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ORIGINAL ARTICLE

Treatment of recurrent complicated urinary tract infections in children with vesicoureteral reflux

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Background: Urinary tract infections (UTIs) in children with vesicoureteral reflux (VUR) are often caused by uropathogens with a high rate of drug resistance and are associated with a high rate of recurrence with a single pathogen. In this study, we evaluated the incidence of recurrent UTI and the drug resistance pattern of *Escherichia coli* in children with VUR. We also evaluated whether combination therapy comprising fosomycin plus one other antimicrobial agent is effective for treatment of recurrent UTIs.
Methods: We retrospectively reviewed the medical records of all children with VUR who developed at least one episode of UTI during the period January 1, 2003 to December 31, 2013 at a single medical center. The effectiveness of fosfomycin plus amikicin for *Enterobacteriaceae* or ceftazidime for *Pseudomonas aeruginosa* infections was prospectively studied in six children with recurrent relapsing UTIs.
Results: The study population comprised 129 children (age range, from 1month to 15 years; mean ± standard deviation, 2.37 ± 2.91 years) with VUR who developed at least one UTI during the 10-year study period; 68 (52.7%) had recurrent UTIs. The presence of an underlying urinary tract anomaly was predictive of recurrence ($p = 0.028$). The rates of susceptibility of *E. coli* to

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cefazolin ($p < 0.001$) and cefotaxime ($p < 0.001$) were significantly lower in patients with recurrent UTIs. Combination therapy with fosfomycin plus amikacin or ceftazidime was shown to be an effective therapeutic option for recurrent UTIs due to a single uropathogen.
Conclusion: The rates of susceptibility of *E. coli* to commonly used antimicrobials were significantly lower in children who developed more than one episode of UTI. The empiric choice of cefazolin or cefotaxime was usually ineffective. Administration of fosfomycin plus amikacin or ceftazidime was an effective therapeutic and preventive strategy in children with VUR and recurrent relapsing UTI.

Introduction

Urinary tract infections (UTIs) are one of the most common bacterial diseases in children, with a prevalence rate of 7.0% among febrile infants.[1] Recurrent UTI is a major cause of renal scarring, which can cause hypertension, chronic renal failure, and end-stage renal disease.[2,3] Vesicoureteral reflux (VUR) is diagnosed in 18–40% of children who are investigated for a first episode of UTI. These children are at an increased risk of developing recurrent urinary tract and kidney infections, which, over time, can result in renal damage.[2,3] Risk factors of recurrent UTI in children with VUR include high reflux grade, delayed contrast passage on voiding cystourethrograms, bilateral VUR, and age < 1 year.[3–5]

Preventive strategies to reduce the risk of acute infection and renal injury in children with VUR include the administration of prophylactic antibiotics, endoscopic injection of dextranomer hyaluronic acid, antireflux surgery, maintenance of good perianal hygiene, and adequate hydration.[6] However, breakthrough infections due to drug-resistant uropathogens sometimes occur, leading to significant morbidity.

Management of recurrent UTIs in children with VUR is difficult. Our hypothesis is that multiple factors may lead to treatment failure in patients with recurrent UTI, including drug-resistant uropathogens, the mechanism and duration of antibiotics, surgical damage, and biofilm formation. The aims of this study were to evaluate the incidence of recurrent UTI among children with VUR, to evaluate the incidence of drug resistance among *Escherichia coli* isolates from children with recurrent UTI, and to initiate a pilot study to evaluate the therapeutic effectiveness of fosfomycin for preventing recurrent UTI.

Methods

We retrospectively enrolled all children who were treated for a first episode of UTI and who subsequently received a diagnosis of VUR at the Taichung Veterans General Hospital, a 1200-bed tertiary hospital in central Taiwan, during the period from January 1, 2003 to December 31, 2013. Risk factors for recurrence, causative uropathogens, and antimicrobial susceptibility test results were obtained from the medical records.

Children with VUR were separated into a recurrent UTI group or a nonrecurrent UTI group. Clinical parameters for statistical analysis included gender, age, grade of VUR, and additional urinary tract anomalies. The degree of reflux on voiding cystourethrography was determined according to the International Reflux Study classification.[7] Additional urinary tract anomalies included ureteropelvic junction stenosis, renal collecting system anomalies (duplication, renal dysplasia, or ureterocele), bladder exstrophy, and neurogenic bladder. Children with recurrent UTI were also stratified into a reinfection or relapse group. Receipt of surgical intervention including endoscopic injection of dextranomer hyaluronic acid or antireflux open surgery was also evaluated.

A UTI was defined in this study as a single pathogen with adequate colony forming units (CFU)/mL cultured from a urine specimen obtained from voiding urine (> 100,000 CFU/mL), catheterized urine (> 10,000 CFU/mL), or suprapubic puncture (> 1000 CFU/mL).[8] Recurrent UTI was defined as significant bacteriuria in children with fever or dysuria during a 12-month follow-up period. Reinfection was defined as a recurrent UTI with a new bacterial isolate and relapse was defined as a recurrent UTI with the same bacterial isolate as the primary isolate.

E. coli is the most common cause of community-acquired UTI in children. In this study, children with UTI due to *E. coli* were divided into a first episode group or a recurrent episode group. Sensitivity of isolates to ampicillin, cefazolin, gentamicin, amikacin, trimethoprim–sulfamethoxazole, cefotaxime or ceftazidime, cefepime, ciprofloxacin, meropenem, and piperacillin–tazobactam was tested *in vitro* using the disk diffusion method according to the Clinical and Laboratory Standards Institute standards.[9]

In our pilot study to evaluate the therapeutic effectiveness of fosfomycin for preventing recurrent UTI, we prospectively recruited six children with VUR and recurrent UTI. Patients with UTI due to *Enterobacteriaceae* species were administered fosfomycin 100–200 mg/kg/d every 8 hours for 7–10 days plus amikicin 15 mg/kg/d every 12 hours for 5 days. Patients with UTIs caused by *Pseudomonas aeruginosa* were given fosfomycin 100–200 mg/kg/d every 8 hours for 7–10 days plus ceftazidime 100–150 mg/kg/d every 8 hours for 7–10 days.

Statistical analysis

Ordinal variables are expressed as means ± standard deviation (or median, range) and were compared between