A pilot intervention trial to reduce the use of post-procedural antimicrobials after common endourologic surgeries

Protocol date March 8, 2024

Version 1.2

Principal investigator: Daniel Livorsi, MD, MSc

Data analyst/statistician: Qianyi Shi, PhD; Steven Y. Alberding, MS; Knute D. Carter, PhD

Urology consultants: Ryan Steinberg, MD and Vignesh Packiam, MD

BACKGROUND

Antimicrobial resistance (AMR) is one of today's most urgent public health problems. Not only is the prevalence of AMR increasing, but the discovery of novel antimicrobial agents has slowed. Infections associated with AMR are more difficult to treat and have worse outcomes than infections due to susceptible pathogens.

Antimicrobial use is a key contributor to the emergence and spread of AMR; therefore, an important target for AMR reduction efforts is unnecessary antimicrobial-prescribing. It is estimated that approximately 30% of all antimicrobial-prescribing is unnecessary.[1,2] Early efforts to reduce unnecessary antimicrobial-prescribing have largely focused on hospitalized patients and patients in ambulatory care with acute respiratory tract infections.[3,4]

Opportunities to reduce unnecessary antimicrobial-prescribing in patients undergoing elective ambulatory surgeries have largely gone overlooked. However, several studies describe the extended and often unnecessary use of antimicrobials after ambulatory procedures, including the placement of cardiovascular implantable electronic devices, foot and ankle surgeries, ear/nose/throat surgeries and urologic procedures.[5-8]

While prolonged post-procedural antimicrobials do not confer any benefit, they do place the patient at increased risk of antimicrobial-related harm, particularly *Clostridioides difficile* infection (CDI). This has been documented in multiple studies across a variety of surgical types, including urologic procedures.[6,9,10,11]

Audit-and-feedback has been leveraged to reduce the unnecessary use of post-procedural antimicrobials. In 34 hospitals across South Africa, a pharmacist-driven, audit-and-feedback intervention targeted surgeons' compliance with 4 process measures for peri-procedural antimicrobial prophylaxis. The intervention achieved a significant improvement in antimicrobial-prescribing, including a 16.2% improvement in the appropriate duration of peri-procedural antimicrobials.[12] Only 2 of the 34 hospitals audited urologic procedures.

The Surgical Care Improvement Project (SCIP) also used audit-and-feedback to improve antimicrobial-prescribing among surgical inpatients. SCIP was a nationwide initiative to reduce surgical complications through accountability and public disclosure. Ambulatory surgeries and urologic procedures were not included in SCIP. Compliance with SCIP standard 3, the discontinuation of antimicrobials within 24 hours of the operation, increased from <60% at baseline to 94% in 2012.[13] These improvements were achieved even before CMS tied SCIP measures to hospital reimbursements in fiscal year 2013.

Although audit-and-feedback has been effective in improving antimicrobial-prescribing among certain types of surgical specialties, its benefit among urologic providers is unclear. In 2015, urologists accounted for the 8th highest number of outpatient antimicrobial prescriptions among all specialties.[14] Given such a high frequency of antimicrobial-prescribing, there may be opportunities for enhanced antimicrobial stewardship among urologists.

The Best Practice Policy Statement on Urologic Surgery Antimicrobial Prophylaxis, published by the American Urological Association (AUA), recommends single-dose antimicrobial prophylaxis without post-procedural continuation is recommended for most urologic procedures.[15]

However, the unnecessary use of post-procedural antimicrobials is common after urologic procedures, according to administrative data our group analyzed from the VHA. In a national

cohort of nearly 30,000 patients, extended post-procedural antimicrobials (defined as >24 hours) were prescribed after 37.2% of urologic procedures for a median duration of 3.0 excess days.[5] Based on a manual chart validation, 177 of 211 (83.9%) patients who received excessive post-procedural antimicrobials (i.e. more than 24 hours after the procedure) did not have a clear indication for antimicrobial therapy. At the hospital-level, the use of excessive post-procedural antimicrobials varied widely. For example, after transurethral resection of bladder tumors, the median frequency of excessive post-procedural antimicrobial-prescribing at the hospital-level was 27.9% with an interquartile range of 14.7-55.0%. Overall, we estimate that there are 30,000 days of unnecessary antimicrobial therapy per year in VHA patients undergoing these three urologic procedures.

