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Research Article

Urinary Tract Infection and Antimicrobial Susceptibility Pattern Associated with Asymptomatic Bacteriuria in those Receiving Clean Intermittent Catheterization for Neurogenic Bladder

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Abstract

Clean intermittent catheterization (CIC) is a frequently performed procedure on patients with neurogenic bladder to assist with voiding and is associated with bacteriuria. Due to this bacteriuria, this patient population is frequently subjected to multiple courses of antibiotics, whether appropriate or not and often become colonized with multi-drug resistant organisms. Choosing appropriate empirical antibiotics is a clinical dilemma when encountering these patients at the beginning of an illness. We reviewed antimicrobial susceptibility patterns of urine cultures for 50 myelomeningocele patients over the course of 1 year. Data for 192 organisms was available for analysis and *E. coli* was the most commonly recovered organism. Using univariate analysis we sought to detect differences identifying subjects who were most likely to be colonized with resistant *E. coli* strains versus those subjects that had susceptible strains. Though the probability of resistance is higher than that in the community, it did not proportionately increase with olderage, increased duration of clean catheterization, or related to route of catheterization. Decisions for empirical therapy ought to be guided by individual patient's previous culture results with particular attention to colonization with resistant organisms, but broad spectrum coverage may not be necessary in all patients utilizing clean intermittent catheterization.

INTRODUCTION

Clean intermittent catheterization (CIC) is often employed in patients with neurogenic bladder secondary to spina bifida or spinal dysraphism for normal voiding of the bladder. Due to the frequency of catheterization, patients often present with bacteriuria [1], with the prevalence ranging from 70% [1] to 85% [2]. As these patients are typically non-sensate, they often are classified as episodes of asymptomatic bacteriuria (ABU). While antimicrobial treatment is not associated with elimination of ABU or reduction in urinary tract infection (UTI) [3], antimicrobials are administered when febrile UTI is encountered. Choosing appropriate antimicrobial therapy for the coliforms is emphasized and local susceptibility patterns typically guide selection for clinicians [4]. However, prior exposure to antimicrobials, as frequently occurs in this population for various indications, alters sensitivity patterns. This problem makes it difficult to choose appropriate empirical antimicrobial therapy at the onset of illness in this population, but is essential to minimize morbidity related to UTI [5]. Hence, we sought to prospectively study the incidence of asymptomatic bacteriuria, antimicrobial sensitivity pattern and potential predictive factors for antimicrobial resistance in a cohort of patients with neurogenic bladder on regular CIC for bladder management.

METHODS

Patients

Consecutive patients with neurogenic bladder secondary to myelomeningocele on regular CIC 4-6 times a day were consented

to participate in a prospective randomized trial to study the effect of catheter type on the microbiological milieu of the bladder [6]. Informed consent was obtained by a trained provider both verbally and with a written explanation of the study. The study protocol was approved by the Institutional Review Board for human studies (OHRP Assurance No. FWA00002860) at Nationwide Children's Hospital (IRB number: IRB12-00269) and registered at clinicaltrials.gov (NCT01305681). All those with recent or foreseeable change in the catheterization pattern or preferences due to surgeries, outstation trips or transition from caregiver catheterization to self catheterization were excluded. Other exclusion criteria include antimicrobial chemoprophylaxis and treatment for UTI within the past two weeks. An intended sample size of 50 was achieved over a period of ten months (June 2011 to March 2012). At the beginning of the study period, a clean catheterized sample of urine was obtained using a new catheter. The specimen was transported within one hour to the microbiology department. In addition to the clinical and microbiological information that was obtained as a part of the study, the sensitivity pattern was obtained whenever there was a growth of a potential pathogen. The ChildLab at Nationwide Children's Hospital processed all urine samples per standard protocols plating to sheep blood and MacConkey agar biplates using calibrated loops [7]. Cultures were incubated for a minimum of 16 hours at 35°C in ambient air and quantitation of significant pathogens provided as colonies per milliliter of urine. Isolated colonies were identified to the genus and species level, as appropriate, using standard biochemical or automated identification tests (Vitek 2, bioMerieux. Durham, NC). Sensitivity was determined using disc diffusion method. Demographic data and clinical information pertaining to voiding and urinary infections were obtained.

Statistical analysis was performed using the Prism® software package (GraphPad, La Jolla, CA) and SPSS Statistics® (IBM, Armonk, NY). Descriptive statistics were used for demographic data and reports of resistance patterns, and the univariate analysis to compare the three *E. coli* cohorts used an ordinary one way ANOVA.

