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Discontinuation of Antimicrobial Prophylaxis (AP) in Children With Spina Bifida: A Case Series Analysis

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Abstract

Background: Spina bifida increases the risk for urinary tract infections (UTI). Antimicrobial prophylaxis (AP) reduces symptomatic UTI's but selects resistant organisms. Measures to ensure regular and complete emptying of the bladder combined with treatment of constipation reduce the risk for UTI.
Objectives: Demonstrate that close adherence to a catheterization regimen in children with spina bifida (Selective Treatment - ST) reduces the need for antimicrobial prophylaxis.
Methods: Case series analysis of pediatric spina bifida clinic patients where routine antimicrobial prophylaxis was replaced by clean-catch catheterization and daily bowel regimen (ST). Retrospective chart review of 67 children (mean entry age: 24 months, median age: 4 months; 32 Males, 35 Females) enrolled between 1986 - 2004. Mean follow-up was 128.6 months (range 3 - 257 months). Asymptomatic and symptomatic UTI incidences were noted on AP and ST protocols. Creatinine clearance at study entry and follow-up was calculated by the age appropriate method. A multivariable regression model with delta Glomerular Filtration Rate (GFR) as the dependent variable, independent sample t-test and Wilcoxon rank sum were performed with SAS v. 9.2.
Results: The mean number of infections while on AP was 8.7 (95% CI 5.72, 11.68) and was 1.0 on ST (95% CI 0.48, 1.43). 5 infections on the AP protocol required intravenous (IV) antibiotics due to resistance to oral therapy, but none on ST. Comparing change in GFR between both protocols (AP vs. ST) found a significant difference in the change of GFR by treatment protocol.
Conclusions: AP did not prevent UTIs and resulted in more resistant organisms requiring IV antibiotics. Discontinuing AP allowed the return of susceptibility to oral antimicrobials and significantly improved GFR in those children who had previously been on AP. Adherence to a catheterization regimen with prompt treatment of symptomatic UTI conserved renal function and prevented selection of resistant organisms.

Keywords: Spina Bifida, Urinary Tract Infection, Antimicrobial Drug Resistance, Urinary Catheterization, Cohort Series

1. Background

Pediatric urinary tract infections are a common clinical problem occurring in up to 8% of children between the ages of one month and eleven-years-old (1, 2). Recurrence of these infections may occur in up to 40% of these same children (3). Febrile urinary tract infections (UTI) in infants may lead to renal scarring in up to 10% of these infants (4) and repeated renal scarring has been proposed as a risk factor for later hypertension and end-stage renal disease. However, prompt diagnosis and treatment of urinary tract infections is believed to reduce renal scarring and prevent long-term sequelae of the infection (5).

Children with spinal cord defects are more susceptible to urinary tract infections for several reasons: associated congenital defects, neurogenic bladder, chronic constipation and concurrent presence of vesicoureteral reflux (VUR). Urinary tract infections are a common occurrence in these children and may lead to hospitalization and/or delay of corrective surgeries. Minimizing the number of symptomatic infections and presumed reduction in renal scarring lead to the adoption of antimicrobial prophylaxis. However, Le Saux et al. (6) found that the evidence on whether routine antimicrobial prophylaxis truly reduces the number of infections and which patients should receive prophylaxis was of low quality. Additionally, a study by Zeger et al. (7) found no benefit to antimicrobial prophylaxis in children with spina bifida without vesicoureteral reflux. Furthermore, the guidelines for the management

of pediatric UTI's (8) have excluded children with neurologic or anatomic abnormalities and a meta-analysis by Morton et al. on the use of antimicrobial prophylaxis in spinal cord dysfunction patients excluded children under the age of thirteen (9). Hence, we present the following case series data in an attempt to broaden the body of knowledge on the appropriate urologic management of these children.

2. Methods

A retrospective abstracted chart review of sixty-seven children enrolled in the multi-specialty spina bifida clinical care group between 1986 and 2004. Forty-four children had no hydronephrosis during their initial imaging, thirteen children had mild to moderate hydronephrosis, and the remaining ten had renal dysplasia or other abnormalities. Ten children had grade 2 or higher vesicoureteral reflux, and underwent bladder augmentation (Table 1).

Table 1. Demographics

Variable	Response	N
Renal Ultrasound Result	Normal	44
	Mild Hydro	13
	Other	10
Sex	Female	35
	Male	32
VCUG – Result	No Reflux	57
	Other	10
Bladder Augmentation	No	57
	Yes	10
Clean Intermittent Catheterization	No	14
	Yes	53
Exam Date	Before 01/99	49
	After 01/99	18

Length of follow-up ranged from one year to twenty years. Most patients were enrolled as infants and had a follow-up period of ten years or more (Table 2).

