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Compliance with Antibiotic Prophylaxis in Children with Vesicoureteral Reflux: Results from a National Pharmacy Claims Database

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Abstract

Purpose—Antibiotic prophylaxis (AP) is commonly used for medical management of vesicoureteral reflux (VUR). Little information exists on AP compliance in VUR patients.

Materials and Methods—We queried the Innovus i3 pharmacy claims 2002–2007 database for children ≤18yrs with VUR (ICD-9 code 593.7, plus claim for cystogram) and analyzed those with at least 1yr of follow-up data. Criteria for management with AP were ≥two 30-day supply antibiotic prescriptions or ≥four 14-day supply prescriptions if the antibiotic was a penicillin or cephalosporin. AP compliance was determined using a medication possession ratio, an estimate of the proportion of time that patients have a prescribed drug available for use. Compliance was established as a medication possession ratio of ≥80%, meaning coverage with AP for ≥80% of the year.

Results—5,342 out of 9,496 VUR patients (56.3%) were managed on AP. Most patients were female (81%) and ≤5yrs old (79%). Trimethoprim/sulfonamides were most commonly prescribed (62%); antiseptics were next (24%). 40% of patients on AP were compliant. Compliance was lower for 6–10yr olds (OR .71, 95CI 0.61–0.83) and 11–18yr olds (OR 0.56, 95CI 0.41–0.79) compared to younger children (≤5yrs). Increased compliance was associated with ≥1 hospitalizations (OR 1.70, 95CI 1.48–1.97) and ≥1 urologist visits (OR 1.41, 95CI 1.25–1.58).

Conclusions—40% of VUR patients on AP are compliant, with young age, frequent hospitalization, and specialist visits associated with compliance. This knowledge may help to develop effective interventions to improve compliance and underscores the importance of reporting compliance in clinical studies evaluating the utility of AP in VUR management.

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Keywords

vesicoureteral reflux; antibiotics; prophylaxis; compliance; outcome

INTRODUCTION

Antibiotic prophylaxis (AP) is commonly used for medical management of vesicoureteral reflux (VUR), yet little data exists on patient compliance with AP. VUR may predispose an individual with a bladder infection to pyelonephritis.^{1–3} The goal of intervention for VUR is prevention of pyelonephritis and its possible long term sequelae.

Since 5%–13% of patients with VUR spontaneously resolve their reflux on a yearly basis one management option is maintenance of urine sterility through daily AP until VUR resolution occurs.^{4, 5} However, recently studies have shown UTI, pyelonephritis, and renal scarring rates are not statistically different among VUR patients receiving AP and those not.^{6–8} One possible explanation for these findings is patient noncompliance with AP.

Defining compliance with AP is of increasing importance since noncompliance can be misconstrued as failure of a treatment regimen and potentially lead to unnecessary changes in management. The objectives of this study were to estimate compliance with AP and identify factors associated with noncompliance in children managed on AP for VUR.

METHODS

Study Design

We performed a retrospective study examining AP compliance in VUR patients using insurance claims data from 2002–2007.

Data Source

We used the Innovus i3 database, a private, national pharmacy and medical claims database managed by Ingenix, a wholly-owned subsidiary of UnitedHealth Group. The database was purchased for use by the Urologic Diseases in America Project. The claims data is derived from the UnitedHealthcare family of health insurance plans which operates in all 50 states, although we do not have information regarding the specific geographic distribution of the database population. There are greater than 39 million patients with longitudinal follow-up data over a five-year period within this database. Innovus i3 has information on demographic characteristics, diagnoses, procedures performed, medications administered, radiographic studies executed, and hospitalizations. Diagnoses were defined via ICD-9 codes. Procedures and radiographic studies were delineated by CPT codes. Prescription information included prescribing physician, drug prescribed, dose, duration, and refills obtained.

