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ARTICLE

Asymptomatic bacteriuria and antibiotic resistance profile in children with neurogenic bladder who require clean intermittent catheterization

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STUDY DESIGN: A retrospective cohort study.
OBJECTIVES: To document the prevalence of asymptomatic bacteriuria and to characterize the resistance patterns to antibiotics among children with neurogenic bladder who require clean intermittent catheterization, with an emphasis on multidrug resistance.
SETTING: A national referral pediatric and adolescent rehabilitation facility in Jerusalem, Israel.
METHODS: Routine urine cultures were collected before urodynamic studies in suitable individuals during 2010–2018. None of them had symptoms of urinary tract infection at the time of specimen collection. Cultures were defined as being positive if a single bacterial species was isolated together with a growth of over 10^5 colony-forming units/ml. Resistance patterns were defined as extended-spectrum beta-lactamase (ESBL) and resistant to 3 antimicrobial groups (multi-drug resistant, MDR).
RESULTS: In total, 281 urine cultures were available for 186 participants (median age 7 years, range 0.5–18). Etiologies for CIC included myelomeningocele ($n = 137$, 74%), spinal cord injury ($n = 16$, 9%) and caudal regression syndrome ($n = 9$, 5%). Vesicoureteral reflux was diagnosed in 36 participants (19%), 14 of whom were treated with prophylactic antibiotics. Asymptomatic bacteriuria was present in 217 specimens (77%, 95%CI [0.72–0.82]). The bacteria species were E. coli (71%), Klebsiella (13%), and Proteus (10%). ESBL was found in 11% of the positive cultures and MDR in 9%, yielding a total of 34 (16% of positive cultures) positive for ESBL and/or MDR bacteria.
CONCLUSIONS: Asymptomatic bacteriuria and resistance to antimicrobials are common in pediatric individuals who require CIC.

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INTRODUCTION

The mainstay of neurogenic bladder treatment is clean intermittent catheterization (CIC) and anticholinergic medication. CIC contributes to the preservation of renal function through reduction of bladder storage pressures and urinary stasis, thereby decreasing the risk of infection and damage to the renal parenchyma, in addition to being essential to the attainment of social continence [1, 2]. Bacteria are introduced to the bladder through catheterization of the bladder, widely causing asymptomatic bacteriuria among children and adolescents with neurogenic bladder who require CIC [3, 4]. Resistance to antibiotic agents is an emerging serious public health threat mainly related to widespread use of antibiotics [5, 6]. Individuals with neurogenic bladders are commonly exposed to antibiotic treatment due to various coexisting medical conditions. Moreover, accurate diagnosis of urinary tract infections in individuals treated with CIC might be challenging since bacterial growth detected in the urine sample can represent only colonization of the intermittently catheterized urinary bladder [7], which often leads to unnecessary antibiotic treatment and resistance.

The aim of the study was to document the prevalence of asymptomatic bacteriuria and to characterize the resistance patterns to antibiotics among children with neurogenic bladder who require CIC, with an emphasis on multidrug resistance. To our knowledge, reports of multidrug resistance bacteria in the urine of children requiring CIC, according to the standard definitions set by the Magiorakos et al. [6] has not yet been published.

METHODS

Data was gathered retrospectively from a single pediatric rehabilitation center where children with neurogenic bladders are treated in a dedicated multidisciplinary clinic, and who serves as a referral center which cares for the majority of children with neurogenic bladder in the author's country. The study protocol was reviewed and approved by the local IRB which waived informed consent. Participants who routinely required CIC at least 4 times a day for a time duration of more than a month, and who underwent urodynamic studies during 2010–2018 were eligible for study inclusion. Urine cultures routinely sampled before urodynamic studies were analyzed. Urine cultures were obtained via sterile urethral catheterization and sent to participants' local laboratories by primary

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physicians. None of the study participants had symptoms of urinary tract infection at the time of routine specimen collection. Children who exhibited symptoms suggestive of urinary tract infection were excluded from the study (fever, feeling sick or tired, discomfort or pain over kidney or bladder, worsening of incontinence, increased frequency of catheterization, cloudy urine, foul smell in the urine). Urine cultures were defined as being positive if a growth of over 10^5 colony-forming units/ml of a single bacterial species was isolated. Included participants were scheduled for a urodynamic evaluation according to institutional protocol for follow-up of children with neurogenic bladder, which includes routine investigations as well as studies performed to investigate changes in clinical condition. Excluded were participants older than 18 years of age and those who had undergone bladder augmentation with bowel segments.

