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Preventing Prostate Biopsy Complications: to Augment or to Swab?

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OBJECTIVE To use data from a large, prospectively- acquired regional collaborative database to compare the risk of infectious complications associated with three American Urologic Association- recommended antibiotic prophylaxis pathways, including culture-directed or augmented antibiotics, following prostate biopsy.

METHODS Data on prostate biopsies and outcomes were collected from the Pennsylvania Urologic Regional Collaborative, a regional quality collaborative working to improve the diagnosis and treatment of prostate cancer. Patients were categorized as receiving one of three prophylaxis pathways: culture-directed, augmented, or provider-discretion. Infectious complications included fever, urinary tract infections or sepsis within one month of biopsy. Odds ratios of infectious complication by pathway were determined, and univariate and multivariate analyses of patient and biopsy characteristics were performed.

RESULTS 11,940 biopsies were included, 120 of which resulted in infectious outcomes. Of the total biopsies, 3246 used "culture-directed", 1446 used "augmented" and 7207 used "provider-discretion" prophylaxis. Compared to provider-discretion, the culture-directed pathway had 84% less chance of any infectious outcome (OR= 0.159, 95% CI = [0.074, 0.344], $P < 0.001$). There was no difference in infectious complications between augmented and provider-discretion pathways.

CONCLUSIONS The culture-directed pathway for transrectal prostate biopsy resulted in significantly fewer infectious complications compared to other prophylaxis strategies. Tailoring antibiotics addresses antibiotic-resistant bacteria and reduces future risk of resistance. These findings make a strong case for incorporating culture-directed antibiotic prophylaxis into clinical practice guidelines to reduce infection following prostate biopsies. UROLOGY 00: 1–8, 2021. © 2021 Elsevier Inc.

There were an estimated 1.2 million new cases of prostate cancer diagnosed worldwide in 2018,[1] making it the second most common malignancy diagnosed in males following lung cancer. The majority of these cases are identified through a combination of prostate-specific antigen screening and digital rectal exam, followed by a confirmatory prostate biopsy. Since the introduction of the systematic, imaging- guided prostate biopsy by Hodge et al. in 1989[2] and subsequent addition of more lateral and anterior core biopsies, the transrectal approach has become the most common method for diagnosis of prostate cancer. Though transrectal ultrasound guided prostate biopsy (TRUSB) remains the most commonly performed procedure for obtaining prostatic tissue, it is not without complications and risks. Among the most frequent complications is infection, with the incidence reported to be between 2.9%-7.2%[3-7] and the rate of infection rising over the years.[8] Nearly 92% of hospitalizations within 30 days of prostate biopsy are the result of infection.[9] Urinary tract infections

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(UTIs), prostatitis, epididymitis and bacteremia are frequently encountered infectious outcomes, with *Escherichia coli* most commonly identified. Common risk factors for the development of post-TRUSB infections include Diabetes Mellitus[10–12] and chronic immunosuppression.[13] While progression to sepsis occurs in only 2% of patients,[14] it represents significant disease burden and is a costly sequela, with one study reporting expenses upwards of $19,100.[15]

To minimize infectious complications, antibiotic prophylaxis in the pre-biopsy period has been recommended by the AUA, with oral fluoroquinolones the traditional choice. However, the rate of fluoroquinolone resistance in this population has risen, approaching 10%-25% of men.[16] This is concerning as fluoroquinolone resistance is associated with poorer TRUSB outcomes, including a 4-5 times greater risk of infection[5,16,17] and an 8 times greater risk of sepsis.[14] Protocols from other institutions aimed at combating rising fluoroquinolone resistance have included the implementation of local antibiogram-guided antibiotic prophylaxis,[3] a step-wise flowsheet incorporating local antibiograms and a patient's personal infectious risk factors,[16] and the use of dual antibiotic regimens.[18,19] Another approach to minimize infection outcomes following TRUSB is through the use of pre-biopsy swabs to culture the flora of the rectal vault. This tailored antibiotic selection has shown mixed efficacy, with some studies finding a lower risk of infection with swab use[4,6,20] while others have demonstrated mixed[5] or worse rates of infectious outcomes.[7]

As fluoroquinolone resistant *E. coli* and other multidrug resistant organisms (MDROs) continue to increase in prevalence in the urologic patient, we can anticipate the number of infectious complications following TRUSB to have a corresponding surge. A large study of antibiotic prophylaxis is necessary to settle the varying results of other studies of infectious biopsy complications, and to identify factors associated with clinically relevant infectious outcomes. Utilizing data from the Pennsylvania Urologic Regional Collaboration (PURC), a database on prostate cancer, we sought to investigate the performance of three commonly- used TRUSB prophylaxis regimens and determine the associated risk of infectious complications with each. We hypothesized that the "culture-directed" pathway for prophylaxis reduces the risk of infectious outcomes compared to the "augmented" or "provider-discretion" pathways. We also hypothesized that particular comorbidities such as elevated Body Mass Index (BMI), Diabetes Mellitus (DM) and Acquired Immunodeficiency Syndrome (AIDS), are associated with an increased risk of infectious outcomes following biopsy.

