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Fluoroquinolone-Probiotic Combination Therapy to Treat Recurrent Urinary Tract Infections in Children

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Introduction

Urinary tract infection (UTI) is one of the most common bacterial infections in children. Recurrent UTI (rUTI) occur in about one-third of these patients.[1] Children with rUTI are at risk of renal scarring leading to renal failure in the long term.[2] Prevention often entails months to years of daily antibiotics. This strategy has variable success in reducing recurrence and invariably results in an increased risk of subsequent drug-resistant infections.[3, 4]

Two primary sources for rUTI have been proposed. First, the intestinal and vaginal tracts have been well established as reservoirs for uropathogenic bacteria such as *Escherichia coli* that recurrently ascend into the urinary tract via the urethra. Probiotic organisms may alter the intestinal and vaginal tract flora to reduce or resist pathogens. The probiotic yeast *Saccharomyces boulardii* has been shown to significantly reduce the intestinal burden of uropathogenic *E. coli* in children between 1.5 and 16 years of age.[5] Treatment with this probiotic may therefore also help in reducing the risk of rUTI.

Second, among subjects with prior UTI, recurrent infections may arise from bacteria that are latent within the bladder epithelium. Common uropathogens such as *Escherichia coli* and *Klebsiella pneumoniae* have been shown to invade bladder epithelial cells and rapidly proliferate within intracellular bacterial communities (IBCs). [6–8] In the late stages of acute cystitis as modeled in mice, the bacteria enter into quiescent foci in the bladder epithelium where they may persist for months and reemerge to produce recurrent infections. Most of the traditional antibiotics fail to penetrate the epithelium and eradicate these quiescent intracellular bacteria. However, fluoroquinolones such as ciprofloxacin, given at sufficient

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doses and time of exposure, have intracellular accumulation above minimal inhibitory levels to eradicate intracellular *E. coli*.[9]

Children with normal urinary tract anatomy and function and highly recurrent UTI suffer from a lack of alternatives when antibiotic prophylaxis and "watchful waiting" approaches fail. Our pediatric urology and infectious diseases clinics have a large number of children who have failed these standard approaches to rUTI prevention. To fill this gap in medical care, we previously instituted a prophylactic strategy using the otherwise benign fluoroquinolone-probiotic combination with the goal of targeting the aforementioned mechanisms of recurrent infections. We now retrospectively reviewed the outcomes of ten of the first children receiving this combination therapy in an attempt to quantify a reduction in rUTI that was perceived by both clinicians and patient families.

Methods

After IRB approval, all patients previously managed with a fluoroquinolone-probiotic combination in the Pediatric Infectious Diseases clinic for rUTIs were identified. Their regimen included a 14-day course of ciprofloxacin (20 mg/kg) twice daily and 1 packet (250 mg) of *Saccharomyces boulardii* daily for 1 year. All patients were advised to consume one particular brand of the yeast in order to ensure that all patients received similar therapy. Prior to referral, all patients obtained a thorough evaluation by a pediatric urologist. In addition to the studies noted in Table 1, bladder and bowel dysfunction was assessed in all patients by using a validated dysfunctional elimination syndrome questionnaire.[10] In addition, stool character was quantified by documentation of the Bristol Scale. Patients were noted to be on stable bowel regimens for constipation prior to institution of the combination UTI prophylaxis regimen. Patients with symptoms of constipation were maintained on their bowel care regimen consisting of dietary changes to increase fiber intake and/or a stool softener. Compliance with bowel care and fluoroquinolone-probiotic regimen was determined by clinicians at outpatient visits approximately every 3 months by parental report of missed doses and tolerance of the regimen. Their medical charts were retrospectively evaluated for confirmation of a diagnosis of rUTI (>1 episode of a complicated or uncomplicated UTI within a year and at least 1 episode with records available to confirm a positive urinalysis (positive [leukocyte esterase OR nitrite] AND [≥5–10 WBC]) and a positive urine culture (≥50,000 CFU/ml), results of urologic evaluation, and absence of predisposing conditions (neurogenic bladder, VUR, spinal dysraphism) for inclusion. Patients with a history of voiding dysfunction or constipation were continued on their regimens. Patients with follow-up of <3 months were excluded.