In a separate study, we found that fluoroquinolones are frequently prescribed for extended surgical prophylaxis in patients undergoing urologic procedures.[16] The frequent use of fluoroquinolones is concerning given the strong association between fluoroquinolone use and several adverse events, including CDI.[17]

In December 2018, our study team surveyed 110 hospitals within the research network of the Society for Healthcare Epidemiology of America. Forty hospitals (36.4%) responded. Among the 38 hospitals that performed urologic procedures, 18 (47.4%) had never audited whether urologists at their facility adhered to the AUA guidelines for post-procedural antimicrobial use. In the hospitals that did audit, 30% reported that antimicrobials were always prescribed for more than 24 hours. Another 30% reported prolonged post-procedural courses were prescribed in some patients.

These findings suggest that there is an unrecognized opportunity to evaluate and potentially improve antimicrobial-prescribing in patients undergoing urologic procedures. The following study will leverage audit-and-feedback plus additional implementation strategies with the goal of reducing unnecessary post-procedural antimicrobial use after 3 common urologic procedures. The findings from this pilot trial could inform a larger intervention across the VHA to reduce the use of excessive post-procedural antimicrobial prophylaxis in urologic patients.

METHODS

Trial design:

We will use a before/after quasi-experimental design, which will be analyzed with an interrupted time-series analysis.

Participants:

Eligibility criteria: There will be 3 intervention VHA hospitals. To be eligible, a VHA hospital must perform the following 3 urologic procedures: transurethral resection of the prostate (TURP), transurethral resection of a bladder tumor (TUBRT), and ureteroscopy (URS). Eligible VAMCs needed to perform these three index procedures, perform at least 75 qualifying procedures per year, and utilize excess post-procedural antimicrobial in the highest tertile for all sites.

Method of recruitment: The Chief of Urology at an eligible intervention sites will be contacted by e-mail. A follow-up Microsoft Teams or Zoom call will be scheduled to explain the project, if the Chief of Urology is interested in potentially participating.

Interventions:

- Content: Feedback on the percentage of patients who underwent a qualifying procedure and received an antimicrobial on post-procedural day 1

- Delivery method: At baseline, feedback will be given via a video-conferencing call in which we show the team their feedback report and explain what it means. All subsequent feedback will be delivered through e-mail.

- Unit of delivery: The feedback will be given to all practicing urologists at a site.

- Deliverer: The baseline video-conferencing call will be attended by the study team (Drs. Livorsi, Steinberg and Packiam). The electronic feedback will be sent from the PI's e-mail account.

- Setting: The intervention will be delivered via video-conferencing (baseline) or via e-mail (months 1, 3, 5, 7, 9, and 11).

- Exposure quantity and duration: Feedback will be given at baseline and every 2 months

- Time span: 12 months

- Activities to increase compliance or adherence: During the introductory call, the study team will review the AUA's guidelines on antimicrobial prophylaxis and the potential harms of extending antimicrobial prophylaxis beyond a single dose.[15,18] The Chief of Urology at each site will be encouraged to be a local champion for more judicious use of post-procedural antibiotics.

Objectives:

- Study objectives: Evaluate whether a pilot audit-and-feedback intervention across 3 hospitals can safely reduce the unnecessary use of post-procedural antimicrobials in patients undergoing urologic procedures.
- Hypotheses: An bundled intervention across 3 hospitals will facilitate safe reductions in post-procedural antimicrobial-prescribing.

Outcomes:

Clinical outcomes are listed below. Data for all clinical outcomes will be extracted from the Corporate Data Warehouse (CDW) using the VA Informatics and Computing Infrastructure (VINCI).

Primary outcome

Excess post-procedural antimicrobial use is defined as a prescription for a designated antimicrobial agent on post-procedural day one. Designated antimicrobials will be antimicrobial agents potentially used for a urinary tract-related indication, as outlined in our prior work.[5] This definition will be used to minimize the chance of including patients receiving antimicrobials for non-urologic or non-prophylactic indications.