METHODS

The Pennsylvania Urologic Regional Collective is a partnership of eleven organizations based in Pennsylvania and New Jersey with the Health Care Improvement Foundation. The aim of this consortium is to collect regional prostate biopsy and cancer data to reduce variation in access and care, and track outcomes for prostate cancer and treatments. Patient data is abstracted from patients' medical charts and input into to a shared database, and covers many aspect of the treatment course from PSA laboratory values, to prostate biopsies, to medical, surgical and radiation treatments.

Variables of interest included patient demographics, number of previous biopsies, biopsy type, prophylaxis pathway, infectious outcomes and comorbidities, among others (Table 1). Patients in the database were documented as receiving one of three antibiotic prophylaxis pathways (Fig. 1), as abstracted from provider notes. The "culture-directed" pathway targeted prophylaxis to the results of a patient's rectal swab. The "augmented" pathway indicated that a baseline antibiotic was used, and was augmented with an additional antibiotic based on the local/hospital antibiogram to address possible resistance. Finally, the "provider-discretion" pathway indicated that while providers gave an antibiotic for prophylaxis, it was not culture-based, nor was a second antibiotic given for additional coverage. The antibiotics prescribed in this pathway were given at the discretion of the provider. Fluoroquinolones such as ciprofloxacin, and first- through- third generation cephalosporins, have historically been prescribed for empiric prophylaxis and are recommended by the AUA, as they provided coverage for gram-negative gastrointestinal bacteria. The "provider-discretion" pathway typically used one of these antibiotics. "Infectious outcomes" included the occurrence of fever, urinary tract infection, or sepsis within one month following prostate biopsy. Data on each patient in the database is collected by the respective institutions' abstractors who receive regular notifications to perform a chart review and update patient profiles. In this way, the occurrence of infectious complications, hospitalization and treatment details are routinely added to patient profiles in the PURC database (as applicable). This notification system ostensibly mitigates patients lost to data abstraction follow-up.

Inclusion criteria consisted of having received a prostate biopsy at one of the participating PURC institutions. Descriptive summaries by the three pathways were summarized. To address missing covariates in the data, a statistician conducted multivariate imputation by chained equations (MICE) proposed by Van Buuren, Boshuizen, and Knook[21] with a widely used R package MICE.[22] It specified the imputation model on each missing value variable based on other observed variables. They fitted logistic regression models to each of 40 imputed datasets and combined each set of estimates into an overall set of estimates.

Univariate association- including odds ratios and tests of significance- of infectious outcomes with the queried covariates were conducted using logistic regression. Upon completion of univariate analyses, candidate variables with P-values < 0.25 were selected for the multivariate analysis. The significance level for this logistic regression was finalized at 5%. All data analyses were performed using R 3.6.0.

RESULTS

The dataset included 11,940 prostate biopsies taken from 2015 to 2019. Forty-four patients were then eliminated due to a BMI or gland volume value that fell outside the respective ranges. Of the 11,896 patients included in the analysis, 122 (1.0%) biopsies resulted in infectious outcome. Seven of 3246 (0.2%) "culture-based" biopsies, 20 of 1446 (1.4%) "augmented" biopsies, and 95 of 7207 (1.3%) "provider-discretion" biopsies experienced an infectious outcome.