Study Population

Patients included in this study met the following criteria: 1) Age was ≤ 18 years, 2) ICD-9 diagnosis of VUR was present (593.70–593.73), 3) Fluoroscopic (CPT 74455) or nuclear (CPT 78740) VCUG was performed, and 4) at least one year of follow-up was maintained in the database after VUR diagnosis. We excluded patients with codes for ureterocele and ureteral obstruction (753.2), neurogenic bladder and spina bifida (596.5, 741), posterior urethral valves (753.6), bladder exstrophy (753.5), renal transplant (V42), and prune belly syndrome (756.71). Patients meeting these criteria were classified as on AP by the presence of $\geq$ two 30-days supply antibiotic prescriptions or four 14-days supply antibiotic

prescriptions if the antibiotics were penicillins or cephalosporins. Penicillins and cephalosporins were allowed this exception since when prescribed as suspensions they typically require refills every 14 days. Patient weight was not indicated in the database which prevented us from identifying patients on AP by the typical features of low-dose, once-daily administration since drug dosing in children is based on weight.

We grouped antibiotics into five categories including: Trimethoprim/Sulfonamides, Antiseptics, Penicillins, Cephalosporins, and Other. Antibiotics within Trimethoprim/Sulfonamides included trimethoprim and sulfonamides prescribed alone and in combination. Antiseptics were composed of nitrofurantoin and methenamine mandelates. The Other category consisted of macrolides, quinolones, and tetracyclines. In determining the most frequently prescribed antibiotics, multiple refill prescriptions of the same antibiotic in an individual patient were counted only once.

Outcomes

The primary outcome measure was compliance with AP in the setting of VUR. Compliance was determined using a medication possession ratio (MPR), the number of days of prescription supply in an observation period divided by the total days in the observation period. Compliance was established as a $MPR \geq 80\%$ since this is a common cut point used in the literature.⁹ This signifies that the patient had coverage with AP for $\geq 80\%$ of the observation period.

The observation period was one year as this is a frequent duration cited in other studies.^{9, 10} After meeting the inclusion criteria, the fill date of the first 14-day or 30-day antibiotic prescription marked the initiation of the 365-day observation period. Patients with a breakthrough UTI or other infection were not excluded. Antibiotics taken for acute infection contributed to the total days supply of antibiotic. When patients crossed over to antireflux surgery, the observation period was adjusted to the length of time between the first fill date and the date of surgery. Also since patients do not typically take their own medications while hospitalized, the MPR was adjusted for days of hospitalization by adding the number of days hospitalized to the “total days of prescription supply” in the numerator.

Exposure Variables

Exposure variables were defined a priori, based on the literature^{11–14}, as age, gender, hospitalizations, specialist visits, and presence of UTI.

Age was categorized into groups based on previous American Urological Association VUR guidelines for preschool children (ages 1–5) and school children (ages 6–10).¹⁵ We extended the range for preschool children to include infants (birth to one year of age) and added a third category (ages 11–19) in order to evaluate all children (age ≤ 18) with VUR managed on AP.

The variables for hospitalizations, specialist visits, and presence of UTI were dichotomized. Patients were considered positive for hospitalization if at least one inpatient hospitalization for any reason occurred during the observation period. Outpatient surgery and emergency room visits were not included as hospitalizations. Similarly, patients with a minimum of one visit to a urologist were categorized as having contact with a urologic specialist.

We captured UTI through the presence of ICD-9 coding for UTI or pyelonephritis (ICD-9 codes 590.0, 590.1, 590.2, 590.3, 590.8, 590.9, 595.0, 595.2, 595.9, 599.0, 771.82), an office visit, and the presence of a short-duration antibiotic prescription (days supply <14 days). Patients were considered positive for UTI if they had ≥ 1 infection of the urinary tract during the study period.

Statistical Analyses

Summary statistics were performed using frequencies and proportions for categorical variables and means and medians for continuous variables. Bivariate analyses were completed with the chi-square test of independence for categorical variables and the t test for continuous variables. The primary outcome measure of compliance was created by dichotomizing the MPR into <80% (noncompliant) and ≥80% (compliant). For multivariate modeling, covariates hypothesized to have clinical significance in relation to the outcome were included in the final model. Multivariate logistic regression was performed to determine factors associated with compliance. Statistical analyses were performed using SAS®, version 9.1 software (SAS Institute, Cary, NC). All analyses were two-sided and $p < 0.05$ was statistically significant.

RESULTS

Clinical Characteristics

From 2002–2007 a total 9,496 patients ≤18 years of age met the inclusion criteria for study entry. 5,342 patients (56.3%) were managed on AP (Figure 1). The majority of the patients were five years or younger and female (Table 1). VUR management was performed entirely by a primary care physician in 40% of the patients.

