

Uropathogens and Pyuria in Children With Neurogenic Bladders

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abstract

BACKGROUND: A recent study revealed that specific uropathogens are associated with lower odds of pyuria in a general pediatrics population. Children with neurogenic bladders who require clean intermittent catheterization (CIC) frequently have pyuria. Our objective with this study was to determine if an association exists between pyuria and type of uropathogen in CIC-dependent children.

METHODS: We obtained urinalysis and urine culture results from electronic medical records from January 2008 through December 2014 for patients ≤ 18 years of age with neurogenic bladders managed at a single institution. Cultures without concurrent urinalyses were excluded from analysis, as were cultures that yielded no growth, fungal growth, or growth of unidentified mixed organisms. We used logistic regression to determine the association of pyuria and leukocyte esterase with specific uropathogens.

RESULTS: We included 2420 cultures in this analysis. The growth of *Enterococcus* on urine culture was associated with lower odds of both pyuria and leukocyte esterase. In contrast, the growth of more than 100 000 colony-forming units per milliliter of *Proteus mirabilis* was associated with increased odds of both pyuria and leukocyte esterase, and the growth of *Pseudomonas aeruginosa* was associated with increased odds of leukocyte esterase but not pyuria. Certain etiologies of neurogenic bladder, such as bladder exstrophy and cloacal malformations, were also associated with increased odds of pyuria compared with neurogenic bladder due to myelomeningocele.

CONCLUSIONS: In children with neurogenic bladders who require CIC, *Enterococcus* may grow in urine culture without pyuria or positive leukocyte esterase. Accordingly, urine cultures should be obtained in symptomatic children, regardless of urinalysis results.



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Dr Forster designed the study, collected the data, drafted the initial manuscript, conducted the initial analyses, and reviewed and revised the manuscript; Drs Shaikh and Hoberman assisted with interpretation of the data and critically reviewed and revised the manuscript; Dr Jackson conceptualized and designed the study, supervised data collection, and critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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WHAT'S KNOWN ON THIS SUBJECT: The growth of *Enterococcus* in urine culture is associated with lower odds of pyuria in children with a normal genitourinary tract. Children with neurogenic bladders who require clean intermittent catheterization frequently have pyuria, which may confound this association.

WHAT THIS STUDY ADDS: *Enterococcus* in urine culture from children with neurogenic bladders is associated with lower odds of pyuria. In a symptomatic child, urine culture should be performed regardless of the urinalysis results.

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Children with neurogenic bladders who require clean intermittent catheterization (CIC) frequently have bacteriuria. Routine urinalysis is often used at the point of care to diagnose a urinary tract infection (UTI). In a general pediatric population, specific uropathogens (eg, *Enterococcus* species, *Klebsiella* species, and *Pseudomonas aeruginosa*) were less likely to be associated with pyuria than *Escherichia coli*.¹ However, children with neurogenic bladders who require CIC frequently have chronic urethral inflammation, which may confound the association between pyuria and uropathogens.² Therefore, we sought to determine if the presence of pyuria was associated with specific uropathogens in children with neurogenic bladders.

METHODS

We obtained urinalysis and urine culture results from electronic medical records between January 1, 2008, and December 31, 2014, for patients ≤ 18 years of age with neurogenic bladders managed at a single institution. We identified neurogenic bladder through the use of the following *International Classification of Diseases, Ninth Revision* (ICD-9) codes: neurogenic bladder (ICD-9 596.54), spina bifida (ICD-9 741), paraplegia (ICD-9 344.1), or quadriplegia (ICD-9 344). We then conducted a manual review of electronic medical records to ensure that patients were actively performing CIC during the study period. We excluded from analyses urine cultures with either no growth ($n = 3259$), fungal growth ($n = 68$), or growth of unidentified mixed organisms ($n = 239$), as well as cultures without concurrent urinalyses ($n = 2779$). Urine cultures were performed by using standard laboratory technique. The study was approved by the institutional review board.

Definitions

In this article, urinalysis refers to the combination of both urine dipstick and urine microscopy. At our institution, urine microscopy is performed only if the dipstick shows the presence of blood, protein, nitrites, or leukocyte esterase, or if the sample is from a patient < 2 years of age whose urine sample is sent from the emergency department. We defined positive leukocyte esterase as either small, moderate, or large leukocyte esterase on urinalysis. We defined pyuria as ≥ 5 urinary white blood cells per high-powered field.³ We defined a positive urine culture result as $\geq 10\,000$ CFU/mL on a specimen obtained by catheter. We chose 10 000 CFU/mL rather than 50 000 CFU/mL as the threshold, because at our institution, bacterial growth of $< 100\,000$ CFU/mL was reported as being between 10 000 and 100 000 CFU/mL rather than a specific colony count for several years during the study period.