Descriptive summaries of the data by prophylactic pathway can be found in Table 1. Across the three pathways, the average

Table 1. Descriptive summaries by antibiotic prophylaxis pathways

Variables of Interest	Culture (N = 3246)	Augmented (N = 1443)	Provider- Discretion (N = 7207)	Total (N = 11896)
Race, n (%)				
African American	333 (19.1%)	180 (30.8%)	793 (21.4%)	1306 (21.6%)
Asian	25 (1.4%)	15 (2.6%)	113 (3.0%)	153 (2.5%)
Caucasian	1335 (76.5%)	352 (60.3%)	2730 (73.6%)	4417 (73.2%)
Other	51 (2.9%)	37 (6.3%)	74 (2.0%)	162 (2.7%)
Missingness, *n*	1502	859	3497	5858
Age, n (%)				
Age >80	52 (2.9%)	20 (3.3%)	257 (6.8%)	329 (5.3%)
Age <80	1750 (97.1%)	588 (96.7%)	3520 (93.2%)	5858 (94.7%)
Missingness, *n*	1444	835	3430	5709
Number of previous biopsies, n (%)				
1 biopsy	140 (4.5%)	220 (17.2%)	786 (12.8%)	1146 (10.9%)
More than one biopsy	105 (3.4%)	110 (8.6%)	335 (5.4%)	550 (5.2%)
0 biopsies	2867 (92.1%)	946 (74.1%)	5036 (81.8%)	8849 (83.9%)
Missingness, *n*	134	167	1050	1351
Histology found on biopsy, n (%)				
Adenocarcinoma	2913 (99.8%)	764 (100.0%)	3895 (99.8%)	7572 (99.8%)
Other	6 (0.2%)	0 (0.0%)	9 (0.2%)	15 (0.2%)
Missingness, *n*	327	679	3303	4309
Glandvol (gram or cc), Mean (SD)				
Mean (SD)	50.202 (27.270)	54.347 (34.198)	51.331 (30.287)	51.749 (30.804)
Missingness, *n*	2775	122	734	3631
Biopsy Type, n (%)				
TRUS	2801 (93.1%)	1111 (77.6%)	5951 (83.1%)	9863 (85.0%)
Perineal	3 (0.1%)	1 (0.1%)	58 (0.8%)	62 (0.5%)
TURP	39 (1.3%)	30 (2.1%)	301 (4.2%)	370 (3.2%)
MRI/Fusion	164 (5.5%)	290 (20.3%)	855 (11.9%)	1309 (11.3%)
Missingness, *n*	239	11	42	292
Infectious Outcome n (%)				
Yes	7 (0.2%)	20 (1.4%)	95 (1.3%)	122 (1.0%)
Peripheral Vascular Disease, n (%)				
Yes	15 (1.0%)	1 (0.4%)	41 (1.8%)	57 (1.4%)
No	1418 (99.0%)	254 (99.6%)	2290 (98.2%)	3962 (98.6%)
Missingness, *n*	1813	1188	4876	7877
Diabetes, n (%)				
Yes	585 (18.0%)	126 (8.7%)	581 (8.1%)	1292 (10.9%)
No	2661 (82.0%)	1317 (91.3%)	6626 (91.9%)	10604 (89.1%)
Cerebral Vascular Disease, n (%)				
Yes	33 (2.3%)	9 (3.5%)	65 (2.8%)	107 (2.7%)
No	1400 (97.7%)	246 (96.5%)	2266 (97.2%)	3912 (97.3%)
Missingness, n	1813	1188	4876	7877
Dementia, n (%)				
Yes	1 (0.1%)	1 (0.4%)	3 (0.1%)	5 (0.1%)
No	1432 (99.9%)	254 (99.6%)	2328 (99.9%)	4014 (99.9%)
Missingness, n	1813	1188	4876	7877
2nd Solid Tumor, n (%)				
Yes	81 (2.5%)	11 (0.8%)	215 (3.0%)	307 (2.6%)
No	3165 (97.5%)	1432 (99.2%)	6992 (97.0%)	11589 (97.4%)
Renal Insufficiency (Cr>3), n (%)				
Yes	4 (0.3%)	1 (0.4%)	45 (1.9%)	50 (1.2%)
No	1429 (99.7%)	254 (99.6%)	2286 (98.1%)	3969 (98.8%)
Missingness, *n*	1813	1188	4876	7877

gland size was approximately 51 grams, and the majority of patients had undergone no previous biopsies. Comparable rates of comorbidities (diagnoses of AIDS, DM, and renal insufficiency among others) were observed between the three pathways.

Univariate logistic regression of infectious outcomes revealed that prophylactic pathway, gland volume, number of previous biopsies and biopsy type were significantly associated with infection (Table 2). Due to the extremely low incidence of infectious outcomes in patients with AIDS, dementia, hemiplegia, liver disease or a blood malignancy, these comorbidities were not included in the univariate analysis. There was no significant association on univariate analysis between the other comorbidities and infectious outcome.

