population frequently requires clean intermittent catheterization (CIC) which leads to a high rate of asymptomatic bacteriuria and chronic, non-infectious cystitis.[1,2,3] Both of these conditions may produce pyuria (urinary white blood cells [WBCs]) but do not require treatment with antibiotics.[4,5,6]

Prior research has been done to define a true UTI for patients with spina bifida, with significant heterogeneity in required symptoms and urinary findings.[7] Criteria proposed by Madden-Fuentes, et al. suggest pyuria (at a threshold of >10 WBC per high power field [HPF]) in addition to ≥2 urologic symptoms and a >100k colony forming units (CFU) per mL urine culture (UC) for UTI diagnosis.[8] While based upon expert opinion, these criteria are emerging as a commonly cited standard (for example, in the UMPIRE study cohort).[9]

Despite this definition, overtreatment with antibiotics remains a problem. Pyuria without appropriate urologic symptoms has been found to be strongly associated with antibiotic overtreatment among patients with spina bifida seen in the emergency department (ED).[10] This suggests that despite the non-specific nature of pyuria, it may be overly relied upon in the UTI diagnosis. Such overuse of antibiotics has been associated with numerous adverse health outcomes and increased antimicrobial resistance.[5,11-13]

A possible contributing factor is the relatively low threshold for what is consider "significant" pyuria for this population. While >10 WBC/HPF is certainly abnormal among neurologically intact volitional voiders, this range is much more common among those who require CIC.[14] Establishing a more optimal threshold for significant pyuria could help reduce overtreatment

among patients with spina bifida by "normalizing" urinary WBC/HPF values that do not correlate with symptomatic UTI.

To that end, the purpose of this study is to identify the association between pyuria and the remaining two components of the Madden-Fuentes, et al. UTI criteria, namely having ≥2 urologic symptoms and a >100k CFU/mL UC ("symptomatic bacteriuria") among children with spina bifida evaluated in the ED. This study also seeks to identify an optimal threshold value of urinary WBC/HPF to identify symptomatic bacteriuria. The authors hypothesize that the current threshold of >10 WBC/HPF will not be associated with this outcome but that a more optimal threshold can be found with improved test statistics.

Methods

Design

A single-institution retrospective database of children with spina bifida (age < 21 years) evaluated in the ED between January 2016 and January 2020 was queried. All ED encounters took place at a free-standing pediatric acute care hospital. Patients who had UA and UC performed and who were reliant on either clean intermittent catheterization (CIC), volitional voiding, or who were permissively incontinent were included. Patients who were started on therapeutic antibiotics for UTI prior to the ED encounter or had other genital infections such as epididymitis were excluded. Patients with bladder augmentation and/or catheterizable channel were included. Patients with incontinent urinary diversion (including vesicostomy) were excluded. Patients meeting inclusion and exclusion criteria underwent chart review with extraction of demographic and clinical data. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was adhered to for study design.[15]

Primary exposure

The primary exposure was pyuria as defined in the Madden-Fuentes, et al. UTI criteria: >10 WBC/HPF on UA.[8] UA samples underwent automated cell counting using the Iris iQ200 Automated Urine Microscopy Analyzer (Beckman-Coulter, Brea, CA).

Primary outcome

The primary outcome was "symptomatic bacteriuria" (the non-pyuria components of the Madden-Fuentes, et al. UTI criteria) which was defined as 1) having ≥2 urologic symptoms (fever ≥38 C, abdominal pain, back and/or flank pain, change in urine quality [malodor and/or cloudiness], new urinary incontinence, and pain with catheterization) and 2) having >100k CFU/mL UC, regardless of UA findings.[8] The authors chose not to exclude patients with multiple organisms on UC as to avoid unnecessarily excluding patients with concomitant urinary colonization who also have symptomatic UTI. Symptoms not explicitly documented as present were presumed to be absent.

Secondary outcomes

Secondary outcomes were chosen to investigate the relationship between pyuria and each of the other components of the proposed UTI criteria. This included its association with 1) less stringent diagnostic criteria for UTI using the combination of ≥1 urologic symptom with a >100k CFU/mL UC, 2) having ≥1 or ≥2 urologic symptoms regardless of UC results, and 3) having >50k CFU/mL or >100k CFU/mL UC regardless of urologic symptoms.

Sensitivity analysis

Sensitivity analysis was performed to identify an optimal WBC/HPF threshold for classification of each primary and secondary outcome. The optimal threshold was defined as one which maximized the area under the receiver-operator curve (AUC) with respect to classifying that outcome. AUC values were interpreted with an AUC ≥ 0.7 being acceptable.[16] Test characteristics including sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) were also calculated.

Subgroup analysis

Subgroup analysis was performed to determine if the primary or secondary outcomes were associated with the method of bladder management. This was dichotomized as CIC vs non-CIC. Non-CIC patients included those who voided volitionally or were permissively incontinent.

Statistical analysis

Medians and ranges were calculated for continuous variables. Frequencies and proportions were calculated for categorical variables. Mann Whitney U test was used to assess continuous variables, while Chi square or Fisher exact test were used to assess categorical variables. The 95% confidence interval (CI) for the differences between test statistics were calculated using the bootstrap method incorporating patient clustering (multiple encounters per patient). All statistical tests were two-sided and a p-value of <0.05 was considered statistically significant. Statistical analysis was performed in R version 4.2.2.[17]

Results

Demographic and baseline factors

Between January 2016 and January 2020 there were 809 ED encounters by children with spina bifida at our institution. Among these, 256 encounters were included (84 unique patients). The median patient age at each encounter was 8.6 years (range 0.1 – 20.8 years). Patients were majority female (61%), had public insurance (93%), had history of myelomeningocele (72%) with supra-sacral lesion (77%), had a ventricular shunt present (61%), and were ambulatory (63%). (Table 1) Most identified as Hispanic (52%) or non-Hispanic Black (34%). 80% were managed with CIC and most (80%) urine specimens were collected by catheterization.

