# Compliance With Antibiotic Prophylaxis in Children With Vesicoureteral Reflux: Results From a National Pharmacy Claims Database

Hillary L. Copp,* Caleb P. Nelson, Linda D. Shortliffe, Julie Lai, Christopher S. Saigal, William A. Kennedy and the Urologic Diseases in America Project

*From the Department of Urology, UCSF, San Francisco (HLC), Department of Urology, Stanford University School of Medicine, Stanford (LDS, WAK) and UCLA/RAND, Santa Monica (JL, CSS), California, and Department of Urology, Children's Hospital Boston, Boston, Massachusetts (CPN)*

**Abbreviations and Acronyms**

AP = antibiotic prophylaxis

MPR = medication possession ratio

UTI = urinary tract infection

VCUG = voiding cystourethrogram

VUR = vesicoureteral reflux

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* Correspondence: 400 Parnassus Ave., A-610, UCSF, San Francisco, California 94143-0330 (telephone: 415-476-1611; FAX: 415-476-8849; e-mail: CoppHL@urology.ucsf.edu).

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**Purpose:** Antibiotic prophylaxis is commonly used for medical management of vesicoureteral reflux. Little information exists on compliance with antibiotic prophylaxis in patients with vesicoureteral reflux.

**Materials and Methods:** We queried the i3 Innovus (Ingenix®) pharmacy claims 2002 to 2007 database for patients 18 years old or younger with vesicoureteral reflux (ICD-9 code 593.7 plus claim for cystogram) and analyzed those with at least 1 year of followup data. Criteria for management with antibiotic prophylaxis were 2 or more 30-day supplies of antibiotic prescriptions, or 4 or more 14-day supplies of prescriptions if the antibiotic was a penicillin or cephalosporin. Antibiotic prophylaxis 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% or greater, meaning coverage with antibiotic prophylaxis for 80% of the year or more.

**Results:** Of 9,496 patients with vesicoureteral reflux 5,342 (56.3%) were treated with antibiotic prophylaxis. Most patients were female (81%) and 5 years old or younger (79%). Trimethoprims/sulfonamides were most commonly prescribed (62%) and antiseptics were next (24%). Of patients prescribed antibiotic prophylaxis 40% were compliant. Compliance was lower for 6 to 10-year-olds (OR 0.71, 95% CI 0.61–0.83) and 11 to 18-year-olds (OR 0.56, 95% CI 0.41–0.79) compared to younger children (5 years or less). Increased compliance was associated with 1 or more hospitalizations (OR 1.70, 95% CI 1.48–1.97) and 1 or more urologist visits (OR 1.41, 95% CI 1.25–1.58).

**Conclusions:** Among patients with vesicoureteral reflux who are prescribed prophylactic antibiotics 40% are compliant with treatment. Young age, frequent hospitalization and specialist visits are 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 usefulness of antibiotic prophylaxis in vesicoureteral reflux management.

**Key Words:** antibiotic prophylaxis, patient compliance, treatment outcome, vesico-ureteral reflux

ANTIBIOTIC prophylaxis is commonly used for medical treatment of vesicoureteral reflux, although few data exist on patient compliance. Vesicoureteral reflux may predispose an individual with bladder infection to pyelonephritis.[1–3] The goal of intervention for reflux is prevention of pyelonephritis and its possible long-term sequelae.



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Since reflux resolves spontaneously in 5% to 13% of patients with VUR annually, a treatment option is maintenance of urine sterility through daily AP until the condition resolves.[4,5] However, recent studies have shown UTI, pyelonephritis and renal scarring rates are not statistically different among patients with VUR receiving vs not receiving AP.[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 to identify factors associated with noncompliance in children treated with AP for VUR.

