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Efficacy of Fluoroquinolone/Probiotic Combination Therapy for Recurrent Urinary Tract Infection in Children: A Retrospective Analysis

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ABSTRACT

Purpose: Children with normal urinary tract anatomy and function and highly recurrent urinary tract infection (rUTI) may have a lack of alternatives when antibiotic prophylaxis and "watchful waiting" approaches fail. This retrospective review reports the outcomes in children who received a fluoroquinolone/probiotic combination in an attempt to quantify a reduction in rUTI that was perceived by both clinicians and patients' families.

Methods: Data from all children with rUTIs previously managed with a fluoroquinolone/probiotic combination at the Pediatric Infectious Diseases Clinic at Duke University Medical Center (Durham, North Carolina) were identified and analyzed.

Findings: Data from 10 children were eligible for inclusion. Compared with before therapy initiation, total UTI episodes were significantly fewer after therapy initiation (57 vs 4; $P = 0.0001$). Seven (70%) were free of rUTIs during the follow-up period. Of the 8 patients with known compliance, 7 (88%) were free of rUTIs.

Implications: Given the chronic nature of these patients' symptoms, the significant decrease in UTI after the initiation of therapy, and the increase in the interval without an infection and/or its symptoms, this treatment regimen has the potential to improve overall quality of life, decrease antibiotic courses, and decrease health care costs in children with rUTI. These results will be validated with a larger cohort of patients in a prospective, randomized trial. (*Clin Ther.* 2015;▮:▮▮▮–▮▮▮)

Key words: children, fluoroquinolone, probiotics, recurrent urinary tract infections.

INTRODUCTION

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

Two primary sources of rUTI have been proposed. First, the intestinal and vaginal tracts have been well established as reservoirs of uropathogenic bacteria such as *Escherichia coli* that recurrently ascend into the urinary tract via the urethra. Probiotic organisms may alter the flora in the intestinal and vaginal tracts to reduce or resist pathogens. The probiotic yeast *Saccharomyces boulardii* has been reported to significantly reduce the intestinal burden of uropathogenic *E coli* in children aged 1.5 to 16 years.[5] Treatment with this probiotic may therefore also help in reducing the risk for rUTI. Second, among patients with prior UTI, recurrent infections may arise from bacteria that are latent within the bladder epithelium. Common

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uropathogens such as *E coli* and *Klebsiella pneumoniae* have been reported to invade epithelial cells in the bladder and rapidly proliferate within intracellular bacterial communities.[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 infection. Most of the conventional antibiotics fail to penetrate the epithelium and eradicate these quiescent intracellular bacteria. However, fluoroquinolones such as ciprofloxacin, given at sufficient doses and durations of exposure, have intracellular accumulation above minimal inhibitory concentrations to eradicate intracellular *E coli*.[9]

Children with normal urinary tract anatomy and function and highly recurrent UTI may have a lack of alternatives when antibiotic prophylaxis and "watchful waiting" approaches fail. The Pediatric Urology and Infectious Diseases clinics at Duke University Medical Center (Durham, North Carolina) have a large number of children who have failed these standard-of-care 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 infection. We retrospectively review the outcomes of 10 of the first children who received this combination therapy in an attempt to quantify a reduction in rUTI that was perceived by both clinicians and patients' families.

MATERIALS AND METHODS

After approval of the protocol of this retrospective review was received from the Duke University Institutional Review Board, all patients with rUTIs previously managed with a fluoroquinolone/probiotic combination at the Pediatric Infectious Diseases Clinic were identified. Their regimens included a 14-day course of ciprofloxacin 10 mg/kg BID and 1 packet (250 mg) of *S boulardii* daily for 1 year. All patients were advised to consume 1 particular brand of the yeast to ensure that all patients received similar therapy. Before referral, all patients underwent a thorough evaluation by a pediatric urologist. In addition to the studies noted in Table I, bladder and bowel dysfunction were assessed in all patients using a validated dysfunctional elimination syndrome questionnaire.[10] In addition, stool character was quantified by documentation of the Bristol Scale. Eligible patients were on stable anticonstipation regimens before the institution of the combination UTI prophylaxis regimen. Patients with symptoms of constipation were maintained on their bowel-care regimens, consisting of an increased intake of dietary fiber and/or a stool softener. Compliance with bowel care and the fluoroquinolone/probiotic regimen was determined by clinicians at outpatient visits approximately every 3 months by parental report of missed doses and tolerability of the regimen. Medical records were retrospectively evaluated for eligibility, including 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 white blood cells per high-power field]) and a positive urine culture (≥50,000 colony-forming units per milliliter), results of urologic evaluation, and absence of predisposing conditions (neurogenic bladder, vesicoureteral reflux, and spinal dysraphism). Patients with a history of voiding dysfunction or constipation were continued on their regimens. Patients with a duration of follow-up of <3 months were excluded.

RESULTS

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

The median duration of follow-up after the institution of the antibiotic/probiotic combination was 9 months (range, 3–15 months). Four episodes of on-treatment rUTI occurred among 3 patients, 2 of whom had therapeutic noncompliance reported. Among the patients with on-therapy recurrences, the median duration of follow-up was 10 months. The median duration of follow-up in patients without rUTI was 7 months. Each patient was followed up well past their previously recorded mean interval between UTI episodes. Compared with before therapy initiation, total UTI episodes were significantly fewer after therapy