Primary exposure

Pyuria was identified in 68% of encounters (Table 1). There were no statistically significant differences in patient demographic factors between those with vs. without pyuria. Those with pyuria had a higher proportion of supra-sacral lesion level compared to those without pyuria (82% vs. 68%, respectively, $p = 0.02$) and a high proportion of management with CIC (85% vs. 69%, respectively, $p = 0.004$).

Primary outcome

Symptomatic bacteriuria (≥2 urologic symptoms with >100k CFU/mL UC) was identified in 17% of encounters (Table 2A). Among those with symptomatic bacteriuria, a higher proportion had pyuria compared to those without symptomatic bacteriuria (85% vs 65%, respectively, $p = 0.019$). Otherwise, there was no statistically significant difference in any patient demographics, baseline clinical factors, reconstructive status, or non-urologic symptoms.

Primary outcome sensitivity analysis

Those with symptomatic bacteriuria had higher median urine WBC/HPF than those without symptomatic bacteriuria (68 [range 2 – 1859] vs. 31 [range 0 – 3607], respectively, $p = 0.009$)

(Figure 1A). Evaluation of all possible threshold values identified the threshold of >45 WBC/HPF to maximize the AUC with respect to classifying symptomatic bacteriuria (AUC = 0.602).

Test statistics for classifying symptomatic bacteriuria were calculated and stratified by urinary WBC/HPF threshold. (Table 3) Compared to the >10 WBC/HPF threshold, the >45 WBC/HPF threshold resulted in a statistically significant decrease in sensitivity for classifying symptomatic bacteriuria (83% to 65%, $p = 0.024$), an increase in specificity (35% to 55%, $p < 0.001$), and increase in accuracy (43% to 57%, $p < 0.001$). There were no statistically significant changes in PPV or NPV. The AUC for the >10 WBC/HPF threshold was not statistically different from that of the >45 WBC/HPF threshold (0.589 vs 0.602, respectively, $p = 0.7$).

Secondary outcomes

The combination of ≥1 urologic symptom with >100k CFU/mL UC (a less stringent UTI definition) occurred in 40% of encounters (Table 2B). Patients with this outcome had a higher proportion of pyuria compared to those without the outcome (84% vs. 65%, respectively, $p = 0.02$) and had a higher median WBC/HPF value (65 [0 - 3607] vs. 19 [0 - 1260], respectively, $p < 0.001$) (Figure 1B).

For urologic symptoms, patients with ≥2 urologic symptoms (regardless of culture results) had a higher proportion of pyuria compared to patients with <2 symptoms (77% vs. 62%, respectively, $p = 0.02$) (Table 2B) This corresponded to a statistically significant difference in median WBC/HPF value as well. (Figure 1C and 1D) UC with growth at >50k CFU/mL and >100k CFU/mL both had a higher rate of pyuria and higher median urinary WBC/HPF compared to those without these outcomes (Table 2B, Figure 1E and 1F).

Secondary outcomes sensitivity analysis

Sensitivity analysis was conducted to identify an optimal WBC/HPF threshold for each secondary outcome. Again, the threshold >45 WBC/HPF was identified based upon maximization of the classification AUC for each outcome. Differences in test statistics for each secondary outcome are summarized in Table 3. Similar to the primary outcome, no statistically significant difference in AUC values were identified for any secondary outcome comparing the >10 WBC/HPF to the >45 WBC/HPF thresholds.

Subgroup analysis

Most encounters (80%) included a patient performing CIC. Patients on CIC were more likely to have history of myelomeningocele compared to those not on CIC (81% vs. 35%, respectively, $p < 0.001$), have a ventricular shunt (72% vs. 20%, $p < 0.001$), be non-ambulatory (43% vs. 14%, $p < 0.001$), and have history of bladder augmentation (17% vs. 0%, $p < 0.001$) (Supplemental). There was no significant difference in age between those on CIC compared to those not on CIC (8.6 years [range 0.1 – 20.8] vs. 10.5 years [range 0.4 – 20.3], respectively, $p = 0.8$). There were no statistically significant differences in urinalysis findings between those on CIC vs. not on CIC except for pyuria (73% vs 51%, respectively, $p = 0.004$) and the median urine WBC count (49 [range 0 – 3607] vs. 12 [range 0 – 760], respectively, $p < 0.001$).

There was no statistically significant difference in the rate of primary outcome (19% vs. 10%, $p = 0.14$) or secondary outcomes between those on CIC vs. not on CIC, except for >50k CFU/mL urine culture being more common among those on CIC (66% vs. 47%, $p = 0.015$). Among those on CIC, there was no difference in rates of pyuria among those with vs. without the primary outcome (85% vs. 70%, respectively, $p = 0.1$) (Supplemental).

Among those on CIC, there were no statistically significant difference in bladder augmentation rates between those with vs. without pyuria (19% vs 11%, respectively, p = 0.15) nor differences in rates of catheterizable channel (12% vs. 7%, respectively, p = 0.45) (Table 1).

Test statistics and sensitivity analysis were also performed for patients on CIC and for those not on CIC with respect to an optimal WBC/HPF threshold to identify the primary and secondary outcomes. These results mirrored those for the entire cohort, except for the culture result outcomes for those not on CIC. For UC >100k CFU/mL and >50k CFU/mL among those not on CIC, the normal pyuria threshold (>10 WBC/HPF) was found to achieve a maximal AUC (0.675 and 0.732, respectively) (Table 3).

Discussion

In this retrospective study of patients with spina bifida presenting to the ED, pyuria was associated with symptomatic bacteriuria. However, the sensitivity and specificity of pyuria to identify symptomatic bacteriuria were 83% and 35%, respectively, with an accuracy of 43%. In contrast, commonly cited sensitivity and specificity for pyuria to diagnose UTI among neurologically intact children are 73% and 82%, respectively.[14] These results continue to support the notion that pyuria is an inaccurate sole predictor of symptomatic UTI among patients with spina bifida.