Definitions

"Bacteriuria" in this population is not well defined, since colonization is known to occur with intermittent catheterization. Previously used definition of $>10^4$ colony-forming units or more obtained by bladder catheterization was used to define significant bacteriuria [8]. Febrile Urinary Tract Infection was defined as a positive urine culture result with fever >101 degree Fahrenheit, abdominal pain, change in continence pattern or change in color or odor of urine [1]. Those who had febrile UTI more than once were categorized as recurrent UTI [9]. *Enterobacteriaceae* and other bacteria known to cause UTI were categorized as potential pathogens. Lactobacilli, corynebacterium, coagulase negative staphylococci and other bacteria that are not clinically relevant were categorized as non-pathogens [4]. Significant bacteriuria associated with non-susceptibility to at least one agent in one or more antimicrobial categories was categorized as colonization with resistant pathogen [10]. Multidrug resistant organisms (MDRO) were defined according to the CDC's definition: acquired non-susceptibility to at least one agent in one or more antimicrobial categories [11].

In our patient cohort analysis, we divided patients up based on the susceptibility pattern of their recovered *E. coli* species. Patients who only grew *E. coli* species that were pan-sensitive to all antimicrobials tested were included in the "sensitive" cohort. Conversely, a "resistant" cohort was comprised of patients who grew *E. coli* species that were resistant to first line therapies ampicillin and co-trimoxazole PLUS drug resistance to another drug class. If patients grew *E. coli* species with intermediate resistance, like resistance to ampicillin only or resistance to another class of antimicrobials, that patient was included in the "mixed" cohort. If a patient grew multiple strains of *E. coli* of varying susceptibility patterns during the study period, the assignment to cohort followed the most resistant strain available. For example, if a patient grew a strain resistant to ampicillin, co-trimoxazole, and a cephalosporin in one culture and another entirely sensitive *E. coli* strain in a later culture, the patient was included in the resistant cohort. Our practice when choosing empirical therapy is that the presence of a previous multidrug resistant organism influences a clinician to select a more broad spectrum agent.

RESULTS

230 patients from our myelomeningocele clinic were assessed for eligibility. 116 patients were excluded on the basis of: (i) presentation with active UTI, (ii) ongoing antimicrobial chemoprophylaxis for recurrent UTI or vesicoureteral reflux (iii) scheduled urinary tract surgery during study period, (iv) or poor compliance with CIC. 64 patients declined to participate; the remaining 50 patients consented to participate (Figure 1). The demographic parameters are given in (Table 1).

In total, 286 species were recovered from 184 urine samples. 29 collected samples did not demonstrate any growth and were considered culture-negative. Of the 286 species evaluated, antibiotic susceptibility was determined for 192 species (Figure 1). The sensitivity pattern of the predominant pathogens associated with urinary tract infection is given in (Table 2). *E. coli* was the most commonly recovered species and more than half (N = 53) were resistant to at least one typical first line therapy, ampicillin or co-trimoxazole. 47 species demonstrated resistance to antibiotics beyond first line therapies and 16 of those qualified as multidrug resistant strain, with resistance to ampicillin, co-trimoxazole, and another class of antimicrobial agent. An additional 9 *Pseudomonas* species were recovered but their sensitivity patterns are so different from other gut coliforms they were not included in the table. Another 21 various potentially pathogenic species are also not included in the table due to their small numbers, but those sensitivity patterns are reported in our [Supplemental Table 1].

To evaluate for factors that may identify myelomeningocele patients at risk for carriage of multidrug resistant strains, we examined three cohorts of patients. *E. coli* is the most commonly recovered uropathogen from all UTI patients and was the most commonly recovered potential uropathogen from our patient population, thus we chose to use this species to compare groups. 46 participants had at least one strain of *E. coli* recovered during the study period. Of the remaining 4 participants, 2 patients had culture negative results at all time points and 2 patients did not grow an *E. coli* species. The first cohort of participants