Results

Ten patients referred to our clinic with a history of recurrent UTI met inclusion criteria. Their mean age was 8.2 years old (range 4–13). The mean number of UTIs in the year prior to initiation of therapy was 5.5 (range 2–10). No anatomical urologic abnormalities were noted on urologic evaluation (Table 1). All patients reported soft, regular stools with 80% taking maintenance medications for constipation. The most common reported symptom and sign from prior UTIs were dysuria and fever, respectively.

After institution of the antibiotic-probiotic combination, the median follow-up was 9 months (range 3–15). Four episodes of on-treatment recurrent UTI occurred among 3 patients, 2 of whom had reported therapeutic non-compliance. Among the patients with on-therapy recurrences, median follow-up was 10 months. Median follow-up in patients without rUTI was 7 months. It should be noted that each patient was followed well past their previously recorded average interval period between UTI episodes. There was a highly significant decrease in the total number of UTI episodes in all 10 patients before and after initiation of therapy (57 vs. 4; p=0.0001). In our cohort, 7 out of 10 patients (70%) were free of rUTIs during the follow-up period. Of the patients with known compliance, 7 out of 8 were free of rUTIs (88%).

Urinalysis and culture data prior to the initiation of therapy (where available) and with rUTI are reported in Table 2. Data were available for UTI episodes where care was obtained within the study health system. Prior to initiation of therapy, the most common UTI etiology was *E. coli,* followed by *K. pneumonia,* and *P. aeruginosa.* These pathogens had variable sensitivity to β-lactams but were uniformly sensitive to fluoroquinolones. Antibiotic susceptibility data were not available prior to therapy for 2 subjects. On-therapy rUTIs were due to *E. coli* (2; fluoroquinolone susceptibility unknown), enterococcus (1), and *C. freundii* (1; fluoroquinolone susceptible).

Discussion

The management of rUTI is challenging to pediatricians, emergency department physicians, and urologists, particularly for children without anatomic or functional urinary tract disease. Currently, no guidelines exist to guide initial evaluation and subsequent treatment of these children. Particularly important is the lack of strategies aimed at reducing recurrences. An understanding of the underlying factors predisposing patients to rUTI has been elusive and thus limits the employment of rational, effective therapies and guidelines. As a result, patients with rUTIs are exposed to multiple antibiotic courses which may portend a selection to multi-drug resistant organism and more complicated infections. Here we report our early experience with a clinical practice entailing 2 complementary therapies to target the known reservoirs of uropathogens responsible for rUTI and thus lowering rates of recurrence. In our patient cohort, 70% of children who had a history of highly frequent, recurrent UTIs did not experience rUTI within the therapeutic period we reviewed.

Our rational design for UTI prevention entails targeted reduction of uropathogenic bacteria within the reservoirs in which they reside and blocking their transition from reservoirs into the urinary tract. The intestinal and vaginal tracts are known reservoirs for uropathogenic bacteria, particularly *E. coli*, the leading cause of UTI. Hooton *et al* used molecular and antibiotic susceptibility patterns to identify clones of *E. coli* in the feces and vagina of adult healthy women 2 weeks preceding the eventual development of UTI with a matched *E. coli* strain.[11] Stapleton *et al* demonstrated a strong reciprocal relationship between levels of vaginal *Lactobacilli*, vaginal *E. coli,* and the development of recurrent UTI.[12]

Probiotics may have a role in reducing uropathogens in rUTI reservoirs. Administration of the probiotic yeast *S. boulardii* to 24 children resulted in a significant decrease in the number

of *E. coli* colonies and appropriately higher counts of *S. boulardii* in stool specimens.[5] A randomized study of 41 women diagnosed with UTI demonstrated that, after antimicrobial therapy for a UTI, women given *Lactobacillus* vaginal suppositories were approximately 50% less likely to develop rUTI than women given a placebo vaginal suppository.[13] Similarly a study in children with VUR also showed that the use of the probiotic *Lactobacillus acidophilus* resulted in a reduction in rUTIs at a rate comparable to the use of prophylactic antibiotics.[14] These data suggest that the reduction of uropathogen reservoirs and replacement by non-uropathogenic flora may have a role in reducing the risk for rUTIs. *Saccharomyces boulardii* has some advantage over *Lactobacillus* probiotics because of resistance to anti-bacterial antibiotics. This characteristic, combined with data on its reduction of uropathogenic *E. coli* in the gut reservoir, was the basis for its inclusion in a rUTI prophylactic regimen.