Urinary WBC/HPF were not able to achieve an acceptable classification AUC for all but one outcome in this study, regardless of the threshold value.[16] This finding agrees with a study of Cheng, et al. who analyzed over 46,000 UA/UC results among adult patients across their health system and found a >25 WBC/HPF threshold to also perform poorly (AUC = 0.637).[18] More recently, Forester, et al. conducted a large, multi-institutional study examining UA and UTI

diagnosis among patients with spina bifida.[19] While that study did not stratify by specific urinary WBC/HPF values, they similarly found pyuria to be an inaccurate classifier.

Subgroup analysis for those on CIC and not on CIC identified similar results to the full cohort. However, those on CIC experienced a higher median urinary WBC/HPF and higher rate of >50k CFU UC as compared to those not on CIC. This has been well documented historically.[1-4] This highlights a limitation of the UTI criteria proposed by Madden-Fuentes, et al, which do not consider CIC status.[8] Those on CIC were more likely to fulfill the pyuria criterion of Madden-Fuentes, et al. without any significant difference in symptomatic bacteriuria rates. This suggests that the underlying criteria may benefit from modification to stratify by CIC as urinary WBC/HPF appears especially mis-aligned with the other components of the UTI criteria. It should be noted that the only outcome to achieve an acceptable AUC was among the non-CIC subgroup for pyuria to identify a >50k CFU/mL UC (AUC = 0.732). The test statistics for this subgroup/outcome align with those of neurologically intact volitional voiders and the results published by Forester, et al. This suggests pyuria is a more important finding among those not on CIC.[19]

The spina bifida UTI criteria as proposed by Madden-Fuentes, et al. place pyuria as an equal part of UTI diagnosis alongside urologic symptoms and culture results.[8] However, in practice there may be an overreliance on the presence of pyuria in the decision-making process about use of antibiotic therapy. Indeed, Kucherov, et al. found an 11-fold higher likelihood that a spina bifida patient with pyuria >10 WBC/HPF would receive antibiotics for treatment of a presumed UTI, which was associated with antibiotic overtreatment.[10,20] Gupta et al. similarly identified a positive linear correlation between the number of WBC/HPF on preoperative UA and receipt of inappropriate antibiotics.[21] These authors also showed these patients were at higher risk for

subsequent *clostridioides difficile* infection, a known adverse outcome associated with antimicrobial receipt.[11,12]

Given that urinary WBC/HPF do not correlate well with urologic symptoms and culture results among patients with spina bifida, what value do they contribute to UTI diagnosis? It may be argued that pyuria should be used as a screening test for UTI - a low threshold for "significant" pyuria would therefore be useful to avoid missing clinically meaningful infections. This approach would be consistent with the sensitivity identified in our study of 83%. However, a key principle of high sensitivity screening tests is that they should be followed by a specific, confirmatory test. Meeting all components of the UTI criteria should be this confirmatory test (i.e., if all components are present, the "test" is positive). However, in practice close to 50% of such patients may be overtreated with antibiotics, with a majority of overtreatment resulting from inadequate urologic symptoms.[10] In our study, symptomatic bacteriuria in the absence of pyuria occurred only in 7 encounters (3% overall, Table 2B), of whom 5 received antibiotics (data not shown). This suggest that the absence of pyuria would appear to "miss" very few patients who otherwise have suggestive symptoms.

Additional biomarkers beyond UA results may also serve to further confirm the diagnosis of UTI. Neutrophil gelatinase-associated lipocalin (NGAL) is a marker of epithelial injury that has been found to be both sensitive and specific for differentiating urinary colonization from symptomatic UTI.[22] Numerous other biomarkers have shown promise as well, including procalcitonin (for pyelonephritis specifically) and BH3 interacting domain death agonist (BID)/cathepsin S (CTSS) (both for prediction of positive UC).[23,24] However, patients' symptoms (known at the time of evaluation) should still form the bedrock of UTI diagnosis and require no new technology or added cost.

To that point, the results of this study contribute to a body of literature to deemphasize the sway of UA findings in UTI diagnosis for this population.[19] Patient symptoms should fundamentally drive management. For patients whose symptoms cannot be reliably ascertained, additional biomarkers should play a role. The authors suggest that the importance of pyuria for UTI diagnosis for this population should be minimized in the absence of appropriate and reliably ascertained urologic symptoms, especially among those on CIC.

This study should be interpreted in the context of its limitations. The spina bifida UTI criteria proposed by Madden-Fuentes, et al. are not validated with respect to patient-centered endpoints.[8] Thus, while this definition is emerging as a gold standard, it is ultimately expert opinion. Numerous other UTI definitions could have been utilized (as have been well documented by Forster, et al), however will less consensus.[7] Multi-institutional prospective studies on endpoints relevant to antibiotic receipt (e.g., resolution of symptoms) would be useful to create a functional definition of "true" UTI in this population.

We did not include several important patient parameters such as bowel programs, urodynamic data, imaging studies, and bacterial speciation results, all of which can help define underlying patient risk. Pyuria was evaluated as the sole predictor of the study outcomes. The addition of other evaluation tools (such as other UA or serum findings) may have produced better test characteristics. While all possible encounters during the period were assessed for inclusion, no formal power analysis was performed. A larger sample size across multiple institutional may also have produced more statistically and clinically significant differences in test characteristics than was capable in our data set.

Conclusions

Pyuria was found to perform poorly at classifying symptomatic bacteriuria among patients with spina bifida, regardless of urinary WBC/HPF threshold value or patient use of CIC. Patients on CIC in particular experienced higher rates of pyuria and bacteriuria without differences in symptomatology. Overall, the use of pyuria in UTI evaluation for these patients should be rethought as it appeared to provide little value to the diagnostic process.