## METHODS

### Study Design and Data Source

We retrospectively studied AP compliance in patients with VUR using insurance claims data from 2002 to 2007. We used the i3 Innovus database, a private, national pharmacy and medical claims database managed by Ingenix. The database was purchased for use by the Urologic Diseases in America Project. The claims data are derived from the UnitedHealthcare® family of health insurance plans, which operates in all 50 states, although we do not have information regarding the specific geographical distribution of the database population. There are more than 39 million patients with longitudinal followup data spanning a 5-year period within this database. i3 Innovus 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. Age was 18 years or younger, ICD-9 diagnosis of VUR (593.70 to 593.73) was present, fluoroscopic (CPT 74455) or nuclear (CPT 78740) VCUG was performed and at least 1 year of followup 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 inclusion criteria were classified as receiving AP by the presence of 2 or more 30-day supplies of antibiotic prescriptions, or 4 or more 14-day supplies of antibiotic prescriptions if the antibiotics were penicillins or cephalosporins. Penicillins and cephalosporins were allowed this exception because, 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 receiving AP by the typical features of low dose, once daily administration, since drug dosing in children is based on weight.

We grouped antibiotics into 5 categories, including trimethoprims/sulfonamides, antiseptics, penicillins, cephalosporins and other. Antibiotics within trimethoprims/sulfonamides included trimethoprims and sulfonamides prescribed alone and in combination. Antiseptics were composed of nitrofurantoins and methenamine mandelates. The category of other 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 an MPR, or 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 of 80% or greater, since this cut point is commonly used in the literature.[9] This finding signified that the patient had coverage with AP for at least 80% of the observation period.

The observation period was 1 year, since this duration is frequently 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 from study. Antibiotics taken for acute infection contributed to the total days of antibiotic supply. 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, as age, gender, hospitalizations, specialist visits and presence of UTI.[11–14] Age was categorized into groups based on previous American Urological Association VUR guidelines for preschool children (1 to 5 years) and school-age children (6 to 10 years).[15] We extended the range for preschool children to include infants (birth to 1 year) and added a third category (11 to 19 years) to evaluate all children (up to 18 years) with VUR treated with AP.

The variables for hospitalizations, specialist visits and presence of UTI were dichotomized. Patients were considered positive for hospitalization if at least 1 inpatient hospitalization for any reason occurred during the observation period. Outpatient surgery and emergency department visits were not included as hospitalizations. Similarly patients with a minimum of 1 visit to a urologist were categorized as having contact with a urology 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-term antibiotic prescription (14-day supply or less). Patients were considered positive for UTI if they had at least 1 urinary tract infection 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 less than 80% (noncompliant) and 80% or greater (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® software, version 9.1. All analyses were 2-sided and $p < 0.05$ was statistically significant.

**Table 1.** *Characteristics of patients treated with antibiotic prophylaxis from 2002 to 2007*

| | No. Pts (%) |
|---|---|
| Age at diagnosis (yrs): | |
| 5 or Younger | 4,210 (79) |
| 6–10 | 957 (18) |
| 11–18 | 175 (3) |
| Gender:* | |
| M | 998 (19) |
| F | 4,342 (81) |

* Gender was not specified in 2 patients.

## RESULTS

### Clinical Characteristics

A total of 9,496 patients 18 years old or younger met the inclusion criteria for study entry. Of the patients 5,342 (56.3%) were treated with AP from 2002 to 2007 (fig. 1). Most patients were 5 years old or younger and female (table 1). VUR management was performed entirely by a primary care physician in 40% of the cases.

Physicians overwhelmingly prescribed trimethoprims/sulfonamides (fig. 2). Antiseptics were the second most commonly prescribed class with greater than 99.9% of this class consisting of nitrofurantoins. Less than 4% of the population received a 14-day supply of AP prescriptions. Of the children 80% were maintained on the same AP during a 1-year period. Approximately 50% of the cohort remained without UTI on AP. During the study period 19% of the population required inpatient hospitalization.

### Compliance with AP

Overall, 40% of the patients receiving AP achieved a MPR of 80% or greater and were classified as compliant with AP during the 1-year period. MPR may vary by agent tolerability. Of the patients who were prescribed only nitrofurantoins 98% were noncompliant. Figure 3 shows 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 or more hospitalizations and 1 or more urologist visits. Increased compliance was not associated with an absence of UTI.