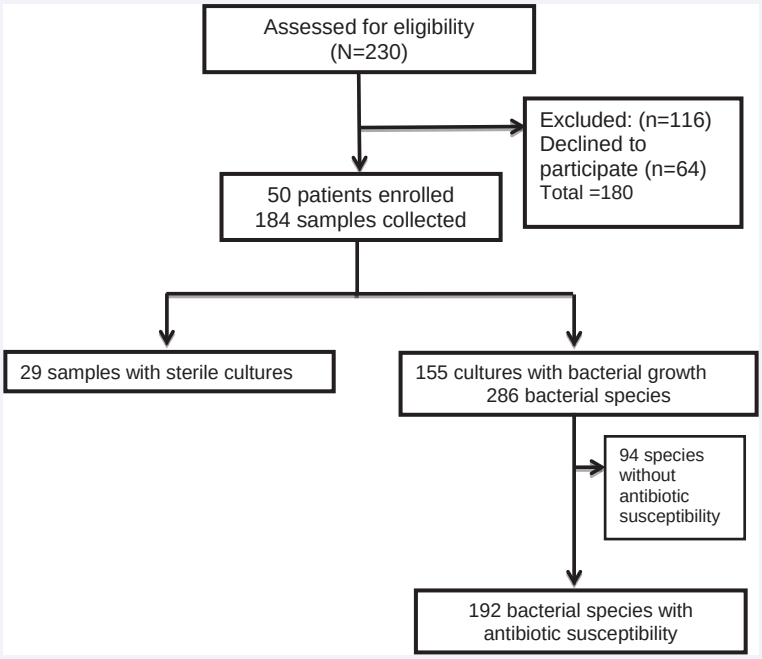

Figure 1 Patient enrollment consort and cultures obtained.
Abbreviations N: number

includes 16 strains of *E. coli* obtained from 9 unique patients that demonstrated resistance to ampicillin, co-trimoxazole, and another drug class.The second cohort includes 33 strains of *E. coli* that were sensitive to all antibiotics tested obtained from 16 unique patients. The final cohort demonstrated mixed susceptibility patterns for 27 strains of *E. coli* from 15 unique patients. We examined these three cohorts for potential risk factors listed in (Table 3). We compare cohorts in terms of age, sex, and total duration of catheterization (in years). We further examined whether subjects employed night drainage (the practice of leaving a catheter in place overnight to allow emptying of the bladder), whether they had previous undergone bladder augmentation, and whether they performed catheterization through the urethra or a surgically created channel in the abdomen called the Mitrofanoff procedure. Univariate analysis did not find any statistically significant difference between cohorts to identify potential risk factors for carriage of MDROs (Table 3).

DISCUSSION

Bacteriuria is often encountered in neurogenic bladder patients who require clean catheterization for bladder emptying and the incidence is one of the highest among populations studied. Though bacteriuria is usually asymptomatic, UTI can occur, and urologists continue to debate on the appropriate metrics for diagnosis of infection in this population [12-14]. It is our practice to focus on objective symptoms like fever, systemic illness, with turbid or malodorous urine, lower abdominal pain or change in continence pattern when diagnosing a UTI in this population. Diagnosis of pyelonephritis in patients with myelomeningocele tends to be even more challenging due to sensory impairment, body habitus and the higher prevalence of asymptomatic bacteriuria. Antimicrobials are frequently administered in this group to treat recurrent UTI, to eliminate bacteriuria or following a febrile episode with positive culture and no other localizable infection. However, antimicrobial prophylaxis has been proven to be ineffective in eradicating bacteriuria in this group of patients [15,16], and repeated exposure to antimicrobials is known to be associated with increased risk of resistance [5]. Recurrent UTI and treatment with beta-lactam antibiotics within the preceding three months has been noted to increase the risk of infection with resistant organisms in the community [17]. Treatment with antimicrobial agents like co-trimoxazole results in higher incidence of *Enterobacteraceae* resistant to co-trimoxazole [18]. With this change in susceptibility pattern, knowledge of the microbial pattern seen in this select group of patients will enable initiating the most appropriate antimicrobial when indicated,

Table 1: Patient demographics.

Patient Demographics	
Sex Male Female	 22 28
Age	0.92-42 years (Median: 10.5 years)
Years of catheterization	0.5 – 30 years (Median: 6.75 years)
Route of catheterization Urethra Mitrofanoff	 40 (80%) 10 (20%)
Bladder augmentation	12 (24%)
Night time drainage	12 (24%)
# of UTIs in past 2 years	0-15 episodes (mean: 2)
Abbreviations UTI: Urinary Tract Infection	

Table 2: Sensitivity patterns for commonly recovered organisms.
1. Due to intrinsic properties, *Enterococcus species* have a limited susceptibility pattern and our laboratory only reports results for Ampicillin, Vancomycin, and Dalfopristin/quinupristin.
2. *Klebsiella species* all have instrinsic resistance to ampicillin.