Data from electronic records were extracted on participants' demographics, etiology of neurogenic bladder, renal anomalies, vesicoureteral reflux status, use of prophylactic antibiotics, frequency of CIC and self-CIC vs. CIC performed by caregivers. Resistance to commonly used oral antibiotics, 1st and 2nd generation cephalosporin's or Sulfamethoxazole/Trimethoprim (SMX/TMP) was documented. Bacteria were categorized as multi-drug resistant (MDR, resistant to 3 different antimicrobial groups) and extensive drug resistance (XDR, resistant to all but 2 or fewer antimicrobial groups) according to the classification by Magiorakos et al. [6]. Rates of non-E. coli bacteria and extended-spectrum beta-lactamase (ESBL, a significant resistance pattern of Enterobacteriaceae) [8] were also recorded.

Study findings were reported using descriptive statistics. Categorical variables were reported as frequency and percentage. Confidence interval of proportion was calculated for asymptomatic bacteriuria rate. Chi-square test and Fisher exact tests were performed to compare the difference of asymptomatic bacteriuria rates and significant resistant patterns among cultures, respectively, between the self-CIC group and the CIC by caregiver group. A p value of <0.05 was considered statistically significant. There were no missing data, as all participants who undergo a urodynamic evaluation in our institution must have a preprocedural urine culture. SPSS was used for all statistical analyses (IBM SPSS statistics for windows, version 25, IBM Corp, Armonk, New York, USA).

RESULTS

A total of 281 urine cultures were obtained during 2010–2018 from 186 enrolled children, median age of 7 years (range 0.5–18 years).

Table 1. Characteristics of the study group.

	n	%
Total	186	100
Sex		
Male	103	55
Female	83	45
Vesicoureteral reflux		
Total	36	19
Intermediate - High grade reflux (III-V)	16	9
Continuous prophylactic antibiotics	14	8
Renal anomalies		
Total	7	4
Etiology of Neurogenic bladder		
Myelomeningocele	137	74
Spinal cord injury	16	9
Caudal regression syndrome	9	5
Lipomeningocele	6	3
Spinal cord tumor	6	3
Primary tethered cord	3	2
Post-myelitis injury	3	2
Arteriovenous malformation	3	2
Others	3	2

Their demographic information is presented in Table 1. A total of 155 urine cultures were collected from female participants and 126 urine cultures from male participants. Seventy-two individuals who underwent several urodynamic studies during the study period had 2 or more cultures that were available for analysis (39 female participants and 33 male participants) (Table 2).

Common etiologies of neurogenic bladder were myelomeningocele ($n = 137$, 74%), spinal cord injury ($n = 16$, 9%) and caudal regression syndrome ($n = 9$, 5%) (Table 1). Thirty-six (19%) children had documented vesicoureteral reflux (16 of which were intermediate-high grade), 14 children were treated with continuous prophylactic antibiotics of them 2 were treated with intravesical instillation of gentamycin (Table 1) [9]. Seven children (4%) had congenital anomalies of kidneys and urinary tract (CAKUT) consisting of 4 horseshoe kidneys, 2 single kidneys and one ectopic crossed-fused kidney.

Sixty-four of the 281 urine cultures (23%) exhibited no growth and 217 (77%, 95%CI [0.72–0.82]) had a single pathogen with over 10^5CFU/ml being isolated. The most prevalent isolate was E. coli, which was detected in 155 cultures (71% of the positive cultures and 55% of all cultures). Non-E.coli pathogens were detected in 62 cultures (29% of the positive cultures and 23% of all cultures). The most common non-E.coli isolates included: Klebsiella pneumoniae ($n = 28$) and Proteus mirabilis ($n = 23$). Other non-Enterobacteriaceae family bacteria were Pseudomonas ($n = 3$), Enterococcus ($n = 3$), and MRSA ($n = 1$) (Table 3).

Resistance to commonly used oral prophylactic antibiotics agents, including 1st and 2nd generation cephalosporin's or SMX/TMP, was found in 92 (42%) of the positive cultures. Sixty (28%) of the positive cultures were resistant to 1st and 2nd generation cephalosporin's, while 66 (30%) were resistant to SMX/TMP, of

Table 2. Rates of asymptomatic bacteria.

Cultures	First culture ($n = 186$)	Repeated cultures ($n = 95$)	Total ($n = 281$)
Positive	144 (77%)	73 (77%)	217 (77%)
Negative	42 (23%)	22 (23%)	64 (23%)

Table 3. Characterization of cultures and the isolated bacteria.