Abbreviations: ED = emergency department, UA = urinalysis, UC = urine culture, UTI = urinary tract infection, WBC/HPF = white blood cells per high power field, CFU/mL = colony-forming units/mL

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Figure 1: Box plot of primary (A) and secondary (B-F) outcomes compared to urinary WBC/HPF measured on a logarithmic scale.

Each box top and bottom represent the interquartile range of values. The notch is the 95% confidence interval of the median value. The width of the box is proportional to the sample size. ns = $p > 0.05$, * = $p \leq 0.05$, ** = $p \leq 0.01$, *** = $p \leq 0.001$, **** = $p \leq 0.0001$

Table 1: Comparison of covariables to primary exposure (pyuria)

		Full cohort (n = 256)					CIC (n = 205)					Non-CIC (n = 51)				
		Pyuria Yes		No			Pyuria Yes		No			Pyuria Yes		No		
		175	(68%)	81	(32%)	p	149	(73%)	56	(27%)	p	26	(51%)	25	(49%)	p
Demographics/baseline clinical data																
Age in years (range)		8.7	(0.4 - 20.8)	9.8	(0.1 - 20.3)	0.690	8.6	(0.4 - 20.8)	8.6	(0.1 - 18.9)	0.420	10	(0.6 - 20.1)	11	(0.4 - 20.3)	0.610
Sex	Male	70	(40%)	31	(38%)	0.891	61	(41%)	23	(41%)	1.000	9	(35%)	8	(32%)	1.000
	Female	105	(60%)	50	(62%)		88	(59%)	33	(59%)		17	(65%)	17	(68%)	
Race/ethnicity																
	Non-Hispanic Other	1	(1%)	1	(1%)	0.047	1	(1%)	1	(2%)	0.340	0	(0%)	0	(0%)	0.484
	Non-Hispanic Black	66	(38%)	22	(27%)		61	(41%)	20	(36%)		5	(19%)	2	(8%)	
	Non-Hispanic White	27	(15%)	7	(9%)		25	(17%)	6	(11%)		2	(8%)	1	(4%)	
	Hispanic	81	(46%)	51	(63%)		62	(42%)	29	(52%)		19	(73%)	22	(88%)	
Low/very low COI	Yes	63	(36%)	34	(42%)	0.406	57	(38%)	20	(36%)	0.872	6	(23%)	14	(56%)	0.023
	No	112	(64%)	47	(58%)		92	(62%)	36	(64%)		20	(77%)	11	(44%)	
Insurance																
	Unknown	1	(1%)	1	(1%)	0.589	1	(1%)	1	(2%)	0.433	0	(0%)	0	(0%)	1.000
	Mixed	4	(2%)	3	(4%)		4	(3%)	3	(5%)		0	(0%)	0	(0%)	
	Private	6	(3%)	4	(5%)		5	(3%)	3	(5%)		1	(4%)	1	(4%)	
	Public	164	(94%)	73	(90%)		139	(93%)	49	(88%)		25	(96%)	24	(96%)	
Myelomeningocele	Yes	130	(74%)	54	(67%)	0.233	118	(79%)	48	(86%)	0.325	12	(46%)	6	(24%)	0.144
	No	45	(26%)	27	(33%)		31	(21%)	8	(14%)		14	(54%)	19	(76%)	
Supra-sacral lesion	Yes	143	(82%)	55	(68%)	0.017	120	(81%)	43	(77%)	0.564	23	(88%)	12	(48%)	0.003
	No	32	(18%)	26	(32%)		29	(19%)	13	(23%)		3	(12%)	13	(52%)	
Bladder augmentation	Yes	29	(17%)	6	(7%)	0.052	29	(19%)	6	(11%)	0.152	0	(0%)	0	(0%)	1.000
	No	146	(83%)	75	(93%)		120	(81%)	50	(89%)		26	(100%)	25	(100%)	
Catheterizable channel	Yes	18	(10%)	4	(5%)	0.230	18	(12%)	4	(7%)	0.448	0	(0%)	0	(0%)	1.000
	No	157	(90%)	77	(95%)		131	(88%)	52	(93%)		26	(100%)	25	(100%)	
Ventricular shunt	Yes	111	(63%)	46	(57%)	0.336	103	(69%)	44	(79%)	0.224	8	(31%)	2	(8%)	0.075
	No	64	(37%)	35	(43%)		46	(31%)	12	(21%)		18	(69%)	23	(92%)	
Non-ambulatory	Yes	65	(37%)	30	(37%)	1.000	59	(40%)	29	(52%)	0.154	6	(23%)	1	(4%)	0.099
	No	110	(63%)	51	(63%)		90	(60%)	27	(48%)		20	(77%)	24	(96%)	
No respiratory adjuncts	Yes	168	(96%)	73	(90%)	0.084	142	(95%)	48	(86%)	0.031	26	(100%)	25	(100%)	1.000
	No	7	(4%)	8	(10%)		7	(5%)	8	(14%)		0	(0%)	0	(0%)	
Immunosuppression	Yes	3	(2%)	2	(2%)	0.653	2	(1%)	1	(2%)	1.000	1	(4%)	1	(4%)	1.000
	No	172	(98%)	79	(98%)		147	(99%)	55	(98%)		25	(96%)	24	(96%)	
UTI prophylaxis	Yes	53	(30%)	16	(20%)	0.096	43	(29%)	14	(25%)	0.727	10	(38%)	2	(8%)	0.019
	No	122	(70%)	65	(80%)		106	(71%)	42	(75%)		16	(62%)	23	(92%)	