During the time period reviewed, the clinical management of these children changed substantially. Initially, all children had a urine culture obtained at each visit and every positive culture was treated. In addition, these children were routinely placed on antimicrobial prophylaxis with either nitrofurantoin or co-trimoxazole given at bedtime (Antimicrobial Prophylaxis). In 1999, routine antimicrobial prophylaxis was discontinued and only symptomatic (fever, poor oral intake, irritability, and vomiting) infections were treated (Selective Treatment).

Almost all of the children utilized clean intermittent catheterization (CIC) as part of their neurogenic bladder management. Beginning in 1999, ditropan or detrol were routinely used to aid in the maintenance of urinary continence. Stool softeners and stimulating agents were utilized as needed to prevent constipation.

Renal ultrasounds were obtained upon clinic enrollment with annual follow-up exams in patients with stable disease and more frequently if any dysplasia, hydronephrosis or duplicated collecting systems had been noted. Voiding cystourethrograms (VCUG) were performed in all but two children, who had normal renal ultrasounds and age-appropriate renal function. VCUGs were repeated in children with known VUR or if hydronephrosis was noted on interval renal ultrasounds. Dimercaptosuccinic acid (DMSA) renal scans were not routinely obtained.

Parameters examined were initial renal function, most recent renal function, and number of infections while on and off of antimicrobial prophylaxis. Patients served as their own control. The emergence of resistant organisms while on antimicrobial prophylaxis was also noted. We used the Schwartz equation, which uses height (0.55 x length (cm)/ Serum creatinine) (10) to calculate creatinine clearance since the initial weight was only recorded on the chart abstract in thirteen of the sixty-seven patients. The Cockcroft-Gault equation was used in those patients over eighteen years old [(140-age0*wt/(Serum creatinine * 72)] with a correction factor of 0.85 in females (11).

SAS v 9.2 was used for all analyses. The descriptive statistics reported for categorical variables include frequency and percent. The range, mean and 95% confidence intervals for all continuous variables were calculated. The data was not normally distributed, hence the Wilcoxon Sign Rank Test was used to determine whether the median glomerular filtration rate (GFR), Blood urea nitrogen (BUN) level and number of UTIs statistically differed between initial and follow-up visits by AP protocol (routine versus selective). We also compared the mean difference in GFR at initial and follow-up visits by routine AP vs. selective AP using an independent pooled t-test. The independent t-test was used because equality of variances was explored and satisfied for GFR.

A linear regression model with delta GFR as the dependent variable was created using Proc GLM. Pearson's correlation coefficients were examined for continuous covariates. When covariates were highly correlated with each other ($|r| > 0.6$ $P < 0.05$), only the covariate with the strongest linear relationship with delta GFR was used. Each covariate was tested singularly with its association with delta GFR and was eliminated if $P > 0.25$. An interaction

Table 2. Enrollment Age and Follow-Up

Variable	N	Minimum	Maximum	Mean	Median
Age at Diagnosis (months)	67	1	180	24	4
Age at Follow Up (years)	67	1	21	12.4	12
Time Between Initial and Follow Up (months)	67	3	257	128.6	129

term was tested in the final model if the univariate P value < 0.05. No significant interactions were found in the final model.

3. Results

The mean number of infections per patient on routine Antimicrobial Prophylaxis was 8.7 (95% Confidence Interval (CI) 5.72, 11.68) and with Selective Treatment was 1.0 (95% CI 0.48, 1.43). Five infections on the Antimicrobial Prophylaxis protocol required intravenous antibiotics due to resistance to oral agents, but none on the Selective Treatment protocol (Table 3).

GFR at follow up is greater than GFR initially due to the negative sign rank Stat (S) and the actual differences in the GFRs are -83.3 and -26.1 for the AP and ST groups. The number of infections is also greater initially than at follow up under the new method of treatment. We did not find a significant difference in any of the initial and follow up measurements. This is important to note because when we simply check to see if adjusted creatinine clearance is significantly different without controlling for protocol type, we find that there is a significant difference as the 95% CI in table 3 for adjusted GFR does not contain 0. When we control for protocol we see that this difference is only present in the prophylaxis protocol (S = -563.5, P value < 0.0001), but not in the selective treatment protocol (S = -22.5, P value = 0.1726).

The differences in the means of GFR initially and at follow-up and mean number of infections initially and at follow-up are significantly different from one another in the group of patients who had initial work done during the prophylaxis period (before 01/99). The number of infections is also greater initially than at follow up when prophylaxis had been discontinued (selective treatment protocol) (Table 4).

When we compare change in GFR between the patients measured using both protocols (selective vs. prophylaxis) we find that there is a significant difference in the change of GFR by treatment group (t-stat -2.89 P value = 0.0054).