Isolated bacterial species	Current study		Ottolini et al. [10]	Forster et al. [16][a]
	n	(%)	(%)	(%)
Escherichia coli	155	71	55	34.5
Non-Escherichia. coli	62	29	45	65.5
Klebsiella pneumoniae	28	13	12	10
Proteus mirabilis	23	10	4	4
Pseudomonas aeruginosa	3	1	3	6
Enterococcus	3	1	–	14.3
Morganella morganii	2	1	–	–
Enterobacter cloacae	1	1	–	4.8
Serratia marcescens	1	1	–	–
MRSA	1	1	–	–

[a]Presence or lack of UTI symptoms not reported.
MRSA Methicillin resistant Staphylococcus aureus.

Table 4. Resistance patterns of isolated bacteria.

	n	(%) of first cultures (*n* = 186)	(%) of repeated cultures (*n* = 95)	(%) of positive cultures (*n* = 217)	(%) of all cultures (*n* = 281)
Resistance to common oral prophylactic antibiotics					
SMX/TMP	32	11	16	15	11
1st−2nd generation cephalosporins	26	7	14	12	9
Resistance to both	34	12	16	16	12
Total	92	31	37	42	33
Significant resistance patterns					
MDR	9	3	3	4	3
ESBL	14	3	8	6	5
ESBL and MDR	11	4	4	5	4
Total	34	10	16	16	12

SMX/TMP Sulfamethoxazole/Trimethoprim, *MDR* multi-drug resistant, *ESBL* extended spectrum beta lactamase.

which 34 cultures (16%) were resistant to both SMX/TMP and 1st and 2nd generation cephalosporin's (Table 4).

In total, 34 of the cultures (16% of the positive cultures and 12% of all cultures) had a significant resistance pattern (MDR and ESBL). MDR bacteria were detected in 20 cultures. ESBL-producing bacteria were found in 25 cultures and 11 cultures that had MDR-positive bacteria were also ESBL producers. MDR bacteria were E. coli, except for 2 Klebsiella pneumoniae and 1 MRSA. ESBL bacteria were E. coli in 22 isolates and Klebsiella pneumoniae in 3 (Table 4).

Of all the specimens that were evaluated in this study, 64 were obtained from participants whose CIC was self-performed, and 217 were taken from participants whose CIC was performed by a caregiver. As expected, the median age was older in the former group (14 years compared to 6 years in the latter group). The asymptomatic bacteriuria rates were 83% in the self-CIC group and 75% in the CIC by caregiver group. The resistant bacteria rates were not statistically different between the groups (21% vs 14%, respectively [95%CI], $p = 0.27$).

Fourteen participants were treated with continuous chemoprophylaxis at the time of specimen collection. Of the 19 cultures obtained from those participants that were available for analysis, 13 (68%) were positive, 7 were resistant to either SMX/TMP or 1st and 2nd generation cephalosporin's and 1 was MDR.

DISCUSSION

In this study, bacteriuria was detected in 77% of specimens obtained from asymptomatic children with neurogenic bladder who require CIC. A significant resistance pattern (e.g., MDR or ESBL) was observed in 16% of the positive specimens.

The significance of asymptomatic bacteriuria in pediatric individuals with neurogenic bladder has been the subject of multiple studies. It had been considered in the past as a precursor of symptomatic urinary tract infections and potential renal damage, but later evidence challenged these assumptions. Ottolini et al. published an analysis of 207 pediatric participants treated with CIC and concluded that in the absence of vesicoureteral reflux, asymptomatic bacteriuria does not lead to renal scarring [10]. Zeger et al's. randomized study demonstrated that stopping prophylactic antibiotics in this population reduces bacterial resistance while not subjecting them to a higher incidence of urinary tract infections [11]. The guidelines of the European Association of Urology and the European society of Pediatric Urology state "Urinary tract infections are common in children with neurogenic bladders, however, only symptomatic UTIs should be treated" [9]. Others have reported that prophylactic antibiotics should be reserved for recurrent urinary tract infections and vesicoureteral reflux [12, 13].

Because of the high prevalence of asymptomatic bacteriuria, the diagnosis of a urinary tract infection in children requiring CIC is a clinical challenge. Obtaining a urine culture in an acutely ill child will too often result in a positive culture that may be unrelated to the current illness. The diagnosis of urinary tract infection should, therefore, also rely on other clinical signs, such as cloudy urine, abdominal or flank pain and vomiting, as well as the ruling out of other sources of infection which are common and likely to be present in this fragile population [14]. A survey of 41 European medical centers found little consensus in terms of protocols for preventing, diagnosing and treating urinary tract infections in children with neurogenic bladders [15]. The complexity of a urinary tract infection diagnosis leads to antibiotic treatment targeted at the pathogen identified in a urine culture, which contributes to increased exposure to antibiotics with subsequent emergence of resistant strains. In addition, these individuals are subjected to multiple procedures, hospital admissions and infectious complications originating from systems other than the urinary system, among them orthopedic, neurosurgical, pulmonary, and more. These lead to the acquisition of nosocomial strains as well as to the development of resistant strains through antibiotic treatments. It is not surprising, therefore, that urinary tract infections caused by resistant bacteria are common in children with neurogenic bladder who require CIC. Ortiz et al. age-matched 231 children with neurogenic bladder and urinary tract infection with healthy controls with a urinary tract infection and found a higher rate of non-E. coli and MDR infection in the neurogenic group [4].