Physicians overwhelmingly prescribed Trimethoprim/Sulfonamides (Figure 2). Antiseptics were the second most commonly prescribed class with greater than 99.9% of this class consisting of nitrofurantoin. Less than 4% of the population received 14-days supply AP prescriptions. Eighty percent of the children were maintained on the same AP over an entire year period. Approximately 50% of the cohort remained without UTI on AP. Nineteen percent of the population required inpatient hospitalization over the study period.

Compliance with AP

Overall, 40% of the patients on AP achieved an MPR ≥80% and were classified as compliant with AP over the one year period. MPR may vary by agent tolerability; ninety-eight percent of the patients that were prescribed only nitrofurantoin were noncompliant. Figure 3 illustrates that increased age was significantly associated with decreased compliance. On multivariate analysis assessing for factors associated with compliance, older age remained strongly associated with noncompliance (Table 2). Increased compliance was associated with ≥1 hospitalization and ≥1 urologist visit. Increased compliance was not associated with a lack of UTI.

DISCUSSION

In this large, longitudinal database study we found that more than half the patients managed on AP were noncompliant. We identified that younger age, hospitalizations, and specialist visits were associated with improved AP compliance.

The poor overall compliance is not surprising as adherence with chronic medication usage is known to be poor. For example, adherence to inhaled corticosteroids decreased from 73% at 4 months to 59% at 12 months in a prospective cohort study of pediatric asthma patients.¹⁶ Poor adherence rates are also true in the setting of clinical trials. Approximately 25% of children were not adherent to therapeutic regimens in the PENTA 5 randomized controlled trial evaluating the treatment of HIV with highly active antiretroviral therapy.¹⁷

One additional study evaluating compliance with AP in children with VUR was performed using the PharMetrics database, a national medical and pharmacy claims database populated

with insured patients; however, only 17% of these patients were compliant as defined by an MPR $\geq 80\%$.¹² We hypothesize that they underestimated the true level of compliance due to the use of non stringent inclusion criteria. There was no VCUG requirement and approximately 20% of patients in the analysis did not have this study performed. Therefore a significant number of patients may never have truly had VUR. Also, only one unspecified antibiotic prescription within the study period was required. There was no stipulation in regard to prescription duration or dosing. Likely a number of children on short term antibiotic therapy were falsely included in the study.

Similar to our results, Hensle et al. found that decreased age was associated with increased compliance.¹² One reason for this observation may be that as children age and gain more autonomy they become responsible for taking their own medications. Granting this responsibility too early accounted for decreased adherence observed with antiretroviral therapy in the pediatric HIV population.¹⁸ Furthermore, reasons for regimen noncompliance during adolescence are multi-factorial and complex, involving, but not limited to, issues surrounding body image, self-esteem, decision making, self-motivation, and coping mechanisms, making adherence difficult to achieve in all aspects of healthcare during this period.¹⁹

We assessed additional factors for an association with compliance on multivariate analysis. Our results point to two major factors that may influence medication compliance including contact with the healthcare system and patient/parent perception of the medical condition. First, we found increased compliance with those who had increased healthcare contact including urologist visits and hospitalizations. These opportunities for interaction with the healthcare team may reinforce the importance of adherence to the treatment regimen for the patient/parent. Previous analyses of medication compliance have demonstrated that various interventions by physicians and ancillary healthcare providers such as nurses and pharmacists can play a pivotal role in improving medication adherence.^{11, 13, 20}

Second, increased hospitalizations may influence the patient/parent perception of the long term implications of VUR and emphasize the importance of AP compliance. Although we were unable to ascertain if hospitalizations were specifically related to VUR, in general, those patients/parents who have greater physician and ancillary health staff contact may be more apt to follow healthcare recommendations. In fact, in a study of patients with inflammatory bowel disease, patients were more likely to be compliant with their medications if they had added issues requiring consultation of another health professional.¹⁴ This study also showed that patients with active disease were more likely to be adherent to their treatment regimen compared to those who were symptom-free. In most instances, patients/parents with VUR are physically unaware of their condition; however, an acute admission for pyelonephritis would certainly call attention to the underlying condition of VUR.

