

American Urological Association Antibiotic Best Practice Statement and Ureteroscopy - Does Antibiotic Stewardship Help?

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Abstract:

Purpose: To determine compliance with American Urological Association (AUA) antimicrobial prophylaxis best practice statement and whether the use of postoperative antibiotics is associated with lower rates of postoperative urinary tract infection (UTI) in patients with nephroureterolithiasis and a negative preoperative urine culture undergoing ureteroscopy.

Materials and Methods: A retrospective review of all adult patients undergoing ureteroscopy from 2013-2014 for stone disease with a negative preoperative urine was conducted. Patients who did and did not receive postoperative oral antibiotics beyond 24 hours of surgery were identified. The rates of culture-proven postoperative UTI and unplanned postoperative encounters were determined for both groups. Between group comparisons were made using independent t-test and chi-square analyses.

Results: A total of 1068 patients met inclusion criteria and 31.6% were managed in accordance with the AUA best practice statement by not receiving antibiotics beyond 24 hours of surgery. Overall, 33 patients developed a culture-proven UTI within 30 days following surgery, with no difference in UTI rate between patients who did and did not receive home-going antibiotics (2.9% vs. 3.6%, respectively; $p=0.5$). Rates of unplanned hospital encounters also did not differ between groups (23.7% vs. 27.0%, respectively; $p=0.2$). On multivariate regression, culture-proven UTI within one year prior to surgery was the only factor associated with post-operative UTI (OR 10.8, $p < 0.0001$).

Conclusions: Patients who did and did not receive home-going antibiotics following ureteroscopy demonstrated similar rates of postoperative UTI and unplanned hospital encounters. These results suggest there is no benefit to extended antibiotics following ureteroscopy. The minority of patients managed in accordance with the AUA best practice statement highlights room for quality improvement.

Introduction:

Nephroureterolithiasis is an increasingly common condition with an estimated prevalence of 8.8% in the United States in 2010¹. Technologic advancement in endoscopy have led to increasing use of ureteroscopy in the surgical management of kidney stones^{2, 3}. Postoperative urinary tract infection (UTI) is a known complication of ureteroscopy and can be prevented in part by ensuring urine sterility before surgery⁴. Furthermore, the American Urological Association (AUA) best practice statement on surgical antimicrobial prophylaxis recommends perioperative antibiotic administration of less than 24 hours duration at the time of ureteroscopy⁵. This recommendation is based on evidence that perioperative antibiotics reduce the risk of postoperative pyuria and bacteriuria, though the impact of prophylaxis on reducing the risk of postoperative febrile UTI is less clear⁶⁻⁸.

Evidence supporting the use of antibiotics after ureteroscopy is lacking, and largely based on extrapolated literature and small retrospective reviews⁵. Two recent studies found similar rates of postoperative febrile UTI in patients who did and did not receive postoperative antibiotics in contrast to a third study that showed postoperative antibiotics were associated with a lower rate of UTI⁹⁻¹¹. These studies are limited by small sample size and a low overall incidence of UTIs, thus limiting comparisons between groups. Furthermore, these studies failed to examine other important considerations of antibiotic administration including adverse drug reactions, secondary infections, antimicrobial resistance, or cost¹². With no clear evidence supporting or refuting postoperative antibiotic use, a variety of practice patterns have emerged with up to one third of community urologists prescribing postoperative antibiotics beyond what is recommended by the AUA best practice statement¹³.

The hypothesis of this study is that postoperative antibiotic administration does not reduce the rate of UTI following ureteroscopy for stone disease in patients with a negative preoperative urine culture. The primary aim of this investigation was to determine the proportion of such patients managed in accordance with AUA surgical antimicrobial prophylaxis recommendations and compare rates of postoperative UTI in those who did and did not receive supplemental, home-going antibiotics following

ureteroscopy in a large academic system. The second aim of the study was to assess the effect of supplemental home-going antibiotics on the frequencies of unplanned postoperative encounters, such as emergency department visits and telephone calls, as well as antibiotic-related adverse events.

