

# Outcome After Discontinuing Prophylactic Antibiotics in Children With Persistent Vesicoureteral Reflux

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## Abbreviations and Acronyms

DMSA = technetium-dimercaptosuccinic acid

UTI = urinary tract infection

VCUG = voiding cystourethrogram

VUR = vesicoureteral reflux

Study received institutional review board approval.

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**Purpose:** Treatment for vesicoureteral reflux remains controversial. Lacking an evidence-based treatment protocol, we offered the option of terminating prophylactic antibiotics in otherwise healthy patients with persistent vesicoureteral reflux at age 5 years or greater. We report outcomes with respect to the urinary tract infection incidence and to whether surgical intervention was eventually done.

**Materials and Methods:** We obtained institutional review board approval to retrospectively review the records of all children with vesicoureteral reflux from December 1999 to February 2009. Of this group we selected children 5 years old or older who had been taken off prophylactic antibiotics. We assessed children with primary vesicoureteral reflux in detail.

**Results:** The records of 1,217 that we reviewed showed that antibiotics were discontinued in 185 patients, including 160 girls (89%) and 25 boys (11%), at an average age of 6.2 years. Average followup was 2.0 years with recorded followup up to 8 years off prophylaxis. In 50 girls (91%) and 5 boys (9%), urinary tract infection developed after discontinuing prophylaxis. Correction was done in 57 patients, including open repair in 34 and endoscopic injection in 23. Two patients underwent intervention at parent request after an average of 0.7 years of uneventful observation. We identified no parameter predicting patients at risk for urinary tract infection.

**Conclusions:** Urinary tract infection develops in 29% of patients 5 years old or older with persistent vesicoureteral reflux within 2 years after the cessation of prophylaxis. Most of these cases are febrile. Discontinuing antibiotics is reasonable but a prospective, randomized, long-term, multi-institutional trial is required to determine whether this approach is beneficial.

**Key Words:** bladder, ureter, vesico-ureteral reflux, urinary tract infections, antibiotic prophylaxis

VESICoureteral reflux affects up to 1% of the pediatric population and increases the likelihood of pyelonephritis with possible long-term renal complications, such as scarring, hypertension or chronic renal insufficiency.<sup>1</sup> Open ureteral reimplantation has a 95% to 99% success rate but successful VUR treatment may not prevent future pyelonephritis episodes.<sup>1,2</sup> Definitive VUR cor-

rection in females does not necessarily prevent subsequent cystitis and/or pyelonephritis during pregnancy.<sup>3</sup> With the knowledge that surgical correction for VUR may not prevent future morbidity in this population and due to the lack of an evidence-based treatment protocol, we began to offer the option of terminating prophylactic antibiotics in otherwise healthy patients with persis-

tent primary VUR at age 5 years or greater. We present our experience with discontinuing prophylactic antibiotics in this population with respect to UTI and ultimate surgical correction for VUR.

## MATERIALS AND METHODS

We obtained institutional review board approval to retrospectively review the charts of all patients in whom an ICD-9 diagnosis of VUR (593.70) was established. Data were available from December 1999 to February 2009. Only patients with primary VUR were included in analysis. Of this group we selected for detailed assessment only patients 5 years old or older with persistent VUR who had been taken off prophylactic antibiotics. Study inclusion criteria were the ability to communicate UTI symptoms and normal voiding patterns determined by history before prophylaxis termination. According to our protocol no VCUG is done after age 4 years and antibiotics are discontinued at age 5 years. After the termination of prophylactic antibiotics asymptomatic patients are followed at least annually with renal/bladder ultrasound, blood pressure for detailed assessment and urinalysis. VCUG is repeated after discontinuing prophylaxis if the patient has had 1 febrile UTI, defined as fever 101.5F or greater, positive urine culture with or without flank pain and with or without nausea/vomiting, or recurrent cystitis, defined as 3 positive urine cultures with irritative voiding symptoms and absent fever in 6 months. Particular attention was directed toward gender, VUR presentation (pyelonephritis vs cystitis evaluation), laterality, VUR grade at diagnosis, time of antibiotic discontinuation and history of successfully treated dysfunctional voiding to assess whether any of these factors increased the chance of subsequent UTI after terminating prophylactic antibiotics. The effect of these factors was analyzed using the log rank test and Cox proportional hazards regression. SAS® PROC LIFETEST was used for all calculations with  $p < 0.05$  considered statistically significant.