Urologic symptoms																
Fever ≥38C	Yes	69	(39%)	31	(38%)	0.891	55	(37%)	22	(39%)	0.749	14	(54%)	9	(36%)	0.264
	No	106	(61%)	50	(62%)		94	(63%)	34	(61%)		12	(46%)	16	(64%)	
Abdominal pain	Yes	59	(34%)	30	(37%)	0.672	53	(36%)	21	(38%)	0.871	6	(23%)	9	(36%)	0.368
	No	116	(66%)	51	(63%)		96	(64%)	35	(63%)		20	(77%)	16	(64%)	
Back/flank pain	Yes	20	(11%)	2	(2%)	0.016	18	(12%)	0	(0%)	0.004	2	(8%)	2	(8%)	1.000
	No	155	(89%)	79	(98%)		131	(88%)	56	(100%)		24	(92%)	23	(92%)	
New urinary incontinence	Yes	1	(1%)	1	(1%)	0.534	0	(0%)	0	(0%)	1.000	1	(4%)	1	(4%)	1.000
	No	174	(99%)	80	(99%)		149	(100%)	56	(100%)		25	(96%)	24	(96%)	
Malodorous urine	Yes	33	(19%)	8	(10%)	0.098	31	(21%)	8	(14%)	0.325	2	(8%)	0	(0%)	0.490
	No	142	(81%)	73	(90%)		118	(79%)	48	(86%)		24	(92%)	25	(100%)	
Cloudy urine	Yes	37	(21%)	5	(6%)	0.002	36	(24%)	4	(7%)	0.005	1	(4%)	1	(4%)	1.000
	No	138	(79%)	76	(94%)		113	(76%)	52	(93%)		25	(96%)	24	(96%)	
Urethral pain	Yes	20	(11%)	5	(6%)	0.258	15	(10%)	2	(4%)	0.164	5	(19%)	3	(12%)	0.703
	No	155	(89%)	76	(94%)		134	(90%)	54	(96%)		21	(81%)	22	(88%)	
Non-urologic symptoms																
Neck pain	Yes	4	(2%)	1	(1%)	1.000	3	(2%)	1	(2%)	1.000	1	(4%)	0	(0%)	1.000
	No	171	(98%)	80	(99%)		146	(98%)	55	(98%)		25	(96%)	25	(100%)	
Seizures	Yes	3	(2%)	1	(1%)	1.000	3	(2%)	1	(2%)	1.000	0	(0%)	0	(0%)	1.000
	No	172	(98%)	80	(99%)		146	(98%)	55	(98%)		26	(100%)	25	(100%)	
Constipation	Yes	3	(2%)	1	(1%)	1.000	3	(2%)	0	(0%)	0.564	0	(0%)	1	(4%)	0.490
	No	172	(98%)	80	(99%)		146	(98%)	56	(100%)		26	(100%)	24	(96%)	
Fussiness	Yes	3	(2%)	1	(1%)	1.000	2	(1%)	1	(2%)	1.000	1	(4%)	0	(0%)	1.000
	No	172	(98%)	80	(99%)		147	(99%)	55	(98%)		25	(96%)	25	(100%)	
Chest pain	Yes	4	(2%)	3	(4%)	0.682	4	(3%)	2	(4%)	0.666	0	(0%)	1	(4%)	0.490
	No	171	(98%)	78	(96%)		145	(97%)	54	(96%)		26	(100%)	24	(96%)	
Cough	Yes	4	(2%)	6	(7%)	0.077	4	(3%)	3	(5%)	0.394	0	(0%)	3	(12%)	0.110
	No	171	(98%)	75	(93%)		145	(97%)	53	(95%)		26	(100%)	22	(88%)	
Headache	Yes	30	(17%)	15	(19%)	0.860	28	(19%)	13	(23%)	0.557	2	(8%)	2	(8%)	1.000
	No	145	(83%)	66	(81%)		121	(81%)	43	(77%)		24	(92%)	23	(92%)	
Nausea/emesis	Yes	52	(30%)	29	(36%)	0.386	46	(31%)	21	(38%)	0.405	6	(23%)	8	(32%)	0.541
	No	123	(70%)	52	(64%)		103	(69%)	35	(63%)		20	(77%)	17	(68%)	
Urinalysis findings																
UA nitrites	Yes	91	(52%)	24	(30%)	0.001	77	(52%)	19	(34%)	0.028	14	(54%)	5	(20%)	0.020
	No	84	(48%)	57	(70%)		72	(48%)	37	(66%)		12	(46%)	20	(80%)	
UA turbidity	Yes	91	(52%)	16	(20%)	<0.001	74	(50%)	8	(14%)	<0.001	17	(65%)	8	(32%)	0.025
	No	84	(48%)	65	(80%)		75	(50%)	48	(86%)		9	(35%)	17	(68%)	
UA bacteria identified	Yes	138	(79%)	37	(46%)	<0.001	115	(77%)	28	(50%)	<0.001	23	(88%)	9	(36%)	<0.001
	No	37	(21%)	44	(54%)		34	(23%)	28	(50%)		3	(12%)	16	(64%)	

Other																
Hospital admission	Yes	44	(25%)	18	(22%)	0.642	41	(28%)	14	(25%)	0.860	3	(12%)	4	(16%)	0.703
	No	131	(75%)	63	(78%)		108	(72%)	42	(75%)		23	(88%)	21	(84%)	

CIC = clean intermittent catheterization, COI = Childhood Opportunity Index, UTI = urinary tract infection, UA = urinalysis

Table 2A: Comparison of primary exposure (pyuria) and covariables to primary outcome (symptomatic bacteriuria)