Methods:

This is a retrospective analysis of patients undergoing ureteroscopy at a large, urban, academic health system from 2013 to 2014. Patients were identified through query of the electronic medical record by Current Procedural Terminology (CPT) codes 52352 or 52353 to identify ureteroscopy for kidney stone disease. Patients were excluded from analyses for a positive preoperative urine culture, lack of urine culture within 30 days prior to surgery, or infection-related stone (i.e. struvite). Patient data was automatically and manually extracted. The institutional review board approved this study

Clinical and Demographic Data

All relevant covariates including patient age at surgery, body mass index (BMI), the presence of antibiotic allergy, diagnosis of diabetes mellitus, preoperative urine culture status, positive urine culture within a year prior to surgery, intraoperative ureteral stent placement, stone composition, duration of ureteroscopy, and details of home going oral antibiotic prescriptions were recorded. Patients in the cohort were stratified based upon discharge with or without home going antibiotics. Clinical outcomes within 30 days following surgery were postoperative urine culture and unplanned encounters, including postoperative telephone calls and/or emergency room visits. Clinical outcomes were confirmed with chart review to be surgically relevant, and unrelated encounters (i.e. unrelated chronic conditions) or those as part of routine follow-up were excluded.

A positive urine culture was defined as $> 50,000$ colony forming units per milliliter of a single pathogenic organism. Pyuria was defined as 10 or more WBC per high powered field or moderate to large leukocyte esterase on pre-operative urinalysis. Primary stone composition was defined as $\geq 50\%$ of one stone type upon analysis. Unplanned encounters: telephone calls and emergency department visits were categorized as: (1)

suspected postoperative infection (fever, malaise, or other constitutional symptoms); (2) antibiotic-related adverse events (gastrointestinal upset, rash, yeast infection); (3) postoperative pain; or (4) other urologic complaints (catheter problems, hematuria).

Statistical Analysis

Simple descriptive statistics were performed and data presented as means and standard deviations. Univariable analyses were conducted using Student's t-test for continuous variables, based upon normally distributed data, and categorical variables were compared using chi-square analysis, with Fisher's exact-test as indicated for small cell sizes. A multivariable regression analysis was performed for post-operative culture-prove UTI with relevant univariable factors, including age, gender, BMI, diabetic status, operative time, home going antibiotics, intraoperative stent placement, and positive urine culture one year prior to surgery. All statistical tests were two-sided with $p < 0.05$ indicating statistical significance. All statistical analyses were performed using JMP Pro 12 (SAS Institute, Inc., Cary, NC).

Results:

A total of 1,722 patients were identified across 4 hospitals within the health system. The sample was comprised of, surgical cases from 9 Urologists who regularly perform endourologic procedures. From the original sample of 1722 patients, 458 patients were excluded for lacking a pre-operative culture within the 30 days prior to surgery, and 196 were excluded for positive pre-operative urine cultures. of the remaining 1,068 patients were included in analyses and adherence to the AUA antibiotic best practice statement was 31.6% (N=337) in this sample. The major stone composition of the group was Calcium Oxalate (38%) followed by calcium phosphate (17%).

Groups of patients (Table 1) who did and did not receive supplemental, oral, home-going antibiotics did not differ with regard to gender, age, presence of an antibiotic allergy, prevalence of diabetes mellitus, and operative time. However, patients who received supplemental antibiotics had a significantly greater BMI (30.52 ± 7.33 vs 29.59 ± 5.57 kg/m², $p = 0.0394$) and were significantly less likely to have undergone intraoperative stent placement (32.4% vs 40.1%, $p = 0.0149$). The types of supplemental antibiotics given

included Amoxicillin (N=10), Amoxicillin-Clavulanate (N=13), Trimethoprim-Sulfamethoxazole (N=137), Ciprofloxacin (N=437), Cephalexin (N=88), and Nitrofurantoin (N=33). Perioperative antibiotic prophylaxis consisted of Amoxicillin (N=4), Ampicillin (N=12), Cefazolin (N=349), Ciprofloxacin (N=344), Gentamicin (N=131), Vancomycin (N=58), Piperacillin-Tazobactam (N=29), or other antimicrobials (N=123).

A total of 33 patients (3.09%) developed a postoperative culture-proven UTI (Table 2) and rates of UTI did not differ with or without homegoing-antibiotic prescription (2.87% vs 3.56%, $p=0.546$). Upon univariable and multivariable analyses, post-operative UTI was not associated with differences in age, gender, BMI, antibiotic allergy, pre-operative pyuria, intraoperative stent placement, diabetic status, operative time, or the prescription of supplemental home-going antibiotics. On univariable analysis, a culture-proven UTI (positive urine culture) within the year prior to surgery was significantly associated with post-operative UTI (12.7% vs 1.43%, $p<0.0001$). On multivariable regression, culture-proven UTI (positive urine culture) within one year of surgery was the only factor significantly associated with post-operative UTI (OR 10.8, $p<0.0001$).