## RESULTS

Level 4 evidence is presented. To date 1,217 patients with an ICD-9 diagnosis of VUR have been identified, of whom 778 have primary VUR. We identified 214 patients 5 years old or older with persistent VUR, including 160 girls (89%) and 25 boys (11%) whose parents elected to terminate prophylactic antibiotics. Of the 185 patients 142 (75%) and 32 (17%) were diagnosed with VUR and recurrent cystitis, respectively, after evaluation for febrile UTI. A total of 105 patients (57%) had bilateral VUR at diagnosis with an average grade of 2.4 on each side (right and left sides range 1 to 5). Patients were on prophylaxis an average of 2.9 years. Antibiotics were terminated at an average age of 6.2 years (median 5.9) and average followup while off antibiotic prophylaxis was 2.0 years (range 0.1 to 8.0). Although we begin taking children off antibiotics at age 5 years, most

are not taken off until followup after the fifth birthday. Based on the most recent VCUG 78 of 185 children (42%) still had bilateral VUR at antibiotic cessation with an average grade of 2.1 on each side (right and left sides range 1 to 5 and 1 to 4, respectively). Of patients taken off antibiotics 47 (25%) were previously treated for dysfunctional voiding.

After discontinuing antibiotic prophylaxis UTI ultimately developed in 55 patients (29%), including 42 girls (90%) and 5 boys (10%) with a febrile UTI at an average of 1.1 years (range 0.1 to 5.3) after antibiotic cessation. Recurrent cystitis developed in 8 girls with the first infection an average of 1.8 years (range 0.1 to 5.2) after antibiotic cessation. Of the patients 48 (87%) were originally diagnosed with VUR after evaluation for febrile UTI. Of 55 children 35 (61%) had bilateral VUR at diagnosis with an average grade of 2.4 on the right and 2.5 on the left side (each range 1 to 4). At antibiotic cessation average patient age was 6.1 years (median 6.0) and average followup off prophylaxis was 2.8 years (range 0.5 to 8). Of the 55 patients 29 (52%) had bilateral VUR at antibiotic termination with an average grade of 2.3 on the right and 2.2 on the left side (each range 1 to 4). Of the 55 patients taken off antibiotics 14 (25%) were ultimately treated for dysfunctional voiding.

On univariate and multivariate analysis no variable, including gender ( $p = 0.76$ ), VUR presentation ( $p = 0.27$ ), laterality ( $p = 0.84$ ), VUR grade at diagnosis ( $p = 0.69$ ), VUR grade when antibiotics were discontinued ( $p = 0.25$ ) and dysfunctional voiding history ( $p = 0.93$ ), showed statistical significance in regard to who would have a UTI after being taken off prophylaxis. Only multivariate analysis  $p$  values are presented.

Surgical correction for VUR was ultimately done in 57 patients after discontinuing antibiotics. Two asymptomatic patients underwent intervention at parent request at an average of 0.7 years of observation. Open surgical and endoscopic correction for VUR was done in 34 and 23 patients, respectively. We routinely perform postoperative VCUG approximately 3 months after surgical intervention to correct VUR. Six patients had persistent VUR after attempted surgical correction and all received endoscopic injection. Two patients with negative postoperative VCUGs had recurrent cystitis. To date at an average followup of 1.2 years (range 1 month to 6.7 years) no patient has had a febrile UTI after successful correction for VUR and none was diagnosed with HTN while on or after being taken off prophylaxis.

## DISCUSSION

Treatment for persistent VUR in an otherwise asymptomatic, toilet trained child is controversial.

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