Statistical Analysis

We compared categorical data using χ^2 tests or Fisher's exact tests as appropriate and continuous data using a *t* test. We used logistic regression to determine the association between uropathogens and positive leukocyte esterase and pyuria. Covariates included in the model were etiology of neurogenic bladder, uropathogens, sex, hydronephrosis, vesicoureteral reflux (VUR) and the presence of a mitrofanoff. We ran the models using a cohort that included all cultures with growth $\geq 10\,000$ CFU/mL, as well as those $\geq 100\,000$ CFU/mL. All analyses were done in RStudio (version 0.99.902).

RESULTS

We included 2420 cultures in this analysis. We found that 1651 patients had bacterial growth of $\geq 100\,000$ CFU/mL, 965 patients

had bacterial growth between 10 000 and 100 000 CFU/mL, and 42 patients had bacterial growth of $\geq 10\,000$ CFU/mL. The cohort had a mean age of 11.2 (± 4.5) years, included 61% girls, and was mostly white (72%) (Table 1). The most common etiologies of neurogenic bladder included myelomeningocele (35%), anorectal malformation (11%), and cloacal malformation (8%). The most frequently isolated uropathogen was *E coli* (37%), followed by *Enterococcus* species (14%), and *Klebsiella* species (11%). The remaining 38% include *Acinetobacter*, *Aerococcus*, *Citrobacter*, *Staphylococcus* species, *Corynebacterium*, *Enterobacter*, *Globicatella*, *Morganella*, *Pantoea*, *Proteus*, *Providencia*, *Pseudomonas*, *Rothia*, *Serratia*, and *Streptococcus* species. There was no difference in age, race, or etiology of neurogenic bladder between those with and without pyuria, although there was a higher proportion of girls among patients with no pyuria. There was also a high proportion of patients with a mitrofanoff and VUR in the pyuria group compared with the no pyuria group but no difference in the proportion of patients with hydronephrosis (Table 1).

For the model including cultures with growth $\geq 10\,000$ CFU/mL, male sex, presence of a mitrofanoff, and presence of VUR were associated with pyuria (Table 2). The growth of *Enterococcus* species as well as other causes of neurogenic bladder was associated with decreased odds of pyuria; no uropathogens were associated with increased odds of pyuria (Table 2). In the model that included only cultures with $\geq 100\,000$ CFU/mL, male sex, growth of *Proteus mirabilis*, tethered cord, cloacal malformation, presence of a mitrofanoff and VUR were associated with increased odds of pyuria (Table 2).

For the model including cultures with growth $\geq 10\,000$ CFU/mL,

male sex, cloacal malformation, the presence of a mitrofanoff, and VUR were associated with the presence of leukocyte esterase, whereas the presence of a spinal cord injury was associated with decreased odds of leukocyte esterase. The growth of *P mirabilis* was associated with increased odds, whereas the growth of *Enterococcus* species was associated with decreased odds of leukocyte esterase. Similar

patterns were seen for the model that included $\geq 100\,000$ CFU/mL, with the exception that spinal cord injury was not associated with increased odds of leukocyte esterase (Table 3).

A total of 2779 cultures were excluded from analysis because they did not have urinalysis performed at the time of urine culture. A total of 244 cultures were not included in the model for the outcome of pyuria

because they did not have urine microscopy performed along with the dipstick. Children with *Enterococcus* and *Enterobacter* species in their culture using 100 000 CFU/mL as a cutoff for defining a positive culture result were more likely not to have urine microscopy performed than children with *E coli*.

DISCUSSION

In children who require CIC for neurogenic bladder, the growth of *Enterococcus* species on urine culture was associated with lower odds of both microscopic pyuria and leukocyte esterase. In contrast, the growth of *P mirabilis* was associated with increased odds of both pyuria and leukocyte esterase. We also found that certain etiologies of neurogenic bladder, such as cloacal malformations, were associated with increased odds of pyuria (in the presence of bacteriuria) compared with neurogenic bladder due to

TABLE 1 Demographics and Etiology of Neurogenic Bladder in Patients With Bacteriuria According to the Presence of Pyuria

Characteristic	Pyuria (n = 1907)	No Pyuria (n = 513)	P
Age, y, mean (SD)	11.2 (4.5)	10.9 (4.6)	.13
Girl	1139 (59.7)	351 (68.4)	<.01
White	1364 (71.5)	381 (74.2)	.30
Myelomeningocele	664 (34.8)	171 (33.3)	.56
Anorectal malformation	197 (10.3)	42 (8.2)	.17
Cloacal malformation	163 (8.5)	35 (6.8)	.24
Bladder exstrophy	41 (2.2)	2 (0.4)	.01
Eagle-Barrett syndrome	29 (1.5)	2 (0.4)	.07
Mitrofanoff	558 (29.2)	80 (15.6)	<.01
Hydronephrosis	53 (2.8)	11 (2.1)	.51
VUR	460 (24.1)	64 (12.5)	<.01

Data are presented as n (%) unless otherwise specified.

