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# Effective endoscopic diagnosis and treatment of pediatric occult vesicoureteral reflux with intermediate to long-term follow-up

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**Abstract** *Purpose:* Recurrent febrile urinary tract infections (fUTIs) in children with non-diagnostic voiding cystourethrogram (VCUG) are challenging, as misdiagnosis can lead to renal damage and increased morbidity. We compared fUTI rates before and after endoscopic treatment of patients with suspected occult VUR.
*Methods:* Between January 2009 and December 2012, children with history of fUTI and non-diagnostic VCUG(s) underwent endoscopic ureteral hydrodistention (HD) and injection of dextranomer hyaluronic acid co-polymer (Dx/HA). fUTI rates before and after intervention were evaluated. Demographics, imaging and endoscopic findings were assessed.
*Results:* Thirty-four children (mean age 5.4 ± 2.8 years) underwent bilateral Dx/HA injection for occult VUR. Average follow-up was 28.8 months. Seventeen children had renal scarring. Mean ureteral HD grade was 2.2/3. HD grade for ureters associated with renal scarring was significantly ($p < 0.05$) higher (2.6/3) than those without scarring (2.0/3). Mean injected volume was 1.2 mL. Ureters associated with renal scarring ($n = 21$) required significantly ($p < 0.05$) higher volumes (1.4 mL) than those without scarring ($n = 47$; 1.1 mL). Prior to intervention, the fUTI rate was 0.15/patient/month compared to just 0.02 after treatment ($p < 0.0001$).

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*Conclusions:* Incidence of fUTIs significantly decreased following treatment, supporting the use of Dx/HA injection in carefully selected children when the suspicion for occult VUR is high.


## Introduction

Vesicoureteral reflux (VUR) is one of the most common urologic diagnoses affecting children, with an estimated prevalence of 0.4—1.8% in the general pediatric population and 30% in those with a history of febrile urinary tract infection (fUTI) [1,2]. Pyelonephritis, with or without documented VUR, can lead to renal scarring and subsequent complications such as hypertension, proteinuria, and chronic kidney disease [3,4]. Voiding cystourethrogram (VCUG) is the gold standard for detection of VUR despite false negative rates up to 15—20% [5,6]. While sensitivity is improved with cyclic studies, VUR is frequently an intermittent phenomenon and cyclic VCUGs do not employ continuous monitoring and are not routinely performed.

Given the sensitivity of standard VCUG, it is conceivable to neglect clinically significant VUR despite appropriate evaluation. Treatment of occult VUR with continuous antibiotic prophylaxis or anti-reflux surgery diagnosed by positional instillation of contrast (PIC) cystogram has been shown to reduce the rate of febrile urinary tract infections in children [7]. The likelihood of PIC-VUR has been associated with patulous and laterally displaced ureteral orifices [8]. We assessed the clinical outcomes of children with occult VUR diagnosed by endoscopic ureteral hydrodistention (HD), without the use of fluoroscopy, and treated exclusively with injection of dextranomer hyaluronic acid co-polymer (Dx/HA).

## Materials and methods

Between January 1, 2009, and December 31, 2012, 34 children with a history of fUTI and non-diagnostic VCUG (i.e., suspected occult reflux) underwent endoscopic ureteral HD and injection of Dx/HA. The patient cohort included 18 patients (53%), who were followed in our continence center for bladder and bowel dysfunction (BBD). BBD included urinary frequency and urgency, prolonged voiding intervals, daytime wetting, holding maneuvers, constipation, and encopresis. Children were managed with a strict bowel regimen, which consisted of polyethylene glycol 3350 (MiraLax) and a minimum of 5—10 min of toilet time to allow for complete rectal evacuation. All patients were also counseled on timed voiding every 2 h as well as dietary modifications.

Upon receiving institutional review board approval, the electronic medical charts of these patients were retrospectively reviewed. Surgical indications included recurrent fUTIs ± renal parenchymal defects ("scarring") seen on technetium-99m dimercaptosuccinic acid scan (DMSA), renal ultrasonography, magnetic resonance urography (MRU), or computerized tomography (CT). HD grade was prospectively assigned at the time of cystoscopy and all ureters were injected using the double HIT method [9]. Febrile UTI rates before and after surgical intervention were compared. Demographics, imaging and endoscopic findings were also evaluated. All children underwent VCUG in evaluation of fUTI(s) preoperatively. Febrile UTI was defined as culture documented infection associated with a temperature of $\geq$38.5 °C. Children with prior documented VUR were excluded from study.

The fUTI rate was calculated as the number of culture-proven febrile UTIs per patient per month. The preoperative interval was defined as time from initial fUTI to date of surgery. Follow-up interval was defined as the time from endoscopic intervention to time of last clinical encounter, including nurse phone calls from parents regarding patient status. Statistical analysis (*t* test and chi-square test) was performed using SAS 9.2, with $p < 0.05$ representing statistical significance. Rates were tested by the patient—month scale. Univariate analysis was performed, but adjustment by gender or other patient characteristics was not performed. The denominator size was represented in the estimation of the rate. We hypothesized that the fUTI was more related to VUR rather than individual patients; therefore, patients were analyzed before and after surgery independently. Exact methods were utilized to compare two Poisson rates. The uniformly most powerful unbiased test on the ratio of rates of two Poisson counts with a given time was used where the null hypothesis is whether the ratio of the first rate divided by the second rate equals 1. The rate ratio (pretreatment incidence rate of fUTI/postoperative incidence rate of fUTI) was used to compare the likelihood of fUTI before versus after treatment, and to test whether there was a difference in fUTI rates between the two time intervals. The rate ratio represented statistical significance if the 95% confidence interval did not include unity, "1".

## Results

Thirty-four children (31 females, 3 males) underwent cystoscopy and bilateral Dx/HA injection for suspected occult VUR during the 4-year study period. All male patients were circumcised in the neonatal period prior to initial fUTI. Mean age at the time of surgery was 5.4 ± 2.8 years. Mean number of non-diagnostic VCUGs per patient was 1.47 (range 1—5). Mean time from initial fUTI to surgery was 24.2 months (range 2—116 months). The double hydrodistention implantation technique (HIT) method was utilized for all 68 ureters. Mean ureteral HD grade was 2.2/3. Average injected volume of Dx/HA was 1.2 mL (range 0.5—2 mL). No complications were encountered. Average postoperative clinical follow-up was 28.8 months (range 8—50 months).

Twenty-three children (67.6%) experienced no postoperative fUTIs. There was no statistically significant