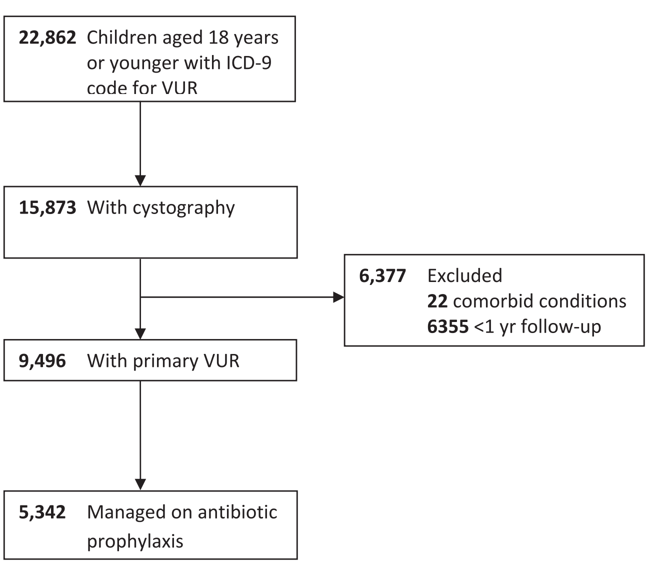


**Figure 1.** Assembly of cohort

## DISCUSSION

In this large, longitudinal database study more than half of the patients treated with 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, since adherence to long-term medication 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 patients with asthma.[16] Poor adherence rates also apply in the setting of clinical trials. Approximately 25% of children were not adherent to therapeutic regimens in the PENTA 5 randomized controlled trial evaluating treatment of HIV with highly active antiretroviral therapy.[17]