Patients will be eligible for this outcome if they underwent a medical procedure coded with a Current Procedural Terminology (CPT) code or an International Classification of Diseases, 10th version, Procedure Coding System (ICD-10-PCS) code for TURPs, TURBTs, and URSs during

the 2-year baseline period or during the 1-year intervention period. These three procedures were selected because they are all common procedures performed endoscopically with no skin incision required. In addition, for all 3 procedures, the AUA guidelines give a clear recommendation for giving a single dose of antimicrobial prophylaxis.[15]

Secondary outcomes

Excess post-procedural antimicrobial duration is defined as the duration of continuous excessive post-procedural antimicrobial use, as quantified as days of therapy per National Healthcare Safety Network methodology.[19]

Safety outcomes

- Late antimicrobial prescription is defined as the prescription of a designated antimicrobial that does not qualify as a post-procedural antimicrobial (see above) by any provider within 7-30 days of the date of the patient's urologic procedure. All late antimicrobial prescriptions must be agents potentially used for a urinary tract-related indication, as outlined in our prior work.[5]
- Return visits: seeking care in an Emergency Department, Urgent Care Clinic or hospital readmission to an acute-care bed at a VHA facility for any indication within 30 days of the patient's index urologic procedure.

Assignment Method: Intervention sites will be selected from the top tertile of all sites, as ranked on the frequency of excess post-procedural antimicrobial-prescribing. Eligible new sites will be invited until 3 unique sites agree to participate.

Sample Size: This was a pilot trial, so no sample size calculation was performed.

Blinding: None

Unit of Analysis: Each medical center (3 intervention)

Statistical Methods:
Patient demographics, comorbidities, and types of procedures are presented by count and percentages. Observations occurring within the implementation phase (July 2022) were omitted from all analyses. Observations from each of the three sites were stratified into three data sets to accommodate separate analyses on each site.

To model the primary outcome, we used a logistic regression model and a set of three explanatory variables: time, a binary indicator for an observation occurring within the intervention phase, and an interaction term between these two main effects (time and intervention). Time was measured in days divided by 365, giving an annualized figure for the time coefficient estimate and interaction coefficient. In the tables of results of these logistic regression models, the coefficient estimates are exponentiated to display estimated multiplicative effect on the odds; 95% confidence intervals are also provided on the odds scale. The median duration of post-procedural antimicrobial prescriptions at each site were compared using the Wilcoxon rank-sum test.

To model the secondary outcomes, we used a similar approach to what is described above with the addition of a fourth explanatory variable (a binary indicator for the primary outcome) to the

logistic regression model. This last variables was included to assess the risk of these secondary outcomes in patients who were not exposed to post-procedural antimicrobials compared to those who were exposed.

References:

1. Fleming-Dutra KE, Hersh AL, Shapiro DJ, et al. Prevalence of Inappropriate Antibiotic Prescriptions Among US Ambulatory Care Visits, 2010-2011. *JAMA*. May 3 2016;315(17):1864-73. doi:10.1001/jama.2016.4151
2. Cosgrove SE, Seo SK, Bolon MK, et al. Evaluation of postprescription review and feedback as a method of promoting rational antimicrobial use: a multicenter intervention. *Infection control and hospital epidemiology*. Apr 2012;33(4):374-80. doi:10.1086/664771
3. Sanchez GV, Fleming-Dutra KE, Roberts RM, Hicks LA. Core Elements of Outpatient Antibiotic Stewardship. *MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports*. Nov 11 2016;65(6):1-12. doi:10.15585/mmwr.rr6506a1
4. Pollack LA, Srinivasan A. Core elements of hospital antibiotic stewardship programs from the Centers for Disease Control and Prevention. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Oct 15 2014;59 Suppl 3:S97-100. doi:10.1093/cid/ciu542
5. Khaw C, Oberle AD, Lund BC, et al. Assessment of Guideline Discordance With Antimicrobial Prophylaxis Best Practices for Common Urologic Procedures. *JAMA Netw Open*. Dec 7 2018;1(8):e186248. doi:10.1001/jamanetworkopen.2018.6248
6. Asundi A, Stanislawski M, Mehta P, et al. Prolonged antimicrobial prophylaxis following cardiac device procedures increases preventable harm: insights from the VA CART program. *Infect Control Hosp Epidemiol*. Sep 2018;39(9):1030-1036. doi:10.1017/ice.2018.170
7. Branch-Elliman W, Pizer SD, Dasinger EA, et al. Facility type and surgical specialty are associated with suboptimal surgical antimicrobial prophylaxis practice patterns: a multi-center, retrospective cohort study. *Antimicrobial resistance and infection control*. 2019;8:49. doi:10.1186/s13756-019-0503-9
8. Ruta DJ, Kadakia AR, Irwin TA. What are the patterns of prophylactic postoperative oral antibiotic use after foot and ankle surgery? *Clin Orthop Relat Res*. Oct 2014;472(10):3204-13. doi:10.1007/s11999-014-3733-4
9. Poeran J, Mazumdar M, Rasul R, et al. Antibiotic prophylaxis and risk of Clostridium difficile infection after coronary artery bypass graft surgery. *J Thorac Cardiovasc Surg*. Feb 2016;151(2):589-97 e2. doi:10.1016/j.jtcvs.2015.09.090
10. Bernatz JT, Safdar N, Hetzel S, Anderson PA. Antibiotic Overuse is a Major Risk Factor for Clostridium difficile Infection in Surgical Patients. *Infect Control Hosp Epidemiol*. Oct 2017;38(10):1254-1257. doi:10.1017/ice.2017.158
11. Calvert JK, Holt SK, Mossanen M, et al. Use and outcomes of extended antibiotic prophylaxis in urological cancer surgery. *J Urol*. Aug 2014;192(2):425-9. doi:10.1016/j.juro.2014.02.096
12. Brink AJ, Messina AP, Feldman C, Richards GA, van den Bergh D, Netcare Antimicrobial Stewardship Study A. From guidelines to practice: a pharmacist-driven prospective audit and feedback improvement model for peri-operative antibiotic prophylaxis in 34 South African hospitals. *J Antimicrob Chemother*. Apr 1 2017;72(4):1227-1234. doi:10.1093/jac/dkw523

13. Munday GS, Deveaux P, Roberts H, Fry DE, Polk HC. Impact of implementation of the Surgical Care Improvement Project and future strategies for improving quality in surgery. *Am J Surg*. Nov 2014;208(5):835-840. doi:10.1016/j.amjsurg.2014.05.005
14. Durkin MJ, Hsueh K, Sallah YH, et al. An evaluation of dental antibiotic prescribing practices in the United States. *J Am Dent Assoc*. Dec 2017;148(12):878-886.e1. doi:10.1016/j.adaj.2017.07.019
15. Lightner DJ, Wymer K, Sanchez J, Kavoussi L. Best Practice Statement on Urologic Procedures and Antimicrobial Prophylaxis. *J Urol*. Feb 2020;203(2):351-356. doi:10.1097/JU.0000000000000509
16. H Suzuki EP, B Alexander, BE Beck, M Goto, B Lund, R Nair, DJ Livorsi. Fluoroquinolone use at hospital discharge: a new target for antimicrobial stewardship efforts. presented at: The Society for Healthcare Epidemiology of America; 2019; Boston, MA. Session Abstract #258.
17. Stahlmann R, Lode HM. Risks associated with the therapeutic use of fluoroquinolones. *Expert Opin Drug Saf*. Jul 2013;12(4):497-505. doi:10.1517/14740338.2013.796362
18. Granado BAR, Alexander B, Steinberg RL, Packiam VT, Lund BC, Livorsi DJ. Post-procedural Antibiotic Use and Associated Outcomes After Common Urologic Procedures Across a National Healthcare System. *Urology*. Jan 2023;171:115-120. doi:10.1016/j.urology.2022.10.014
19. National Healthcare Safety Network. Antimicrobial Use and Resistance Module. Centers for Disease Control and Prevention. Accessed March 8, 2019, https://www.cdc.gov/nhsn/pdfs/pscmanual/11pscaurcurrent.pdf