Post-hoc analysis (Table 2b) of patients who had a UTI within one year prior to surgery revealed that those given home-going antibiotics after ureteroscopy experienced no difference in post-operative UTI rate than those who did not receive supplemental treatment (11.32% vs 15.38% $p=0.458$, respectively). Similar rates were observed for those with no UTI the year before surgery if home-going antibiotics were or were not prescribed (1.44% vs 1.40%, $p=1.000$) respectively). When stratified by home-going antibiotics, increased rates of post-operative UTI remained significantly higher in those having a UTI in the year preceding ureteroscopy with (11.32% vs 1.44%, $p<0.0001$) or without (15.38% vs 1.40%, $p<0.0001$) supplemental antibiotics.

Rates of unplanned post-operative encounters did not differ whether patients were prescribed supplemental home-going antibiotics or not (Table 2). Rates of stent placement significantly differed between patients who did and did not receive home-going antibiotics (32.4% vs 40.1%, $p=0.0149$). When stratified by stent placement, the rates of unplanned post-operative encounters were similar between patients who did and did not receive home-going antibiotics (Table 3 & 4). Independent of antibiotics, stented patients had a

higher rate of unplanned encounters when compared to patients without stents (29.8% vs. 22.0%, $p = 0.005$).

Antibiotic-related adverse events were only noted in telephone calls and none were observed at emergency department visits. A total of 27 patients (2.5% of the cohort) reported an antibiotic-related adverse event, and rates did not differ between patients who did and did not receive home-going antibiotics (2.7% vs. 2.1% $p0.524$, respectively). No serious adverse events occurred whether or not home-going antibiotics were prescribed, with 26 patients reporting gastrointestinal symptoms (2.3% vs. 2.7% $p 0.831$ respectively) and 7 reporting rash (0.7 vs 0.6%, $p 1.000$ respectively). There were no reported cases of *Clostridium difficile* colitis or anaphylaxis in the cohort.

Discussion:

In the recently updated AUA/Endourological Society 2016 guidelines for the surgical management of stones, the committee recommends a single dose of appropriate oral or IV antibiotics within 60 minutes of surgery for patients with negative preoperative urine culture undergoing uncomplicated ureteroscopy¹⁴. This best practice recommendation for perioperative antibiotic prophylaxis does not favor prolonged antibiotic use, and has remained unchanged since 2008⁵. In fact, several studies have demonstrated that antibiotic prophylaxis for 24 or more hours does not decrease the rate of urinary tract infection^{8,9,11}. However there is a great deal of variation in practice pattern, as was evidenced in the current study. Specifically, 69.4 % of practitioners analyzed prescribed supplemental antibiotics, which did not appear to provide any meaningful reduction in the rate of urinary tract infection or unplanned hospital encounters. Although this study was not designed to ascertain the rationale underlying extended antibiotic use, discussions with the surgeons suggest concern for a catastrophic event (i.e., urosepsis) and desire to decrease unplanned encounters primarily drive their prescribing patterns.

The overall rate of UTI was 3.1 % in the study sample, and there was no significant difference between the rates of post-operative UTI in patients treated with less than or greater than 24 hours of antibiotics. Wolf Jr and colleagues identified high risk patients who may benefit from extended antibiotic prophylaxis following ureteroscopy, which

included those with placement of a foreign body into the urinary tract, such as urinary catheters, as well as pre-existing urinary tract infection, and manipulation of an indwelling urinary tube⁵. Based upon these risk factors, the current study excluded all patients who had a positive pre-operative urine culture. Placement of an intraoperative stent¹⁵, duration of surgery¹⁰, and BMI were analyzed with regard to their effects on the primary and secondary outcomes in the current study. Only the presence of a UTI within one year prior to surgery was associated with post-operative UTI. To better understand the influence of previous UTI, a stratified analysis was performed based upon home going antibiotic status. A clinically significant but not statistically significant reduction (15.38% to 11.32%) in postoperative UTI was achieved in patients with UTI the year preceding ureteroscopy. Whereas, those without an infection the year leading into surgery did not see a reduction (1.40% to 1.44%) in post-operative infection rates with or without antibiotics. This suggests that perhaps the best group to target with home going antibiotics may be patients with history of UTI over the last year.