TABLE 2 Association Between Sex, Uropathogen Type, and Etiology of Neurogenic Bladder and Pyuria

Predictors	Cultures $\geq 10\,000$ CFU/mL		Cultures $\geq 100\,000$ CFU/mL	
	Odds of Pyuria	95% CI	Odds of Pyuria	95% CI
Sex				
Female	Reference	—	Reference	—
Male	1.69 ^a	(1.32–2.16) ^a	1.70 ^a	(1.29–2.26) ^a
Uropathogen				
<i>E coli</i>	Reference	—	Reference	—
<i>P aeruginosa</i>	1.00	(0.63–1.61)	0.86	(0.48–1.59)
<i>Staphylococcus saprophyticus</i>	0.93	(0.13–18.60)	^b	^b
<i>Enterococcus</i> species	0.66 ^a	(0.47–0.91) ^a	0.44 ^a	(0.30–0.64) ^a
<i>Klebsiella</i> species	0.95	(0.67–1.36)	0.81	(0.54–1.20)
<i>Proteus</i> species	1.74	(0.93–3.56)	2.16 ^a	(1.05–5.03) ^a
<i>Enterobacter</i> species	1.39	(0.77–2.66)	0.94	(0.53–1.73)
Other	0.86	(0.63–1.17)	0.83	(0.58–1.19)
Etiology of neurogenic bladder				
Myelomeningocele	Reference	—	Reference	—
Anorectal malformation	0.94	(0.63–1.43)	1.16	(0.72–1.92)
Tethered cord	1.22	(0.79–1.91)	1.67 ^a	(1.02–2.83) ^a
Bladder exstrophy	3.24	(0.95–20.28)	3.46	(0.97–22.16)
Cloacal malformation	1.09	(0.71–1.70)	1.84 ^a	(1.04–3.42) ^a
Spinal cord injury	0.98	(0.38–3.06)	2.95	(1.09–10.3)
Eagle-Barrett syndrome	1.61	(0.45–10.28)	^b	^b
Other	0.76 ^a	(0.59–0.98) ^a	1.02	(0.77–1.35)
Presence of mitrofanoff	2.41 ^a	(1.81–3.24) ^a	3.14 ^a	(2.19–4.63) ^a
Presence of hydronephrosis	1.01	(0.51–2.21)	1.22	(0.51–3.42)
Presence of VUR	2.20 ^a	(1.63–3.24) ^a	4.55 ^a	(3.07–6.98) ^a

—, not applicable.

^a Indicates statistical significance.

^b CI unable to be computed because of a small sample size.

TABLE 3 Association Between Sex, Uropathogen, Etiology of Neurogenic Bladder, and Leukocyte Esterase