On multivariate analysis of the candidate factors, it was found that infectious outcomes following prostate biopsy were significantly associated with the prophylaxis pathway utilized, and the biopsy type (Table 3). Compared to the "provider-discretion"

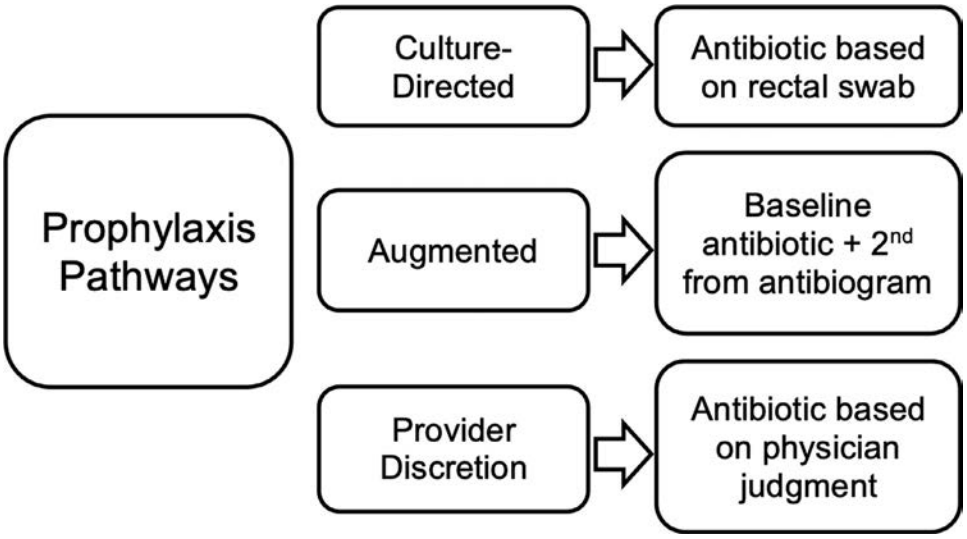

Figure 1. Prophylaxis pathways described by PURC. Three pathways were documented in the PURC system: "culture-directed", "augmented", and "provider discretion". Each pathway entailed its own selection of antibiotics for biopsy prophylaxis

pathway, the "culture-directed" pathway was associated with 84% fewer infectious outcomes after biopsy (OR= 0.159, 95% CI [0.074 to 0.344], $P<0.001$). The "augmented" pathway did not significantly differ in infectious outcomes compared with the "provider-discretion" pathway (OR = 1.014, 95% CI [0.630 to 1.633], $P = 0.953$) (Table 3).

DISCUSSION

Of the nearly 11,900 biopsies analyzed, we found infection outcome rates of 0.2%, 1.4% and 1.3% for biopsies with culture-based, augmented, and provider-discretion pathway prophylaxis, respectively. These rates are lower than previously reported incidences of 3%-7%[3–7]; regional differences in bacterial flora and resistance, antibiotic use and biopsy practices may account for the striking difference in reported infection rates. Patients who experienced infectious complications may have also sought care at non-participating institutions and were potentially lost to follow-up. However, direct comparisons are difficult to make because patient populations and details of antibiotic regimens may differ among studies.

Univariate analysis of each independent variable resulted in multiple significant associations between the number of previous biopsies, gland volume, histology, biopsy approach and prophylaxis pathway, and the number of infectious outcomes. However, a multivariate analysis including all of these independent variables found that biopsy approach and prophylaxis pathway to be significantly associated with infectious outcomes.

Antibiotic Prophylaxis

Analysis of the PURC database shows that utilizing a pre-biopsy rectal swab to select optimal or targeted antibiotics reduces the relative odds of an infectious outcome by 84%, compared to when provider-discretion guides antibiotic selection. Prophylaxis based on local hospital antibiograms is not better than provider-discretion. These results indicate that tailoring antibiotics to *patient-specific* flora is more effective in reducing the number of infections, compared with augmenting the antibiotics or basing the selection on provider discretion.

Previous studies have highlighted the challenging balance between adequate prophylaxis and over-exposure to antibiotics. In 2015, the Michigan Urological Surgery Improvement Collaborative (MUSIC), a physician-led statewide collection of urologic demographics and outcomes, implemented a stepwise approach to minimize these infectious complications and hospitalizations following TRUSB.[23] One recommendation included the use of either culture-guided or augmented antibiotic prophylaxis using levofloxacin. Implementation of this protocol led to a 53% decrease in hospitalizations.[9] However, the vast majority of physicians utilizing the MUSIC protocol gave augmented antibiotics increasing the number of patients receiving multiple antibiotics by 65%,[9] leading to the question of whether this protocol would ultimately breed create more antibiotic resistance in the long term. Other studies have shown that one of the limitations of using a hospital antibiogram for prophylaxis is that it reflects resistance patterns in hospitalized patients, and may not accurately represent the patterns of ambulatory biopsy patients.[16] This is further supported by work suggesting that bacterial isolates used for hospital antibiograms in the Philadelphia-area had the highest sensitivity to AUA-recommended antibiotics (ceftriaxone and fluoroquinolones) but even so were sensitive in only 55.6% of cases.[24] Despite these results and its recommended use by the AUA, adoption of culture-based prophylaxis remains low at 1.5% of biopsies in 2015,[7] perhaps due to concerns about costs, practice implications, or concerns about congruency of flora at the time of swab and biopsy.