		Full cohort (n = 256)					CIC (n = 205)					Non-CIC (n = 51)				
		Symptomatic bacteriuria					Symptomatic bacteriuria					Symptomatic bacteriuria				
		Yes		No			Yes		No			Yes		No		
		43	(17%)	213	(83%)	p	38	(19%)	167	(81%)	p	5	(10%)	46	(90%)	p
Primary exposure																
Pyuria	Yes	36	(84%)	139	(65%)	0.019	32	(84%)	117	(70%)	0.106	4	(80%)	22	(48%)	0.350
	No	7	(16%)	74	(35%)		6	(16%)	50	(30%)		1	(20%)	24	(52%)	
Demographics/baseline clinical data																
Age in years (range)		8.9	(0.8 - 18.6)	8.9	(0.1 - 20.8)	0.756	8.1	(0.8 - 18.6)	8.6	(0.1 - 20.8)	0.958	13	(1.8 - 14.3)	10	(0.4 - 20.3)	0.747
Sex	Male	12	(28%)	89	(42%)	0.123	11	(29%)	73	(44%)	0.103	1	(20%)	16	(35%)	0.654
	Female	31	(72%)	124	(58%)		27	(71%)	94	(56%)		4	(80%)	30	(65%)	
Race/ethnicity																
	Non-Hispanic Other	0	(0%)	2	(1%)	0.625	0	(0%)	2	(1%)	0.872	0	(0%)	0	(0%)	0.380
	Non-Hispanic Black	15	(35%)	73	(34%)		15	(39%)	66	(40%)		0	(0%)	7	(15%)	
	Non-Hispanic White	8	(19%)	26	(12%)		7	(18%)	24	(14%)		1	(20%)	2	(4%)	
	Hispanic	20	(47%)	112	(53%)		16	(42%)	75	(45%)		4	(80%)	37	(80%)	
Low/very low COI	Yes	14	(33%)	83	(39%)	0.493	13	(34%)	64	(38%)	0.713	1	(20%)	19	(41%)	0.636
	No	29	(67%)	130	(61%)		25	(66%)	103	(62%)		4	(80%)	27	(59%)	
Insurance																
	Unknown	0	(0%)	2	(1%)	1.000	0	(0%)	2	(1%)	1.000	0	(0%)	0	(0%)	1.000
	Mixed	1	(2%)	6	(3%)		1	(3%)	6	(4%)		0	(0%)	0	(0%)	
	Private	1	(2%)	9	(4%)		1	(3%)	7	(4%)		0	(0%)	2	(4%)	
	Public	41	(95%)	196	(92%)		36	(95%)	152	(91%)		5	(100%)	44	(96%)	
Myelomeningocele	Yes	33	(77%)	151	(71%)	0.577	31	(82%)	135	(81%)	1.000	2	(40%)	16	(35%)	1.000
	No	10	(23%)	62	(29%)		7	(18%)	32	(19%)		3	(60%)	30	(65%)	
Supra-sacral lesion	Yes	31	(72%)	167	(78%)	0.424	26	(68%)	137	(82%)	0.075	5	(100%)	30	(65%)	0.167
	No	12	(28%)	46	(22%)		12	(32%)	30	(18%)		0	(0%)	16	(35%)	
Bladder augmentation	Yes	7	(16%)	28	(13%)	0.627	7	(18%)	28	(17%)	0.813	0	(0%)	0	(0%)	1.000
	No	36	(84%)	185	(87%)		31	(82%)	139	(83%)		5	(100%)	46	(100%)	
Catheterizable channel	Yes	2	(5%)	20	(9%)	0.549	2	(5%)	20	(12%)	0.382	0	(0%)	0	(0%)	1.000
	No	41	(95%)	193	(91%)		36	(95%)	147	(88%)		5	(100%)	46	(100%)	
Ventricular shunt	Yes	29	(67%)	128	(60%)	0.396	28	(74%)	119	(71%)	0.844	1	(20%)	9	(20%)	1.000
	No	14	(33%)	85	(40%)		10	(26%)	48	(29%)		4	(80%)	37	(80%)	
Non-ambulatory	Yes	16	(37%)	79	(37%)	1.000	15	(39%)	73	(44%)	0.718	1	(20%)	6	(13%)	0.538
	No	27	(63%)	134	(63%)		23	(61%)	94	(56%)		4	(80%)	40	(87%)	
No respiratory adjuncts	Yes	41	(95%)	200	(94%)	1.000	36	(95%)	154	(92%)	0.743	5	(100%)	46	(100%)	1.000