Predictors	Cultures $\geq 10\,000$ CFU/mL		Cultures $\geq 100\,000$ CFU/mL	
	Odds of Leukocyte Esterase Greater Than Trace	95% CI	Odds of Leukocyte Esterase Greater Than Trace	95% CI
Sex				
Female	Reference	—	Reference	—
Male	1.44 ^a	(1.16–1.80) ^a	1.33 ^a	(1.15–1.80) ^a
Uropathogen				
<i>E coli</i>	Ref	Ref	—	—
<i>P aeruginosa</i>	1.53	(0.97–2.51)	1.74	(0.96–3.35)
<i>S saprophyticus</i>	1.56	(0.22–31.07)	^b	—
<i>Enterococcus</i> species	0.63 ^a	(0.47–0.86) ^a	0.45 ^a	(0.31–0.64) ^a
<i>Klebsiella</i> species	0.84	(0.61–1.16)	0.94	(0.66–1.34)
<i>Proteus</i> species	3.14 ^a	(1.67–6.60) ^a	3.40 ^a	(1.68–7.85) ^a
<i>Enterobacter</i> species	1.04	(0.63–1.77)	0.84	(0.50–1.42)
Other	0.97	(0.73–1.28)	1.20	(0.86–1.68)
Etiology of neurogenic bladder				
Myelomeningocele	Reference	—	Reference	—
Anorectal malformation	1.33	(0.92–1.94)	1.32	(0.86–2.09)
Tethered cord	1.19	(0.81–1.75)	1.53	(0.97–2.46)
Bladder exstrophy	1.03	(0.49–2.41)	2.28	(0.83–8.06)
Cloacal malformation	1.49 ^a	(1.01–2.25) ^a	1.85 ^a	(1.10–3.24) ^a
Spinal cord injury	0.41 ^a	(0.18–0.97) ^a	1.12	(0.50–2.62)
Eagle-Barrett syndrome	1.95	(0.64–8.45)	2.62	(0.47–49.49)
Other	1.19	(0.94–1.50)	1.11	(0.86–1.45)
Presence of mitrofanoff	1.80 ^a	(1.40–2.31) ^a	1.93 ^a	(1.42–2.66) ^a
Presence of hydronephrosis	1.06	(0.55–2.17)	1.23	(0.56–3.02)
Presence of VUR	2.32 ^a	(1.77–3.07) ^a	3.25 ^a	(2.33–4.62) ^a

—, not applicable.

^a Indicates statistical significance.^b Unable to be computed because of a small sample size.

myelomeningocele. Additionally, the presence of both a mitrofanoff and VUR was associated with increased odds of both pyuria and leukocyte esterase, whereas the presence of hydronephrosis did not significantly impact the risk of either of these outcomes.

Children with neurogenic bladder who require CIC frequently have bacteriuria.⁴ The results of routine urinalyses are frequently used to determine if empirical antibiotics are warranted before the availability of urine culture results. Although timely initiation of antibiotics can prevent the progression of infection and decrease the risk of renal scars,⁵ unnecessary antimicrobial agents contribute to the emergence of bacterial resistance. In the absence of more accurate biomarkers of infection to help antibiotic selection, understanding the limitations of the routine urinalysis in predicting

specific uropathogens is necessary. Because screening tests, such as the urine dipstick, may be used to determine if a culture is performed, it is important to realize that the lack of leukocyte esterase or pyuria may not be helpful in deciding which urine samples to culture.

The presence of pyuria in a general pediatrics population, in combination with clinical signs and symptoms, is highly suggestive of UTI.⁶ However, pyuria frequently occurs among children with neurogenic bladder.⁷ The authors of the Infectious Disease Society of America guidelines for the diagnosis of catheter-associated UTI do not consider the presence of pyuria to be diagnostic of UTI in patients who require CIC.⁸ The presence of pyuria in this population is multifactorial; chronic inflammation may result from frequent catheterization⁹ as well

as from changes in the underlying genitourinary epithelium. However, in this cohort, only the presence of cloacal malformation was associated with pyuria, suggesting that this condition has a more robust response to bacteriuria. Bladder exstrophy also has an elevated odds ratio and confidence interval (CI) close to statistical significance. However, there were relatively few cultures from patients with bladder exstrophy in our cohort, suggesting a likely association between bladder exstrophy and pyuria that we may not have had sufficient statistical power to detect in this cohort. Biopsy studies of patients with bladder exstrophy reveal the presence of chronic inflammation in the urothelium already present at the time of primary closure.⁹ The pathophysiology underlying the association of pyuria with cloacal malformations remains

to be elucidated. Given that the urothelium plays a critical role in the neural control of the bladder,¹⁰ a neuroimmunologic etiology may explain the association between pyuria and cloacal malformations (and likely bladder exstrophy) because defects in epithelial differentiation have been implicated in the pathogenesis of cloacal malformations.¹¹ Regardless of the etiology of neurogenic bladder, chronic inflammation in CIC-dependent children likely confounds the utility of pyuria to predict either a positive urine culture result or a specific uropathogen. Despite this, enterococcal bacteriuria remains associated with a decreased risk of pyuria compared with *E coli* while controlling for the etiology of neurogenic bladder.

In addition to the association between specific etiologies of neurogenic bladder and pyuria, an association exists between boy sex and pyuria. There are several possible explanations for this finding. Olson et al¹² have demonstrated that male mice are more likely to develop chronic inflammation and persistent bacteriuria after UTI compared with female mice, an association that may be mediated by androgen exposure. In addition, there are several specific etiologies of neurogenic bladder that are only present in boys (eg, posterior urethral valves), or have a male predominance (eg, Eagle-Barrett syndrome). However, the number of patients in this cohort with these conditions were relatively small and unlikely to have caused this effect. In addition, no authors of previous reports have identified associations of these syndromes with pyuria. Although the association between male sex and pyuria may be due to androgen exposure, it is possible that additional unidentified mediators may contribute to this finding.