An analysis of Medicare fee-for-service claims from 2014-2015 found that the average cost of a prostate biopsy

Table 2. Analysis results of univariate logistic regression on infectious outcomes

Variables	OR	95% CI of OR		*P*-value
Demographics				
Race				
African American vs Caucasian	1.073	0.662	1.738	0.775
Asian vs Caucasian	0.990	0.247	3.971	0.989
Others vs Caucasian	1.471	0.496	4.368	0.488
Age >80	1.091	0.470	2.536	0.839
Biopsy Characteristics				
Number of previous biopsies				
1 Biopsy vs No Previous Biopsies	1.456	0.868	2.442	0.155
More than 1 Biopsy vs No Previous Biopsies	2.184	1.226	3.888	0.008*
Gland volume (10gram or 10cc)	1.054	1.008	1.103	0.022*
Histology, others vs Adenocarcinoma	4.247	0.831	21.696	0.086*
Biopsy Type†				
TURP vs TRUS	3.426	1.860	6.313	<.001*
MRI/Fusion vs TRUS	1.684	1.043	2.719	0.033*
Antibiotic Prophylaxis pathway				
Culture-Directed vs Provider-Discretion	0.149	0.069	0.321	<0.001*
Augmented vs Provider-Discretion	1.019	0.635	1.634	0.939
Comorbidities				
BMI	1.007	0.969	1.048	0.713
Peripheral Vascular Disease	1.090	0.222	5.358	0.916
Diabetes	1.312	0.795	2.164	0.288
Cerebral Vascular Disease	1.017	0.360	2.874	0.974
2nd Solid Tumor	1.191	0.438	3.245	0.732
Chronic Renal Insufficiency/ Disease (Cr >3)	1.084	0.185	6.332	0.929

† For transperineal biopsy, no infection
* Indicates a value below the 0.25 significance level selected for candidate variables

was $2,020 (across surgical settings), but it increased to $3,420 when a single infectious complication occurred within 30 days.[25] Additionally, the cost of hospitalization due to an infectious or bleeding complication averaged $13,840.[25] Previous studies have found significant cost-savings in groups of patients receiving culture-based prophylaxis. The cost of targeted prophylaxis per 100 men undergoing TRUSB was $1,346, compared to $5,598 for men receiving empirical prophylaxis.[20] This included the cost of the swab, various routes of drug administration, and treatment for any infectious complication. Thirty-eight patients needed swabs before one infection was prevented. Targeting prophylaxis yielded a cost-savings of nearly $4,500 per averted post-TRUSB infection.[20] Taken together, these studies show that there is a clear financial benefit from implementing rectal culture swabs prior to prostate biopsy. The long-term fiscal benefits of reducing antibiotic resistance and keeping more antibiotics in a clinician's "armamentarium" for treatment of serious infections is also a critical consideration.

Table 3. Analysis results of multivariate logistic regression on infectious outcomes

Variables	OR	95% CI of OR		*P*-value
Antibiotic Prophylaxis pathway				
Culture-Directed vs Provider Discretion	0.159	0.074	0.344	<.001*
Augmented vs Provider Discretion	1.014	0.630	1.633	0.953
Biopsy Type†				
TURP vs TRUS	2.838	1.536	5.242	0.001*
MRI/Fusion vs TRUS	1.416	0.874	2.294	0.158

† For perineal biopsy, no infection
* Indicates a value below the 0.05 significance level

Concern about incongruity between rectal flora on the swab and subsequent biopsy may play a role in the slow adoption of this practice. However, Liss et al. found correlation in resistance results between rectal swabs 2 weeks prior to biopsy, and at the time of biopsy.[26] This bears further study, as our institutional experience has been based on swabs performed within 4 weeks of biopsy to reduce the risk of alterations in rectal flora. At our institution, patients are provided with a script for fluoroquinolone prophylaxis, to be taken one day prior to biopsy. If results of the rectal swab return showing fluoroquinolone resistance, the patient is called and a new script is prescribed. Anecdotally, this practice at our institution takes approximately two minutes, and is done at the time of digital rectal exam. While setting up the response to flagged culture results may take some time initially (e.g. designating the provider who calls patients about new prescriptions), we believe this hurdle is outweighed by the benefit to patients and providers in reducing the incidence of additional disease burden and costs associated with infectious complications of biopsy.