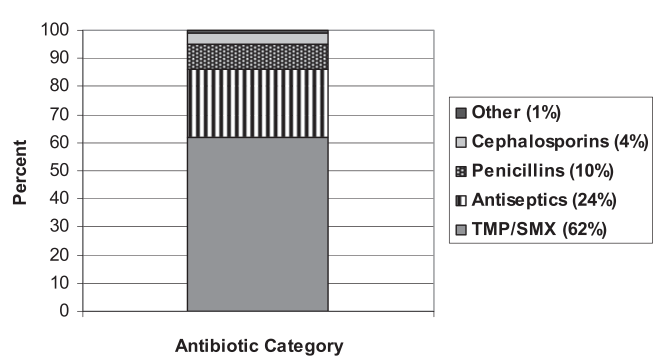


**Figure 2.** Breakdown of antibiotics prescribed by drug category. *TMP/SMX*, trimethoprim-sulfonamide.

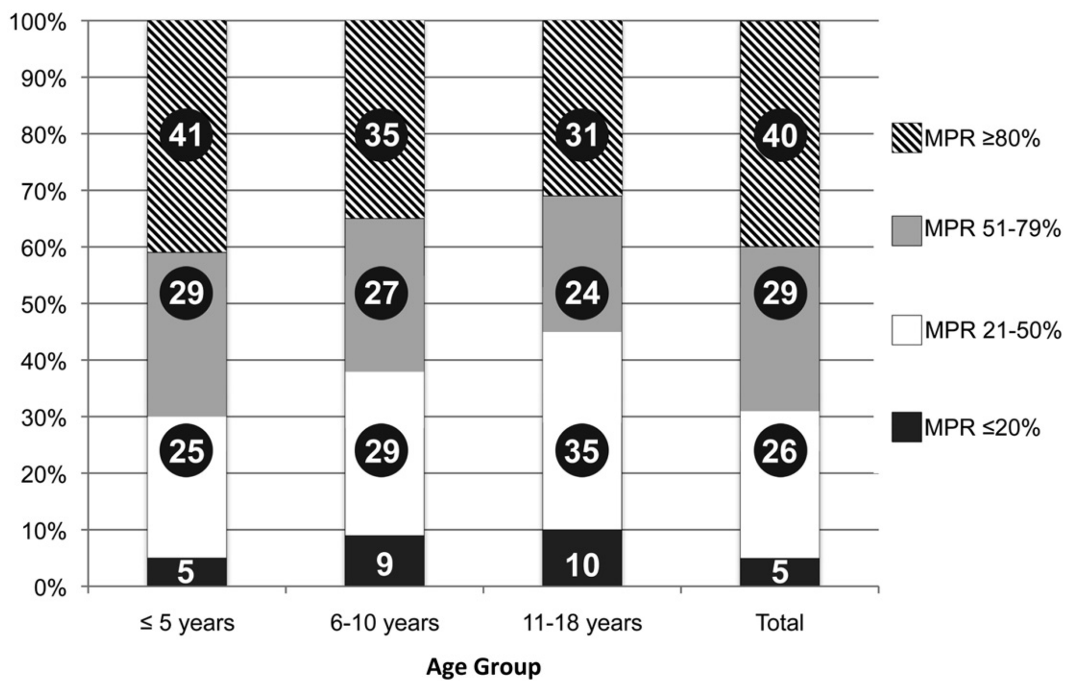


**Figure 3.** Prophylactic antibiotic compliance by age ($p < 0.0001$)

An 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. Only 17% of these patients were compliant, as defined by a MPR of at least 80%.[12] We hypothesize that the true level of compliance was underestimated due to the use of nonstringent inclusion criteria. There was no VCUG requirement and approximately 20% of patients in the analysis did not have the study performed. Therefore, a significant number of patients might not have had VUR. Also, only 1 unspecified antibiotic prescription within the study period was required. There was no stipulation regarding prescription duration or dosing. Likely a number of children on short-term antibiotic therapy were inappropriately included in the study.

**Table 2.** *Factors associated with prophylactic antibiotic compliance on multivariate analysis*

| | OR (95% CI) | p Value |
|---|---|---|
| Gender: | | |
| M | 1 (reference) | |
| F | 1.11 (0.96–1.29) | |
| Age (yrs): | | |
| 5 or Younger | 1 (reference) | |
| 6–10 | 0.71 (0.61–0.83) | <0.0001 |
| 11–18 | 0.56 (0.41–0.79) | 0.0008 |
| No. hospitalizations: | | |
| 0 | 1 (reference) | |
| 1 or More | 1.70 (1.48–1.97) | <0.0001 |
| No. visits to urologist: | | |
| 0 | 1 (reference) | |
| 1 or More | 1.41 (1.25–1.58) | <0.0001 |
| No. UTI episodes:* | | |
| 0 | 1 (reference) | |
| 1 or More | 1.07 (0.94–1.23) | |

Compliance equals MPR 80% or greater.
* Including pyelonephritis.

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] Reasons for regimen noncompliance during adolescence are multifactorial 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 health care during this period.[19]

We assessed additional factors for an association with compliance on multivariate analysis. Our results indicate 2 major factors that may influence medication compliance, including contact with the health care system and patient/parent perception of the medical condition. First, we found increased compliance with patients who had increased health care contact, including urologist visits and hospitalizations. These opportunities for interaction with the health care 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 health care providers such as nurses and pharmacists can have a pivotal role in improving medication adherence.[11,13,20]

Additionally 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, generally those patients/parents with greater physician and ancillary health staff contact may be more apt to follow health care recommendations. In fact, in a study of inflammatory bowel disease patients were more likely to be compliant with 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 the condition. However, acute hospitalization 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 our observation of 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 awareness of 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. Also, using a claims database by definition means that we are investigating a select population that is insured. Accordingly these study results might not be representative of other populations, such as patients with 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. However, we may have falsely identified patients with VUR because we did not have VCUG results to indicate whether VUR was actually present. Additionally patients with UTI and no VUR may have been falsely captured as VUR positive, since patients may initially be coded as having VUR until VCUG is performed to exclude the condition. This situation exists because UTI in a child is a main indicator for ordering VCUG. To limit this possibility, we required a minimum of 2, 30-day supplies or 4, 14-day supplies of prescriptions to account for the period during which a patient was covered with antibiotics until a negative VCUG was obtained. We assumed that most patients would undergo VCUG within 4 to 6 weeks of presentation and, therefore, only those with VUR would have a 2-month or greater supply of AP and a persistent ICD-9 code for VUR.