Moses and colleagues demonstrated an increased rate of unplanned hospital returns among 550 patients discharged without homegoing antibiotic prescriptions in compliance with the AUA best practice statement¹⁰. This observation was based on 19 unplanned emergency department visits in their study sample. In the current study, there were 43 (4.0 %) emergency department visits and 247 (23.1 %) telephone encounters among the 1,068 patients studied. There was no significantly increased rate of unplanned encounters on univariate analysis among patients treated in accordance with the AUA best practice/guideline recommendations. However, it is important to note that the rate of compliance with the AUA best practice/guidelines recommendation in the Dartmouth study was 48.7% and is higher than the 31.6% rate observed in the current study. Nonetheless, there was no benefit of prolonged antibiotics observed in the current study, despite 69.4% of patients receiving them.

While antibiotics are necessary to treat and prevent infections, antibiotic overuse is associated with negative sequelae, including medication side effects, opportunistic infections, and antibiotic resistant organisms¹⁶⁻¹⁸. Considering this, the Centers for

Disease Control released a 2014 call for antibiotic stewardship, which charged physicians to improve prescribing practices¹⁹. Despite lacking level one evidence for the role of antibiotics in several areas of urology, it is critical for Urologists to scrutinize antibiotic use. For example, one study by Swartz et al, retrospectively reviewed postoperative antibiotic use at the time of synthetic midurethral sling surgery and found an increased rate of antibiotic-related adverse events in the group that received postoperative oral antibiotics compared to those who received only preoperative antibiotic prophylaxis. The findings of this study subsequently led to a change in practice within the institution²⁰. Similarly, as a result of the current study, there is an ongoing quality initiative to address the use of antibiotics following ureteroscopy.

Limitations of this study include its retrospective design, which subjects its findings to selection bias. Particularly, it is unclear if patients who received antibiotics had confounding risk factors for infection that were not captured by the variables analyzed. As such, it is possible that these unidentified high risk patients selectively received prolonged antibiotics following their procedure, which normalized their rates of infection following surgery. Large randomized controlled trials are needed to eliminate this bias, which is inherent to all of the retrospective studies reported thus far. Secondly, given the small reported rate of post-ureteroscopy UTI, the power needed to detect a small difference in the rates of post-operative UTI with or without supplemental antibiotics requires the randomization of several thousand men to each treatment arm. This remains a limitation in the other prior studies as well, however, it should be noted that the current study represents the largest sample analyzed to-date. Thirdly, data is lacking regarding the duration of post-operative antibiotic treatment, medication compliance, and standard protocols among the 9 urologist. These clinical parameters could be helpful in identifying risk factors for adverse outcomes, such as post-operative infection, that many clinicians strive to minimize with prolonged antibiotic therapy. Overall, the current study identified no benefit of prolonged antibiotics following ureteroscopy in a large sample of patients from a multi-site academic system consistent of experienced endourologists.

Conclusion:

Prolonged antibiotic treatment did not reduce postoperative urinary tract infections among patients with negative preoperative urines culture undergoing ureteroscopy for stone disease. Although no difference was noted in the rates of antibiotic-related adverse effects within 30 days of surgery, Urologists should strive to practice good antibiotic stewardship in compliance with the new AUA guidelines in order to reduce potential morbidity and cost to patients.

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Abbreviations

AUA – American Urological Association

UTI – Urinary Tract Infection

CPT – Current Procedural Terminology

BMI – Body Mass Index

Table 1: Study Sample

	Total Sample	Supplemental Homegoing Antibiotics	No Supplemental Antibiotics	P-Value
Number	1068 (100%)	731 (68.4%)	337 (31.6%)	-
Number Female (%)	514 (48.1%)	358 (48.97%)	156 (46.3%)	0.415
Age \pm Standard Deviation (years)	54.5 \pm 15.6	54.0 \pm 15.9	54.9 \pm 15.4	0.346
Body Mass Index \pm Standard Deviation (kg / m²)	30.22 \pm 7.11	30.52 \pm 7.33	29.59 \pm 6.57	0.039
Antibiotic Allergy (%)	303 (28.4%)	197 (26.95%)	106 (31.45%)	0.129
Pre-operative Pyuria	233 (21.8%)	164 (22.4%)	69 (20.5%)	0.52
Diabetes Mellitus (%)	259 (24.3%)	183 (25.03%)	76 (22.55%)	0.379
Operative Time \pm Standard Deviation (minutes)	54.63 \pm 15.57	54.94 \pm 15.42	53.96 \pm 15.89	0.346
Intraoperative Stent Placement (%)	372 (34.8%)	237 (32.4%)	135 (40.1%)	0.0149
UTI within a year prior	158 (14.8%)	106 (14.5%)	52 (15.4%)	0.691

Bold text indicates p < 0.05.