Limitations and Further Studies

This large study has the advantage of being based on multiple institutions across a number of years. Nevertheless, it is a retrospective analysis of practices in New Jersey and Pennsylvania, and did not capture actual antibiotic resistance patterns for the patients who experienced an infectious complication. This information may have provided insight into the appropriateness of the antibiotics prescribed for each biopsy, regardless of pathway. Secondly, the data is from a database and therefore subject to associated limitations. With multiple data abstractors, there is a chance that data was abstracted differently despite training provided for the position. It is also incumbent on the abstractors at each participating institution to regularly update patient information. If one institution is behind in updating information, this has the potential to affect the data. In addition, missing data resulted from not every database question requiring an answer from abstractors. Missing data may also account for the

lower rate of infection we observed compared to previously published studies.

Further studies are necessary to examine if there are differences in infection rate based on practice setting (for instance, private vs academic centers) and what may account for any differences. The burden of rectal swabs and prescription alterations on clinical practice and its feasibility in community practice and academic centers should also be investigated. Finally, while data from transperineal biopsies were included, these biopsies were not performed frequently enough to capture their effect on infectious outcomes. This biopsy approach has the advantage of not damaging the integrity of the rectum, thus ostensibly reducing the risk of infection and potential need for targeted prophylaxis, and merits further study.