The inability to account for VUR resolution may also have falsely decreased adherence levels. However, we reduced the odds of accidentally including patients with spontaneous resolution of VUR by limiting our observation period to 1 year. A longer observation period would more likely have included patients who 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 treatment regimen. Finally the lack of urine culture results for UTI confirmation is a major limitation. In clinical practice it is common to start antibiotics empirically for symptoms of 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 indicate that various factors are associated with an increased risk of noncompliance. We may be able to improve compliance through increased patient contact with the health care system, and counseling of parents and older patients to stress the importance of treatment regimen adherence. This information is valuable at a time when we are witnessing increased investigations into the usefulness of AP in VUR management. We must press investigators to monitor closely 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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## EDITORIAL COMMENT

This study tells us several things that we already know. First, compliance with antibiotic prophylaxis in children is poor. This is true not just for antibiotics, but also for compliance with any form of chronic prophylaxis, including steroids and HIV medication, which is notoriously poor. Also, children do not like liquid nitrofurantoin and, no matter how it is flavored, they will not take it (compliance was 2% in this series). Additionally antibiotic prophylaxis compliance is far better in younger children than older children, most likely due to parental anxiety. Lastly despite antibiotic prophylaxis, urinary tract infections can develop, which can lead to hospitalization (19% in this series).

The authors indicate that 1 previous study has been performed evaluating compliance with antibiotic prophylaxis in children with VUR using the PharMetrics database (reference 12 in article). They state that the study showed only a 17% compliance rate in that population, as defined by a MPR of 80% or greater. In fact, the average rate of compliance in that study during a 12-month time frame was 41.4%, meaning that patients purchased enough antibiotics to last for 41.4% of the year (reference 12 in article). Only 17% of the patients in that database had compliance greater than 80%. The 41% compliance is really similar to the 40% compliance noted in the present study, and I suspect the numbers in reality are close.

What is concerning about this report is that 19% of the population wound up being hospitalized, presumably for treatment of urinary tract infection. This is a high number compared to a recent study from Australia, where 576 children were randomized to antibiotic prophylaxis or placebo, and only 8% of the antibiotic group and 10% of the placebo group required hospitalization for urinary tract infection.[1] These results make one wonder if the rate of noncompliance in the present study is in fact higher than reported. In summary, noncompliance is part of the landscape when treating children with VUR, and it has to be considered when looking at the results of various reports concerning prophylaxis versus nonprophylaxis in various clinical trials.

**Terry W. Hensle**
*Department of Pediatric Urology*
*Children's Hospital of New York*
*New York, New York*

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## REPLY BY AUTHORS

One of the original works on compliance with antibiotic prophylaxis in the vesicoureteral reflux population was by Hensle et al (reference 12 in article). It drew our attention to the fact that our patients are not unique and compliance with antibiotic prophylaxis is likely poor, as it is with other chronic medication treatments. Thus we used a national pharmacy claims database to estimate compliance with antibiotic prophylaxis and verify whether compliance rates were as poor as defined by Hensle et al. To clarify, the medication possession ratio is the amount of medication prescribed during the observation period divided by the number of days in the observation period (reference 9 in article). For example, a MPR of 50% means that a patient had enough medication to last them 50% of the year, or approximately 183 days of medication during a 365-day period. We and Hensle et al defined compliance with antibiotic prophylaxis as a MPR of 80% or greater, as this is a common cut point used in the compliance literature (reference 9 in article). In other words, patients who have a medication for 80% or greater of the designated period (292 or more days of medication during a 365-day period) are defined as compliant with the medication. Therefore, when we say the compliance rate is 40% this means that 40% of the population had a MPR of 80% or greater.

Although both studies showed poor compliance, there is a major difference in the compliance rate. Hensle et al demonstrated an average MPR of 40% but a compliance rate of 17%. Thus, on average patients had enough medication to last them 40% of the year but only 17% had enough medication to last at least 80% of the year. On the other hand, our study demonstrated an average MPR of 69% (on average patients had enough medication to last them 69% of the year) and a compliance rate of 40% (40% of the population had enough medication to last them at least 80% of the year).

We agree that the 19% hospitalization rate appears high. However, this rate does not represent hospitalizations solely for UTI and likely the percentage of hospitalizations for UTI alone is lower. Nonetheless, one of the greatest challenges with randomized controlled trials is external validity as these trials often are not completely representative of the general population. It is possible that the patients enrolled in the Australian trial were healthier overall and less susceptible to hospitalization, especially considering that only 576 underwent randomization of an initial 9,482 who were assessed for eligibility (reference 1 in comment).

We agree that compliance with antibiotic prophylaxis is less than optimal. Whether compliance (MPR 80% or greater) is 17%, 40% or somewhere in between, the important message is that it is not 100%. This must be factored in not only when we are analyzing the outcomes of clinical studies, but also when we are deciding how to treat our patients.