	No	2	(5%)	13	(6%)		2	(5%)	13	(8%)		0	(0%)	0	(0%)	
Immunosuppression	Yes	0	(0%)	5	(2%)	0.593	0	(0%)	3	(2%)	1.000	0	(0%)	2	(4%)	1.000
	No	43	(100%)	208	(98%)		38	(100%)	164	(98%)		5	(100%)	44	(96%)	
UTI prophylaxis	Yes	10	(23%)	59	(28%)	0.707	9	(24%)	48	(29%)	0.689	1	(20%)	11	(24%)	1.000
	No	33	(77%)	154	(72%)		29	(76%)	119	(71%)		4	(80%)	35	(76%)	
Urologic symptoms																
Fever ≥38C	Yes	26	(60%)	74	(35%)	0.002	23	(61%)	54	(32%)	0.002	3	(60%)	20	(43%)	0.647
	No	17	(40%)	139	(65%)		15	(39%)	113	(68%)		2	(40%)	26	(57%)	
Abdominal pain	Yes	22	(51%)	67	(31%)	0.022	20	(53%)	54	(32%)	0.024	2	(40%)	13	(28%)	0.624
	No	21	(49%)	146	(69%)		18	(47%)	113	(68%)		3	(60%)	33	(72%)	
Back/flank pain	Yes	7	(16%)	15	(7%)	0.069	6	(16%)	12	(7%)	0.111	1	(20%)	3	(7%)	0.347
	No	36	(84%)	198	(93%)		32	(84%)	155	(93%)		4	(80%)	43	(93%)	
New urinary incontinence	Yes	1	(2%)	1	(0%)	0.308	0	(0%)	0	(0%)	1.000	1	(20%)	1	(2%)	0.188
	No	42	(98%)	212	(100%)		38	(100%)	167	(100%)		4	(80%)	45	(98%)	
Malodorous urine	Yes	19	(44%)	22	(10%)	<0.001	17	(45%)	22	(13%)	<0.001	2	(40%)	0	(0%)	0.008
	No	24	(56%)	191	(90%)		21	(55%)	145	(87%)		3	(60%)	46	(100%)	
Cloudy urine	Yes	18	(42%)	24	(11%)	<0.001	16	(42%)	24	(14%)	<0.001	2	(40%)	0	(0%)	0.008
	No	25	(58%)	189	(89%)		22	(58%)	143	(86%)		3	(60%)	46	(100%)	
Urethral pain	Yes	7	(16%)	18	(8%)	0.154	7	(18%)	10	(6%)	0.020	0	(0%)	8	(17%)	0.580
	No	36	(84%)	195	(92%)		31	(82%)	157	(94%)		5	(100%)	38	(83%)	
Non-urologic symptoms																
Neck pain	Yes	2	(5%)	3	(1%)	0.197	2	(5%)	2	(1%)	0.157	0	(0%)	1	(2%)	1.000
	No	41	(95%)	210	(99%)		36	(95%)	165	(99%)		5	(100%)	45	(98%)	
Seizures	Yes	0	(0%)	4	(2%)	1.000	0	(0%)	4	(2%)	1.000	0	(0%)	0	(0%)	1.000
	No	43	(100%)	209	(98%)		38	(100%)	163	(98%)		5	(100%)	46	(100%)	
Constipation	Yes	0	(0%)	4	(2%)	1.000	0	(0%)	3	(2%)	1.000	0	(0%)	1	(2%)	1.000
	No	43	(100%)	209	(98%)		38	(100%)	164	(98%)		5	(100%)	45	(98%)	
Fussiness	Yes	1	(2%)	3	(1%)	0.523	1	(3%)	2	(1%)	0.461	0	(0%)	1	(2%)	1.000
	No	42	(98%)	210	(99%)		37	(97%)	165	(99%)		5	(100%)	45	(98%)	
Chest pain	Yes	2	(5%)	5	(2%)	0.334	2	(5%)	4	(2%)	0.308	0	(0%)	1	(2%)	1.000
	No	41	(95%)	208	(98%)		36	(95%)	163	(98%)		5	(100%)	45	(98%)	
Cough	Yes	1	(2%)	9	(4%)	1.000	1	(3%)	6	(4%)	1.000	0	(0%)	3	(7%)	1.000
	No	42	(98%)	204	(96%)		37	(97%)	161	(96%)		5	(100%)	43	(93%)	
Headache	Yes	4	(9%)	41	(19%)	0.130	4	(11%)	37	(22%)	0.120	0	(0%)	4	(9%)	1.000
	No	39	(91%)	172	(81%)		34	(89%)	130	(78%)		5	(100%)	42	(91%)	
Nausea/emesis	Yes	17	(40%)	64	(30%)	0.280	16	(42%)	51	(31%)	0.183	1	(20%)	13	(28%)	1.000
	No	26	(60%)	149	(70%)		22	(58%)	116	(69%)		4	(80%)	33	(72%)	
Urinalysis findings																
UA nitrites	Yes	30	(70%)	85	(40%)	<0.001	26	(68%)	70	(42%)	0.004	4	(80%)	15	(33%)	0.058

	No	13	(30%)	128	(60%)		12	(32%)	97	(58%)		1	(20%)	31	(67%)	
UA turbidity	Yes	24	(56%)	83	(39%)	0.044	21	(55%)	61	(37%)	0.043	3	(60%)	22	(48%)	0.668
	No	19	(44%)	130	(61%)		17	(45%)	106	(63%)		2	(40%)	24	(52%)	
UA bacteria identified	Yes	37	(86%)	138	(65%)	0.007	32	(84%)	111	(66%)	0.033	5	(100%)	27	(59%)	0.143
	No	6	(14%)	75	(35%)		6	(16%)	56	(34%)		0	(0%)	19	(41%)	
Other																
Hospital admission	Yes	10	(23%)	52	(24%)	1.000	10	(26%)	45	(27%)	1.000	0	(0%)	7	(15%)	1.000
	No	33	(77%)	161	(76%)		28	(74%)	122	(73%)		5	(100%)	39	(85%)	

CIC = clean intermittent catheterization, COI = Childhood Opportunity Index, UTI = urinary tract infection, UA = urinalysis

Table 2B: Comparison of primary exposure (pyuria) to secondary outcomes

		Full cohort (n = 256)					CIC (n = 205)					Non-CIC (n = 51)				
		Pyuria					Pyuria					Pyuria				
		Yes		No			Yes		No			Yes		No		
		175	(68%)	81	(32%)	p	149	(73%)	56	(27%)	p	26	(51%)	25	(49%)	p
Secondary outcomes																
≥1 urologic symptom + >100k CFU/mL UC	Yes	82	(80%)	20	(20%)	0.001	71	(83%)	15	(17%)	0.007	11	(69%)	5	(31%)	0.132
	No	93	(60%)	61	(40%)		78	(66%)	41	(34%)		15	(43%)	20	(57%)	
≥1 urologic symptom	Yes	148	(71%)	61	(29%)	0.084	126	(75%)	41	(25%)	0.071	22	(52%)	20	(48%)	0.726
	No	27	(57%)	20	(43%)		23	(61%)	15	(39%)		4	(44%)	5	(56%)	
≥2 urologic symptoms	Yes	67	(78%)	19	(22%)	0.023	59	(81%)	14	(19%)	0.071	8	(62%)	5	(38%)	0.523
	No	108	(64%)	62	(36%)		90	(68%)	42	(32%)		18	(47%)	20	(53%)	
>50k CFU/mL UC	Yes	125	(78%)	35	(22%)	<0.001	107	(79%)	29	(21%)	0.008	18	(75%)	6	(25%)	0.002
	No	50	(52%)	46	(48%)		42	(61%)	27	(39%)		8	(30%)	19	(70%)	
>100k CFU/mL UC	Yes	101	(79%)	27	(21%)	<0.001	86	(80%)	21	(20%)	0.012	15	(71%)	6	(29%)	0.023
	No	74	(58%)	54	(42%)		63	(64%)	35	(36%)		11	(37%)	19	(63%)	