CONCLUSION

As the rates of antibiotic resistance continue to rise, there is a need for a compensatory prophylaxis strategy for prostate biopsies. To prevent the dangerous infection complications of biopsy, the AUA has recommended general "pathways" based on rectal cultures or local antibiograms. We found the "culture-directed" pathway, based on a rectal swab, resulted in an 84% lower infection rate (OR = 0.159) when compared to the "provider-discretion" and the augmented pathway. Targeting antibiotics is a common practice to reduce the development of antibiotic resistance. Urologists share the responsibility of antimicrobial stewardship with the entire healthcare community. As the experts in prostate biopsies and procedures, urologists should work to optimize patient care and minimize development of antibiotic resistance. Performing pre-biopsy swabs to target antibiotics is the superior way to manage prophylaxis.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68:394–424.
2. Hodge K, McNeal J, Stamey T. Ultrasound guided transrectal core biopsies of the palpably abnormal prostate. *J Urol*. 1989;142:66–70.
3. Concepcion R, Schaeffer E, Shore N, et al. The effect of local antibiogram-based augmented antibiotic prophylaxis on infection-related complications following prostate biopsy. *Rev Urol*. 2019;21:93–101.
4. Cussans A, Somani B, Basarab A, et al. The role of targeted prophylactic antimicrobial therapy before transrectal ultrasonography-guided prostate biopsy in reducing infection rates: a systematic review. *BJU Int*. 2016;117:725–731.
5. Dai J, Leone A, Mermel L, et al. Rectal swab culture-directed antimicrobial prophylaxis for prostate biopsy and risk of post procedure infection: a cohort study. *Urol*. 2015;85:8–14.
6. Roberts M, Williamson D, Hadway P, et al. Baseline prevalence of antimicrobial resistance and subsequent infection following prostate biopsy using empirical or altered prophylaxis: A bias-adjusted meta-analysis. *Int J Antimicrob Agents*. 2014;43:301–309.
7. Shoag J, Gaffney C, Pantuck M, et al. Risk factors for infection after prostate biopsy in the United States. *Urol*.In press.
8. Halpern J, Sedrakyan A, Dinerman B, et al. Indications, utilization and complications following prostate biopsy: new york state analysis. *J Urol*. 2017;197:1020–1025.
9. Womble P, Dixon M, Linsell S, et al. Infection related hospitalizations after prostate biopsy in a statewide quality improvement collaborative. *J Urol*. 2014;191:1787–1792.
10. Wu Y, Li X, Ke Z, et al. Risk factors for infectious complications following transrectal ultrasound-guided prostate biopsy. *Infect Drug Resist*. 2018;11:1491–1497.
11. Hasanzadeh A, Black P, Pourmand M, et al. Clinical and bacterial risk factors for development of post-prostate biopsy infections. *Urol J*. 2019;16:603–608.
12. Simsir A, Kismali E, Mammadov R, et al. Is it possible to predict sepsis, the most serious complication in prostate biopsy? *Urol Int*. 2010;84:395–399.
13. Wammack R, Djavan B, Remzi M, et al. Morbidity of transrectal ultrasound-guided prostate needle biopsy in patients receiving immunosuppression. *Urol*. 2001;58:1004–1007.
14. Hadjipavlou M, Eragat M, Kenny C, et al. Effect of augmented antimicrobial prophylaxis and rectal swab culture-guided targeted prophylaxis on the risk of sepsis following transrectal prostate biopsy. *Eur Urol Focus*. 2020;6:95–101.
15. Gross M, Alshak M, Shoag J, et al. Healthcare costs of post-prostate biopsy sepsis. *Urol*. 2019;133:11–15.
16. Liss M, Ehdaie B, Loeb S, et al. An update of the american urological association white paper on the prevention and treatment of the more common complications related to prostate biopsy. *J Urol*. 2017;198:329–334.
17. Liss M, Johnson J, Porter S, et al. Clinical and microbiological determinants of infection after transrectal prostate biopsy. *Clin Infect Dis*. 2015;60:979–987.
18. Yang L, Gao L, Chen Y, et al. Prophylactic antibiotics in prostate biopsy: a meta-analysis based on randomized controlled trials. *Surg Infect*. 2015;16:733–747.
19. Womble P, Linsell S, Gao Y, et al. A statewide intervention to reduce hospitalizations after prostate biopsy. *J Urol*. 2015;194:403–409.
20. Taylor A, Zembower T, Nadler R, et al. Targeted antimicrobial prophylaxis using rectal swab cultures in men undergoing transrectal ultrasound guided prostate biopsy is associated with reduced incidence of postoperative infectious complications and cost of care. *J Urol*. 2012;187:1275–1279.
21. Van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. *Stat Med*. 1999;18:681–694.
22. Van Buuren S, Groothuis-Oudshoorn K. Mice: Multivariate imputation by chained equations in R. *J Stat Soft*. 2010:1–68.
23. *Michigan Urological Surgery Improvement Collaborative (MUSIC): Prostate Biopsy Toolkit*. 2015.. Available at; https://musicurology.com/wp-content/uploads/2014/12/MUSIC-Prostate-Biopsy-Toolkit.pdf. Accessed 8 January 2021.
24. Mann M, Calio BP, Mark JR, et al. Hospital-specific antibiograms and antibiotic prophylaxis for prostate biopsies: a reexamination of AUA recommendations. *Can J Urol*. 2020;27:10099.
25. Weiner AB, Manjunath A, Kirsh GM, et al. The cost of prostate biopsies and their complications: A summary of data on all Medicare fee-for-service patients over two years. *Urol Pract*. 2019:10–1097.
26. Liss MA, Nakamura KK, Meuleners R, et al. Screening rectal culture to identify fluoroquinolone-resistant organisms before transrectal prostate biopsy: do the culture results between office visit and biopsy correlate? *Urol*. 2013;82:67.

EDITORIAL COMMENT

We would like to thank the editors for their comment on "Preventing prostate biopsy complications: to Augment or to Swab". They present some of the challenges to implementing a rectal swab prior to transrectal ultrasound (TRUS) biopsy, and offer an alternative using the transperineal (TP) biopsy approach.

Our study of a large database of outcomes following prostate biopsy found a reduced risk of infectious outcomes in rectal-culture directed antibiotics compared to augmented antibiotics or antibiotics prescribed based on physician judgment. The database did include TP biopsies; however, this method of biopsy was significantly outnumbered by the transrectal approach. Therefore, it was impossible to accurately comment on the infectious complication rate following TP biopsy.

Use of transperineal biopsy remains low, with 93% of biopsies conducted transrectally.[1] Challenges to the uptake of TP biopsies have included concerns about cost, time, provider education/training and method of sedation.[2] There have been several retrospective studies and meta-analyses aimed at elucidating the advantages of one approach over another. Among these, Skouteris et al. found that there was a greater risk of infection following TRUS biopsy, but that urinary retention was more common following TP biopsy, and that the incidence of retention increased with increasing age.[3] The authors concluded that consideration of discharge with Foley catheter should be a part of TP biopsies. One of the few prospective, randomized, clinical trials comparing TP and TRUS biopsies have found that there is a trade-off between the approaches: transperineal biopsies took longer, required different types of anesthesia, and was associated with higher rates of pain, whereas TRUS biopsies resulted in higher rates of major complications that required hospitalization or intervention.[4] It should be noted that this study defined adverse outcomes on the severity, not the type of outcome (infectious or otherwise). Other trials are in progress and will hopefully shed more light on the utility of TP and TRUS biopsies.