The presence of a mitrofanoff and VUR, but not hydronephrosis, is also associated with increased odds of pyuria and leukocyte esterase. The association between the mitrofanoff and pyuria is likely explained by the chronic inflammation associated with catheterization through a conduit without urothelium. The association between VUR and pyuria is potentially mediated through an inflammatory response of the kidney to previous infections; dimercaptosuccinic acid scans reveal inflammatory changes in the kidney up to 6 weeks after UTI in children with VUR.¹³ Although there is a component of inflammation associated with both the presence of a mitrofanoff and VUR, that was not the case for hydronephrosis (generally not an inflammatory process) explaining the lack of association with pyuria we found. We chose not to add bladder augmentation into the models in this work because the majority of children with a catheterizable conduit (eg, mitrofanoff) also undergo bladder augmentation,¹⁴ and, therefore, by including both the presence of mitrofanoff and bladder augmentation, we would be introducing collinearity into the model.

Our results reveal that the growth of *Enterococcus* species in urine culture is associated with a decreased risk of both pyuria and leukocyte esterase. However, our data likely represent an underestimation of the association with pyuria. A disproportionate number of cultures with growth of *Enterococcus* species did not have urine microscopy performed on them because of the lack of leukocyte esterase and/or nitrites, and were, therefore, not included in the regression model for the outcome of pyuria. Indeed, in our cohort, 255 of the 375 patients (68%) without leukocyte esterase on urinalysis who did have urine microscopy performed on them also lacked

pyuria, suggesting that the majority of cultures excluded for the lack of urine microscopy likely also did not meet the criteria for pyuria. Despite this potential underestimation, the association between *Enterococcus* species and the absence of pyuria is present in our cohort, a finding consistent with previous reports in the general pediatric population.¹ The authors of a previous report who investigated the association with pyuria and uropathogens in catheter-dependent patients found that the association between pyuria and UTI is stronger for Gram-negative bacilli compared with Gram-positive cocci (ie, *Enterococcus*).¹⁵ This relationship has not been fully examined in the children with neurogenic bladder. The reason behind the negative association between *Enterococcus* species and pyuria is unclear. Neutrophils have a critical role in controlling infections due to *Enterococcus faecalis*.¹⁶ Mouse models of catheterization have revealed a significant increase in neutrophils in the urine after inoculation with *E faecalis*,¹⁶ suggesting that blunting of neutrophil recruitment is not the mechanism. Lack of concordance between the known pathophysiology of enterococcal infections and our findings suggests additional aspects relevant to UTI because of *Enterococcus* in this population that have not been identified.

Limitations of our study include our inability to differentiate between UTI and asymptomatic bacteriuria because of the lack of sufficient clinical information to make this distinction. No validated criteria exist to define UTI in this population.¹⁷ In addition, the reason that the culture was obtained (eg, for clinical suspicion of UTI versus routine surveillance) was also not available, which could have served as a proxy measure for the presence or absence of clinical symptoms. However, our previous work has

shown that pyuria alone is not a good predictor of UTI in children with neurogenic bladder,⁷ suggesting that the presence of pyuria may be more related to the presence of a specific pathogen rather than indicative of an infectious state. A second limitation includes our inability to use a cutoff of $\geq 50\,000$ CFU/mL for defining a positive urine culture result. However, our results are largely the same when a cutoff of $\geq 100\,000$ CFU/mL is used as when a cutoff of $\geq 10\,000$ CFU/mL is used. Lastly, our work was retrospective in nature and limited to 1 center.

CONCLUSIONS

We show that the presence of *Enterococcus* species in urine culture from children with neurogenic bladders who require CIC is associated with a lower likelihood of pyuria compared with *E coli*, controlling for sex, race, etiology of neurogenic bladder, presence of a mitrofanoff, hydronephrosis, and VUR. With these results, we suggest that the current markers of UTI evidenced on urinalysis and urine microscopy are insufficient for predicting bacteriuria in this population. More specific

biomarkers of UTI are needed in this unique patient population. In the symptomatic child at risk for UTI, urine culture should be performed irrespective of the results of the urinalysis.

ABBREVIATIONS

CI: confidence interval
 CIC: clean intermittent catheterization
 ICD-9: *International Classification of Diseases, Ninth Revision*
 UTI: urinary tract infection
 VUR: vesicoureteral reflux

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