CIC = clean intermittent catheterization, UC = urine culture

Table 3: Test statistics and AUC to classify primary and secondary outcomes for each WBC/HPF threshold

	Full cohort (n = 256)				CIC (n = 205)				Non-CIC (n = 51)			
Primary outcome	WBC/HPF Threshold				WBC/HPF Threshold				WBC/HPF Threshold			
≥2 urologic symptoms + >100k CFU/mL UC	>10	>45	Diff.	p	>10	>45	Diff.	p	>10	>45	Diff.	p
Sensitivity	0.83	0.65	0.02	0.024	0.84	0.69	-0.15	0.079	0.73	0.43	-0.30	0.206
Specificity	0.35	0.55	0.21	<0.001	0.30	0.52	0.22	0.000	0.51	0.67	0.16	0.009
PPV	0.20	0.22	0.02	0.271	0.21	0.24	0.03	0.108	0.14	0.11	-0.02	0.650
NPV	0.91	0.89	-0.02	0.395	0.90	0.88	-0.01	0.713	0.95	0.91	-0.04	0.463
Accuracy	0.43	0.57	0.14	<0.001	0.40	0.55	0.15	0.000	0.54	0.65	0.11	0.131
AUC	0.589	0.602	0.014	0.729	0.567	0.605	0.038	0.321	0.621	0.549	-0.071	0.597
Secondary outcomes												
≥1 urologic symptom + >100k CFU/mL UC												
Sensitivity	0.80	0.65	-0.15	<0.001	0.83	0.68	-0.15	<0.001	0.70	0.53	-0.17	0.008
Specificity	0.39	0.63	0.23	<0.001	0.34	0.60	0.25	<0.001	0.57	0.74	0.18	0.008
PPV	0.47	0.53	0.07	0.462	0.47	0.55	0.07	0.774	0.41	0.48	0.07	0.459
NPV	0.75	0.73	-0.02	0.462	0.74	0.73	-0.01	0.774	0.81	0.78	-0.03	0.459
Accuracy	0.56	0.64	0.08	0.031	0.54	0.63	0.09	0.011	0.61	0.68	0.07	0.960
AUC	0.599	0.639	0.040	0.198	0.584	0.638	0.054	0.144	0.632	0.638	0.006	0.803
≥1 urologic symptom												
Sensitivity	0.71	0.51	-0.20	<0.001	0.76	0.55	-0.20	<0.001	0.53	0.36	-0.17	0.003
Specificity	0.43	0.66	0.23	<0.001	0.39	0.63	0.24	0.001	0.60	0.82	0.22	0.123
PPV	0.84	0.87	0.02	0.162	0.84	0.87	0.02	0.231	0.86	0.91	0.04	0.375
NPV	0.25	0.24	-0.02	0.532	0.27	0.25	-0.02	0.490	0.21	0.21	0.00	0.987
Accuracy	0.66	0.54	-0.12	<0.001	0.69	0.57	-0.12	<0.001	0.54	0.44	-0.10	0.058
AUC	0.568	0.587	0.019	0.489	0.573	0.593	0.019	0.567	0.566	0.592	0.026	0.746
≥2 urologic symptoms												
Sensitivity	0.78	0.54	-0.24	<0.001	0.81	0.56	-0.24	<0.001	0.60	0.38	-0.21	0.098
Specificity	0.36	0.55	0.18	<0.001	0.32	0.51	0.19	<0.001	0.52	0.69	0.17	0.011
PPV	0.38	0.37	-0.01	0.772	0.39	0.38	-0.01	0.763	0.29	0.29	0.00	0.965
NPV	0.77	0.70	-0.06	0.071	0.75	0.68	-0.07	0.099	0.79	0.77	-0.03	0.663
Accuracy	0.50	0.54	0.04	0.122	0.49	0.53	0.04	0.203	0.53	0.61	0.07	0.294
AUC	0.570	0.542	-0.028	0.309	0.561	0.535	-0.026	0.362	0.557	0.534	-0.023	0.773
>50k CFU/mL UC												
Sensitivity	0.78	0.60	-0.19	<0.001	0.79	0.62	-0.17	<0.001	0.77	0.47	-0.30	0.150
Specificity	0.48	0.71	0.23	<0.001	0.39	0.68	0.29	<0.001	0.70	0.77	0.08	0.150
PPV	0.71	0.77	0.06	0.142	0.72	0.79	0.08	0.893	0.68	0.64	-0.04	0.025
NPV	0.57	0.51	-0.06	0.142	0.49	0.48	-0.01	0.893	0.77	0.63	-0.14	0.025
Accuracy	0.67	0.64	-0.03	0.352	0.65	0.64	-0.01	0.037	0.73	0.64	-0.09	0.035

AUC	0.630	0.650	0.021	0.715	0.590	0.652	0.062	0.171	0.732	0.620	-0.112	0.055
>100k CFU/mL UC												
Sensitivity	0.79	0.60	-0.19	<0.001	0.80	0.63	-0.17	<0.001	0.73	0.50	-0.23	0.039
Specificity	0.42	0.64	0.22	<0.001	0.36	0.60	0.25	<0.001	0.62	0.76	0.14	0.039
PPV	0.58	0.62	0.05	0.158	0.57	0.63	0.06	0.547	0.55	0.57	0.02	0.127
NPV	0.67	0.62	-0.05	0.158	0.63	0.60	-0.03	0.547	0.77	0.69	-0.08	0.127
Accuracy	0.60	0.62	0.02	0.217	0.59	0.62	0.03	0.044	0.66	0.66	-0.01	0.352
AUC	0.605	0.622	0.016	0.741	0.580	0.616	0.036	0.387	0.675	0.628	-0.046	0.495

CIC = clean intermittent catheterization, PPV = positive predictive value, NPV = negative predictive value, UC = urine culture