	S: all Antibiotics	R: to Amp	R: to co-trimoxazole	R: Other Antibiotics	R: to Amp, Co-trimoxazole, and other Antibiotics
E.coli (N: 94)	46	33	20	47	16
Proteus sp. (N: 16)	1	4	3	14	0
Enterobac-teraceae sp. (N: 11)	0	10	1	10	1
Enterococcus sp. (N: 25)	2	1	N/A[1]	22	N/A[1]
Klebsiella sp. (N: 15)	0	15[2]	4	12	4

Abbreviations S: Sensitive; R: Resistant; Amp: Ampicillin, sp: Species, N/A: Not Applicable

Table 3: Comparison between patients with a resistant *E. coli* species was found and those with a susceptible *E. coli* species.

Factor	Resistant *E. coli* N: 9	Sensitive *E. coli* N:15
Age (years)	2-25 Median: 13	11 months-31 Median: 11
Sex	Male: 3 Female: 6	Male: 6 Female: 9
Duration of catheterization (years)	2-25 Median: 12	11 months – 27 years Median: 7
Number of recurrent UTIs in the past 2 years	0-4 Median: 1	0-10 Median: 1
Overnight drainage (N of patients)	2	3
Augmentation (N of patients)	2	5
Route of catheterization (N of patients)	Mitrofanoff: 3 Urethra: 6	Mitrofanoff: 3 Urethra: 12

Abbreviations: N: number; UTI: urinary tract infection

while awaiting the sensitivity results. Factors that determine the choice of antimicrobial include severity of the infection, renal function, sensitivity patterns in the community, and prior infection's antimicrobial pattern.

One recent retrospective study sought to identify risk factors associated with UTI in myelomeningocele patients with neurogenic bladder and found that younger age and suprasacral cord lesions had a higher association with frequent UTIs. Interestingly, the authors found that increasing age was associated with decreasing odds of UTI [19]. Over the 12 months of follow up during our trial, our patient population collectively experienced only 2 UTIs, which is a similar rate found in other reports [20,21]. With such low numbers, we were unable to compare resistance patterns or risk factors for MDROs among patients with active urinary tract infections. Comparing culture results to identify risk factors is a difficult task, as potential uropathogens are so varied in susceptibility patterns. For this reason, we focused on *E. coli*, an organism that 92% of our study population grew, so we could sort participants into specific cohorts based on their susceptibility pattern of particular strains. We hypothesized that older age and longer duration of catheterization would lead to acquisition of more MDROs, due to likely exposure to more courses of antimicrobial agents. However, in our patient population, prevalence of bacteriuria or a resistant pattern did not correlate with increasing age or duration of catheterization. Despite the low rate of UTIs in our population during the study period, the resistance to co-trimoxazole and ampicillin was found to be high [Table 2].

Our study does have some important limitations to consider. Our study numbers are small and we had strict inclusion criteria, excluding patients with poor CIC compliance. It is possible that patients with improved adherence to CIC have generally lower carriage rates of MDROs. We also excluded patients on antimicrobial prophylaxis and only tracked antimicrobial use in relation to UTIs, so it is possible the urinary culture results were affected by antimicrobials prescribed for indications other than UTI.

Supplemental Table 1: Sensitivity patterns for all remaining less commonly recovered organisms.

	N of isolates	S: to all Abx tested	R to TMP-SMX and amp	R to other Abx	R to Abx other than TMP-SMX and/or amp	S to any abx tested
Aerococcussp	1	0	0	0	1	1
Acinetobacter sp	1	0	0	0	1	1
Bacillus sp	1	1	0	0	0	0
Brevundimonassp	1	0	0	0	1	1
Citrobactersp	4	0	1	1	2	4
Lactose fermenting GNR	1	0	0	0	1	1
Providencia sp	2	0	0	0	2	2
Pseudomonas sp	9	1	0	0	4	8
Shewanellaputrifaciens	1	0	0	0	1	1
Staphylococcus sp	8	1	0	0	6	8
Streptococcus sp	2	1	0	0	0	1

Abbreviations: N: Number; S: Sensitive; R: Resistant; Abx: Antibiotics; TMP-SMX: Co-trimoxazole; Amp: Ampicillin; sp: species

Therefore, when empirical antimicrobial treatment is initiated prior to availability of the sensitivity report, it is prudent to review individual patients' previous urine cultures for guidance. Though the probability of resistance to typical first line antimicrobial agents is higher than that of the community, it does not seem to proportionately increase with the duration of being on clean catheterization or age. Decisions for empirical therapy ought to be made with consideration of the individual patient's previous culture results with particular attention to colonization with resistant organisms, but broad spectrum coverage may not be necessary in all patients utilizing clean intermittent catheterization.

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