This awareness of VUR in the setting of acute infection may contribute to why we observed no association between antibiotic compliance and UTIs. An association between increased compliance and decreased UTIs could have been negated by those individuals who became more compliant with their medications due to disease awareness from the presence of UTI or pyelonephritis. Further prospective studies to evaluate temporal causation need to be performed with AP in the setting of VUR.

This study has limitations. First, our assessment of compliance through prescription refills is an indirect method for measuring adherence. There is no documentation that the patient actually ingested the filled prescription. Second, using a claims database by definition means that we are investigating a select population that is insured. Accordingly, these study results

may not be representative of other populations, such as Medicaid and the uninsured. Furthermore, all findings depend on the completeness of the original documentation and the accuracy of the diagnosis and procedural coding.

We attempted to minimize potential biases by creating more stringent criteria for study inclusion. Despite this, we may have falsely identified VUR patients because we did not have VCUG results to indicate whether or not VUR was actually present. In addition, patients with UTI and no VUR may have been falsely captured as VUR-positive since patients may initially be coded as having VUR until the VCUG is performed to exclude the condition. This situation exists since a UTI in a child is one of the main indicators for ordering a VCUG. To limit this possibility, we required a minimum of two 30-days supply or four 14-days supply prescriptions to account for the time period during which a patient may be covered with antibiotics until a negative VCUG is obtained. We assumed that most patients would obtain a VCUG within 4–6 weeks of presentation and therefore only those with VUR would have greater than or equal to a two months supply of AP and a persistent ICD-9 code for VUR.

The inability to account for VUR resolution may also have falsely lowered adherence levels. However, we decreased the odds of accidentally including patients who spontaneously resolved their VUR by limiting our observation period to one year. A longer observation period would more likely have included patients that had the opportunity for repeat imaging and identification of VUR resolution. Also, we were unable to account for VUR grade which may affect perception of disease severity by the patient/parent and influence adherence to a given management regimen. Finally, the lack of urine culture results for UTI confirmation is a major limitation. In clinical practice it is common to empirically start antibiotics for symptoms of a UTI, particularly in the setting of VUR. The inability to confirm bacterial infection through culture results is likely responsible for the high rate of UTI observed in this population.

CONCLUSIONS

We cannot presume that patients/parents are adherent to the treatment regimens we prescribe. Our findings point to various factors that are associated with an increased risk for noncompliance. We may be able to improve compliance through increased patient contact with the healthcare system and counseling of parents and older patients to stress the importance of treatment regimen adherence. This is valuable information at a time when we are witnessing increased investigations into the utility of AP in VUR management. We must press investigators to closely monitor and report compliance with AP; only in this manner may we confidently interpret the results from studies evaluating the effectiveness of AP.

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Abbreviations and Acronyms

VUR	vesicoureteral reflux
AP	antibiotic prophylaxis
UTI	urinary tract infection
VCUG	voiding cystourethrogram
MPR	medication possession ratio

Figure 1.
Assembly of Cohort

Figure 2.

Breakdown of antibiotics prescribed by drug category

Figure 3.
Prophylactic antibiotic compliance by age*
*p<0.0001

Table 1

Characteristics of patients managed on antibiotic prophylaxis from 2002–2007

Characteristic	Antibiotic Prophylaxis n = 5342 (%)
Age at Diagnosis	
≤5 years	4210 (79)
6–10 years	957 (18)
11–18 years	175 (3)
Gender[†]	
Male	998 (19)
Female	4342 (81)

[†] Gender was not specified in 2 patients

Table 2Factors associated with prophylactic antibiotic compliance on multivariate analysis^a

Characteristics	OR (95% CI)
Gender	
Male	1 [Reference]
Female	1.11(0.96–1.29)
Age	
≤5 years	1 [Reference]
6 to ≤ 10 years	0.71 (0.61–0.83) ^b
11 to ≤ 18 years	0.56(0.41–0.79) ^c
Hospitalizations	
None	1 [Reference]
≥1	1.70 (1.48–1.97) ^b
Visits to Urologist	
None	1 [Reference]
≥1	1.41(1.25–1.58) ^b
UTI Episodes	
None	1 [Reference]
≥1	1.07 (0.94–1.23)

Abbreviations: OR=odds ratio; CI=confidence interval; UTI=urinary tract infection (including pyelonephritis)

^a Compliance equals MPR ≥ 80%^b p < 0.0001^c p = 0.0008