In the past decade and a half, intracellular quiescent bacteria in the bladder epithelium have entered into consideration as a source for recurrent UTI. Uropathogenic *E. coli* rapidly replicates in IBCs within the bladder epithelium and creates latent quiescent reservoirs in bladder epithelial cells that are viable even after many antibiotics.[7] In the murine UTI model, quiescent reservoirs of viable bacteria have been noted in the bladder epithelium for greater than 3 months after the initial infection with concurrent negative urine cultures.[15] These dormant bacteria have been proposed to serve as one source for recurrent infections. Although latent quiescent bacteria in the bladder epithelium have been challenging to demonstrate in humans, intracellular bacteria in the form of IBCs have been observed in shed bladder epithelial cells within urine of adults and children with UTI, suggesting that uropathogens routinely invade the bladder epithelium.[6–8] Prolonged fluoroquinolone administration capitalizes on the high cell penetration of this antibiotic class to eradicate these quiescent communities that may remain viable with shorter antibiotic courses or therapy with agents with poor tissue penetration.[9]

Our observations are limited in several ways. The non-controlled retrospective design limits the extent to which important variables were able to be quantified including therapeutic compliance and heterogeneity in care including constipation management. This combined with the small size limits the applicability to other cohorts. However, given the chronic nature of these patient symptoms, the highly significant difference between the total number of UTI episodes before and after initiation of therapy in this patient cohort and an increase in the interval without an infection and/or its symptoms this treatment regimen has the potential to improve the overall quality of life, decrease antibiotic courses and decrease health care costs. Based on our observations from this retrospective review, we plan to further validate these results with a larger cohort of patients in a prospective, randomized trial.

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Table 1

Patient Characteristics and Clinical Findings

Patient Number	Age (years)	Gender	Urologic Evaluation	Number of UTIs prior to therapy	Signs and Symptoms reported	Number of recurrences	Follow-up (months)
1	4	F	VCUG -, RUS -	2	Fever + Malodourous urine	0	7
2	5	F	VCUG -, RUS -	10	Fever + Vomiting	1	5
3	6	F	VCUG -, RUS -	4	Fever + Dysuria	0	6
4	6	F	VCUG -, RUS -, MAG3 -	6	Fever + Dysuria	0	10
5	8	F	VCUG -, RUS -, MAG3 -	5	Urgency + Dysuria + Abdominal pain	0	7
6	9	F	RUS -	5	Dysuria + Malodorous urine	2	10
7	10	M	RUS -	5	Fever + Dysuria + Vomiting	0	13
8	10	F	VCUG -, RUS -, MAG3 -, UDS -	8	Fever + Abdominal pain	1	15
9	11	M	VCUG -, RUS -	5	Urgency + Dysuria	0	11
10	13	F	VCUG -, RUS -, UDS -	5	Increased frequency + Dysuria	0	3

*UDS - Urodynamics, RUS - Renal Ultrasound, VCUG - Voiding Cystorurethrogram

Table 2

Urinalysis and microbiologic data prior to the start of combined therapy.

Patient Number	Urinalysis result	Predominant Organism	Fluoroquinolone sensitivity
1	1 episode: nitrite and LE +	*E. coli, K. pneumoniae*	Sensitive
2	NA	*E.coli*	Sensitive
3	NA	*E.coli*	NA
4	2 episodes: nitrites and LE +	*E. coli, P. aeruginosa*	Sensitive
5	3 episodes: blood and LE +	*E. coli, K. pneumoniae*	NA
6	3 episodes: >6 WBC/hpf or LE +	*E. coli*	Sensitive
7	5 episodes: blood or nitrites	*E. coli* (including ESBL *E. coli*)	Sensitive
8	4 episodes: blood or nitrite	*E. coli, K. pneumoniae*	Sensitive
9	3 episodes: nitrites and LE +	*E. coli*	Sensitive
10	3 episodes: blood and LE +	*E. coli, P. aeruginosa*	Sensitive

NA = Not Available, LE = Leukocyte esterase