Forster et al's. analysis of positive cultures in children requiring CIC revealed that 4.6% of the isolates were positive for vancomycin-resistant Enterococcus (VRE), 11.1% were resistant to 3rd generation cephalosporin's and 0.4% were carbapenem-resistant Enterobacteriaceae [16]. Their work was based on an analysis of the hospital's database maintained by the Antimicrobial Stewardship Committee and did not include information regarding ESBL and MDR patterns, symptoms or mode of presentation at the time of specimen collection. It is likely that many of their participants were symptomatic, given that they had been admitted to a tertiary pediatric facility. Of the isolates in their study, 65.5% of the isolates were of non-E. coli bacteria, in contrast with our results of 71% E. coli. This difference could also be affected by the inclusion of a different population. Ottolini et al. also reported a higher percentage of non-E. coli, 45%. Of note, the report included cultures with mixed growth (9%) and reported 14% of other bacteria without specification [10].

Opinions in the literature are divided on the subject of periprocedural antibiotic treatment for urodynamic studies, whether it be empiric or culture-driven treatment. Snow-Lisy et al. found a low rate (1.4%) of urinary tract infections following urodynamic studies. Of the 15 participants with an infection, 10 had bacteriuria on their preprocedural cultures. It should be noted that their study group is significantly different from ours: specifically, only 62% of their participants had neurogenic bladder, and only 44% of the studies were performed on participants requiring CIC [17]. While no antibiotic prophylaxis is recommended for adult individuals [18] no consensus exists regarding preprocedural antibiotic prophylaxis in children requiring CIC [17]. Our local protocol calls for a urine culture to be obtained via catheterization prior to an urodynamic study. Preprocedural prophylactic antibiotics are then administered according to the sensitivity of the isolated pathogen. In individuals not requiring CIC, urodynamic studies are withheld until eradication of the pathogen in the event that a urine culture had been found to be positive.

Children who perform CIC themselves are older than those who require caregiver's assistance, and therefore have been exposed to instrumentation of the urinary tract for a longer period of time. Improper technique by a young and often limited child sometimes leads to concerns by parents. On the other hand, children who require assistance with CIC are sometimes treated by more than one caregiver which is also sometimes perceived as a risk factor for introduction of bacteria. In the current study, no differences were found in rates of bacteriuria or of antibacterial resistance between children who performed self CIC when compared to children whose CIC were performed by a caregiver, which could support parental concerns with self-performance of CIC.

The current study has several limitations. It is retrospective in nature, and the lack of symptoms at the time of specimen collection is based on electronic records. Furthermore, urine cultures were not analyzed in a single central laboratory with identical equipment. Rather, it was collected by primary health providers and sent to their local laboratories. We have no access to the primary providers' medical charts and cannot comment on participants' prior admissions or antibacterial treatments which may induce antibacterial resistance. Several factors may affect the generalizability of our findings. The children included in this work are from a single center, which serves as a national referral center for pediatric and adolescent rehabilitation. Moreover, it includes only those who were scheduled for a urodynamic evaluation during the study period. Our approach for scheduling of urodynamics studies is a hybrid one [19], which includes routine studies as well as studies performed in order to investigate changes in children's clinical condition (e.g., incontinence, urinary tract infections). Above all, we believe our work should serve to alert all those caring for this challenging group of individuals to be aware of the ongoing and growing risk of antibiotic resistance. The choice of treatment of possible infection should be prudent. If antibiotic stewardship is an important issue in the general population, it is even more so in this special population.

In Conclusion, asymptomatic bacteriuria and resistance to antimicrobials are common in our study population of pediatric individuals who require CIC. Refraining from unnecessary antibiotic treatment in asymptomatic individuals without signs of active infection is imperative in order to avoid putting them at risk for increased resistance to antibiotics.

DATA AVAILABILITY

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

RB-D and YB-Y conceived the idea and study design, RB-D analyzed the data, and led manuscript writing; FC, SD, RM, EK assisted with study design, data collection, audited data collection integrity. JB-C, RC, and YB-Y provided consult and guidance in manuscript writing. All authors have reviewed and approved this version of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL

The study protocol was reviewed and approved by the Alyns' hospital Helsinki review committee.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to R.B-D. or Y.B-Y.

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