Perhaps a conclusion to draw from the available information is that the biopsy approach should be tailored to the individual patient. Patients at high risk of urinary retention or who do not want to be discharged with a Foley catheter should be given the option for a TRUS biopsy and antibiotic prophylaxis tailored to their rectal flora. Patients at risk of infection (immunosuppressed, previously documented drug-resistant organisms, etc.) and or at risk of greater morbidity from an infection may be more suitable for the transperineal approach.

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REFERENCES

1. Liu W, Patil D, Howard DH, et al. Adoption of prebiopsy magnetic resonance imaging for men undergoing prostate biopsy in the United States. *Urol.* 2018;117:57–63.
2. Roberts MJ, Macdonald A, Ranasinghe S, et al. Transrectal versus transperineal prostate biopsy under intravenous anaesthesia: a clinical, microbiological and cost analysis of 2048 cases over 11 years at a tertiary institution. *Prostate Cancer Prostatic Dis.* 2021;24:169–176.
3. Skouteris VM, Crawford ED, Mouraviev V, et al. Transrectal Ultrasound-guided Versus Transperineal Mapping Prostate Biopsy: Complication Comparison. *Rev Urol.* 2018;20:19–25.
4. Guo LH, Wu R, Xu HX, et al. Comparison between Ultrasound Guided Transperineal and Transrectal Prostate Biopsy: A Prospective, Randomized, and Controlled Trial. *Sci Rep.* 2015;5:16089.

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AUTHOR REPLY

The authors used a large prospectively acquired database to compare culture directed, augmented and provider discretion antibiotic pathways for transrectal prostate biopsy antibiotic prophylaxis. They showed that the culture directed pathway for transrectal prostate biopsies resulted in significantly fewer infections compared to the augmented and provider discretion pathways.[1]

Many studies have shown decreased infection rates when rectal swabs and culture directed prophylaxis are used.[2] This approach helps decrease the overall amount of antibiotics used, and yet only 1.8% of prostate biopsies in 2015 were preceded by a rectal swab.[3] Why do so few urologists use pre-biopsy rectal swabs?

From a practical point of view, physician shortages and increasing volumes of patients make adding any amount of extra clinic time for a potential prostate biopsy patient challenging. A process has to be in place to order the rectal swab, do the swab, check the result of the swab a few days later and then contact the patient should the results suggest resistance. This lack of a streamlined process is likely a stumbling block to more widespread use of culture directed antibiotic prophylaxis.

The authors have demonstrated that such a system can be implemented provided the rectal swab is done at the time of the digital rectal exam, and provided someone is designated to call patients should the prescription need to be changed. It must be done at the first visit, as adding an extra clinic visit for every prostate biopsy patient introduces another hurdle in getting to a

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timely diagnosis. Systems need to be in place to make such a process seamless and routine.

The question of whether to use augmented antibiotic prophylaxis or to use culture directed prophylaxis may eventually be superseded by transperineal prostate biopsies. Transperineal biopsies are usually done under general anaesthesia, and the added time and practice expense associated with this has meant that the rate of uptake has been low. It has been shown than transperineal biopsies can be done under local anaesthesia in the office as well,[4] and as this process avoids the rectum altogether, the infection rate is significantly lower.[5]

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REFRENCES

1. Preventing prostate biopsy complications: to augment or to swab? *Urology*. 2021.
2. Cussans A, Somani BK, Basarab A, et al. The role of targeted prophylactic antimicrobial therapy before transrectal ultrasonography-guided prostate biopsy in reducing infection rates: a systematic review. *BJU Int*. 2016;117:725–731.
3. Shoag JE, Gaffney C, Pantuck M, et al. Risk factors for infection after prostate biopsy in the united states. *Urology*. 2020;138:113–118.
4. Meyer AR, Joice GA, Schwen ZR, et al. Initial experience performing in-office ultrasound-guided transperineal prostate biopsy under local anesthesia using the precisionpoint transperineal access system. *Urology*. 2018;115:8–13.
5. Borghesi M, Ahmed H, Nam R, et al. Complications after systemic, random, and image-guided prostate biopsy. *Eur Urol*. 2017;71:353–365.

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