Table 2: Postoperative Course by Home Going Antibiotic Status

	Supplemental Home Going Antibiotics (n=731)	No Supplemental Antibiotics (n=337)	P-Value
Culture-Proven Postoperative Urinary Tract Infection	21 (2.87%)	12 (3.56%)	0.546
Surgically-Related Emergency Room Visit or Telephone Call	173 (23.7%)	91 (27.0%)	0.240
Surgically-Related Emergency Room Visit	26 (3.56%)	17 (5.04%)	0.250
Surgically-Related Telephone Call	162 (22.2%)	85 (25.2%)	0.270
Emergency Room Visit or Telephone Call for Possible Infection	27 (3.69%)	13 (3.86%)	0.896
Emergency Room Visit for Possible Infection	7 (0.96%)	1 (0.30%)	0.447
Telephone Call for Possible Infection	22 (3.01%)	12 (3.56%)	0.633
Possible Antibiotic Adverse Event	20 (2.74%)	7 (2.08%)	0.524

Table 2b

Those who received home going antibiotics			
	No post op UTI	Post op UTI	P value
UTI within one year of ureteroscopy	616 (98.6%)	9 (1.44%)	p<0.0001
Prior UTI	94 (88.7%)	12 (11.3%)	
Those who received no home going antibiotics			
No UTI within one year of ureteroscopy	281 (98.6%)	4 (1.4%)	p<0.0001
Prior UTI	44 (84.6%)	8 (15.4%)	

Table 3: Postoperative Course With Stent Placement With or Without Antibiotics

	Stent Placed + Antibiotic	Stent Placed No Antibiotic	P- Value
Sample Size (% Stented Group; n=372)	237 (63.7%)	135 (36.3%)	-
Culture-Proven Postoperative Urinary Tract Infection (% Stented Group; n=372)	8 (3.38%)	6 (4.44%)	0.602
Surgically-Related Emergency Room Visit or Telephone Call (% Stented Group; n=372)	71 (29.96%)	40 (29.63%)	0.947
Surgically-Related Emergency Room Visit (% Stented Group; n=372)	12 (5.06%)	5 (3.70%)	0.616
Surgically-Related Telephone Call (% Stented Group; n=372)	68 (28.69%)	39 (28.89%)	0.968
Emergency Room Visit or Telephone Call for Possible Infection (% Stented Group; n=372)	7 (2.95%)	4 (2.96%)	1.000
Emergency Room Visit for Possible Infection (% Stented Group; n=372)	3 (1.27%)	0 (0.00%)	0.556
Telephone Call for Possible Infection (% Stented Group; n=372)	6 (2.53%)	4 (2.96%)	1.000
Possible Antibiotic Adverse Event (% Stented Group; n=372)	10 (4.22%)	2 (1.48%)	0.224

Table 4: Postoperative Course Without Stent Placement With or Without Antibiotics

	No Stent + Antibiotics	No Stent No Antibiotic	P- Value
Sample Size (% No Stent Group)	494 (71.0%)	202 (29.0)	
Culture-Proven Postoperative Urinary Tract Infection (% No Stent Group)	13 (2.63%)	6 (2.97%)	0.803
Surgically-Related Emergency Room Visit or Telephone Call (% No Stent Group)	102 (20.65%)	51 (25.25%)	0.184
Surgically-Related Emergency Room Visit (% No Stent Group)	14 (2.83%)	12 (5.94%)	0.050
Surgically-Related Telephone Call (% No Stent Group)	94 (19.03%)	46 (22.77%)	0.263
Emergency Room Visit or Telephone Call for Possible Infection (% No Stent Group)	20 (4.05%)	9 (4.46%)	0.807
Emergency Room Visit for Possible Infection (% No Stent Group)	4 (0.81%)	1 (0.50%)	0.656
Telephone Call for Possible Infection (% No Stent Group)	16 (3.24%)	8 (3.96%)	0.636
Possible Antibiotic Adverse Event (% No Stent Group)	10 (2.02%)	5 (2.48%)	0.775