4. Discussion

The natural history of our spina bifida patient management allowed us to observe the effect of discontinuing antimicrobial prophylaxis in a high-risk population (selective treatment protocol) with each patient serving as their own control. We found that in the majority of patients regular voiding via clean intermittent catheterization, bladder spasm reduction with the use of oxybutynin or tolterodine, and a bowel regimen that minimized constipation was effective in preventing urinary tract infections. When these measures were inadequate, augmentation of the bladder was effective in reducing the amount of reflux and subsequent hydronephrosis. This approach differs from that recommended in the recent European guidelines where a conservative approach still includes antimicrobial prophylaxis (12). The importance of an appropriate bowel regimen is highlighted by Shaikh et al. who found that bowel and bladder dysfunction in toilet-trained children was an indication for low-dose antimicrobial prophylaxis (13).

The prompt treatment of urinary tract infections in these patients resulted in no detectable changes in renal function through the measurement of serum creatinine or renal ultrasound. Three patients, who had a GFR between 60-90 mL/min upon enrollment in the spina bifida clinic, became symptomatic when their antimicrobial prophylaxis was discontinued and required long-term prophylactic treatment with co-trimoxazole as per the recommendations of Smellie et al. (14). One of these three patients had a duplicated collecting system and grade 3 reflux. The second patient had prominent pyramids without reflux and developed stomachaches whenever she was taken off of prophylactic antibiotics. The third enrolled in the clinic at four years of age and became symptomatic with subsequent UTI whenever her prophylaxis was discontinued. We did not use a third generation cephalosporin as recommended by Oishi et al. (15) due to cost and availability restrictions at the time these children were enrolled in clinic. This may have been fortuitous since Cheng et al. found that the use of prophylactic third-generation cephalosporin was associated with higher rates of multidrug resistant uropathogens (16).

Table 3. Summary of Continuous Covariates[a]

Variable	N	Min	Max	Mean	Median	95% CI
Measures from Initial Visit						
Blood Urea Nitrogen Level	66	5	28	12.2	11.5	11.02, 13.29
Creatinine Level	67	0.2	2	0.5	0.4	0.45, 0.58
Weight[b]	13	3.2	47	9.0	3.8	1.66, 16.41
Height	67	49	147	75.3	63.0	68.61, 82.08
Adjusted Creatinine Clearance[c]	67	11.9	286	87.7	76.5	74.98, 100.51
Measures from Follow-Up Visit						
Blood Urea Nitrogen Level	67	6	26	12.9	12.0	11.93, 13.78
Creatinine Level	67	0.2	0.9	0.60	0.6	0.52, 0.62
Weight	67	11.5	108.9	49.4	47.0	43.37, 55.32
Length	64	75	167.6	136.4	140.4	130.67, 142.05
Adjusted Creatinine Clearance[b]	67	78.4	313.5	157.9	143.7	145.84, 169.89
Number of Infections/Patient						
Routine Antimicrobial Prophylaxis (AP)	67	0	50	8.7	11.7	5.72, 11.68
Selective Treatment (ST)	66	0	10	1.0	1.4	0.48, 1.43

[a] Since some data is not normally distributed medians are also reported
[b] Initial weight was not recorded on record abstract and original chart data was not available.
[c] Schwartz estimated formula was used for children while Cockcroft-Gault formula was used for adults.

Table 4. Wilcoxon Sign Rank Test Results

	Before 01/99 (Prophylaxis)			After 01/99 (Selective)		
Variable	**Difference in Means**	**Sign Rank Stat (S)**	**P value**	**Difference in Means**	**Sign Rank Stat (S)**	**P value**
GFR Initial - GFR at Follow-Up	- 83.3	- 563.5	< 0.0001	- 26.1	- 22.5	0.1726
Infections Initial - Infections Follow - Up	10.2	375	< 0.0001	0.29	3.5	0.6719

We also did not perform DMSA scans in these children and it has been argued that these scans are more sensitive at detecting renal scarring. However, any scarring of clinical significance would have had an associated rise in creatinine or cortical thinning visible on ultrasound (17, 18). We did not see either of these changes during our follow-up and the use of these modalities in place of DMSA scans prevented the imaging-associated radiation exposure. This more restrictive approach to imaging is also in accordance with the recent guidelines developed by the AAP (19). In addition, none of these children developed hypertension during their follow-up period, which is consistent with the work by Hannula et al. on the long-term impact of pediatric urinary tract infections (20).

A dedicated nurse facilitated regular multi-specialty follow-up, which allowed prompt detection of hydronephrosis. The creation of a medical home as recommended by Burke et al. for these children increased coordination of care (21), and helped optimize medical management of these children. The early detection of abnormalities facilitated prompt corrective changes in management.

4.1. Conclusions

In children with spina bifida, antimicrobial prophylaxis did not prevent symptomatic UTIs and resulted in resistant organisms requiring intravenous antibiotics. Discontinuing antimicrobial prophylaxis allowed the return of susceptibility to oral antimicrobials. The discontinuation of AP significantly improved GFR in those children who had previously been on AP. Adherence to a catheterization regimen, and constipation prevention with prompt treatment of symptomatic UTI conserved renal function and prevented selection of resistant organisms.

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