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Study Need and Importance: Risk of infectious complications after transrectal prostate biopsy is reported to be on the rise. Transperineal prostate biopsy has been proposed as the superior alternative due to minimal risk of infection. However, the guidelines related to prostate biopsy procedure are conflicting. The existing data consist entirely of observational cohort analyses, with a distinct lack of randomized comparative studies. We conducted the first randomized controlled trial, with prespecified outcomes, to directly compare the infectious and noninfectious complications associated with the 2 biopsy procedures.

What We Found: Among the 763 men randomized to either the transrectal or transperineal prostate biopsy, postbiopsy composite infectious complications occurred in 2.6% and 2.7% of men, respectively. No cases of sepsis were noted (Figure). Our definition of infectious complications was quite inclusive and incorporated "possible" infectious events. Utilizing a more stringent definition, as used in other studies (documented UTI, sepsis, antibiotics), the infectious complication rates in our study were 1.1% and 1.4% for transrectal and transperineal biopsy, respectively. All biopsy procedures were performed in the office, using local anesthesia, with 1-day antibiotic prophylaxis for transrectal procedures, and only occasional antibiotic prophylaxis for transperineal biopsy. Noninfectious complications rates (urinary retention, emergency visit, hospitalization) were 1.7% and 2.2% after transrectal and transperineal biopsies, respectively. All infectious and noninfectious complications were minor and/or self-limited.

Limitations: The majority of the participants were White (92.6%), and the results may not be applicable to other ethnic groups. Our single-center design can also limit generalizability to some other settings, although the multilocations recruitment and pragmatic design feature can mitigate some of those concerns.

Interpretation for Patient Care: There was no difference in the risk of infectious complications after transrectal and transperineal prostate biopsy. Both procedures were associated with a low risk of minor complications.

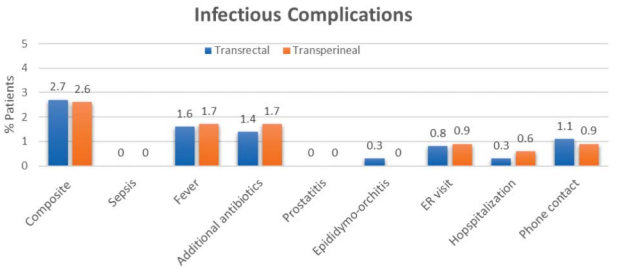

Figure. The risk of composite and individual infectious complications after transrectal and transperineal prostate biopsy procedures. ER indicates emergency room.

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Complications Following Transrectal and Transperineal Prostate Biopsy: Results of the ProBE-PC Randomized Clinical Trial

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Data Availability: The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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Editor's Note: This article is the first of 5 published in this issue for which Category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 337 and 338.

Purpose: Transrectal prostate biopsy has come under scrutiny due to potential for postbiopsy infections and transperineal prostate biopsy is being offered as the safer alternative. However, there is a lack of randomized comparative studies. Our goal was to directly evaluate infectious and noninfectious complications following the 2 biopsy procedures.

Materials and Methods: We conducted a prospective, pragmatic, randomized clinical study in men undergoing prostate biopsy. The participants underwent either transrectal or transperineal prostate biopsy in the office under local anesthesia. The primary outcome was a 30-day composite infectious complication rate, comprising of 1 or more components including fever, genitourinary infection, antibiotic prescriptions, office or emergency visits, hospitalization, or sepsis. Secondary outcomes included 30-day composite noninfectious complications (urinary or hemorrhagic).

Results: Of the 763 randomized participants, 718 underwent either transrectal (351) or transperineal (367) prostate biopsy. A composite infectious complication event occurred in 9 participants (2.6%) in the transrectal and 10 participants (2.7%) in the transperineal group (odds ratio, 1.06; 95% CI, 0.43 to 2.65; $P = .99$). None of the participants developed sepsis in either group. There were no between-group differences in any of the individual component infectious events. A composite noninfectious complication occurred in 6 (1.7%) and 8 (2.2%) participants in the transrectal and transperineal groups, respectively (odds ratio, 1.28; 95% CI, 0.44 to 3.73; $P = .79$). No participants required hospitalization or other interventions.

Conclusions: Among men undergoing transperineal or transrectal prostate biopsy, we could not demonstrate any difference in the infectious or noninfectious complications. Both biopsy approaches remain clinically viable and safe.

Key Words: prostate, biopsy, infection, bleeding, complications

Transrectal systematic prostate biopsy (TR-Bx) has come under scrutiny due to concerns over its diagnostic accuracy and biopsy-related infectious complications. With the increasing utilization of multiparametric MRI (mpMRI) and targeted TR-Bx, the detection of clinically significant prostate cancer (PCa) has improved.[1,2] However, despite the use of enhanced antibiotic prophylaxis, some centers have reported a 2-fold to 4-fold increase in TR-Bx–related infectious complications, which are thought to be related to the emergence of antibiotic-resistant organisms worldwide.[3] With an estimated 2 million prostate biopsy procedures performed annually in the

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United States and Europe, biopsy-related complications pose a significant public health challenge.[4,5]

Several observational studies have demonstrated a significantly reduced risk of postbiopsy infections (<1%) following transperineal prostate biopsy (TP-Bx).[6-9] Due to this potential advantage, TP-Bx has been proposed as a preferred alternative to TR-Bx. However, several potential trade-offs and barriers to the adoption of TP-Bx (additional resources, training, cost, increased pain, urinary complications) have been identified.[10-13] Most important of these is the lack of comparative effectiveness studies demonstrating superior outcomes of 1 procedure over the other. The AUA guidelines suggest waiting for the results of randomized studies before assigning the preferred status to 1 procedure, whereas the European Association of Urology guidelines favor TP-Bx with a strong recommendation.[14]

In the absence of clear guidelines, current recommendations rely on expert opinion, with some calling for abandonment of the current standard, TR-Bx, in favor of TP-Bx.[15-17] This proposed major shift in clinical practice, affecting tens of thousands of physicians and millions of participants annually, should be based on level I evidence. To date, there is a distinct lack of randomized studies with prespecified complications outcomes comparing the TR-Bx and TP-Bx procedures. To address this major gap in knowledge, we designed the ProBE-PC (Prostate Biopsy Efficacy and Complications) study to investigate whether TP-Bx results in fewer complications.

MATERIALS AND METHODS

Trial Design and Oversight

ProBE-PC is a prospective, parallel-group, randomized clinical trial (RCT) designed to test the primary hypothesis that TP-Bx is associated with fewer infectious complications than TR-Bx (ClinicalTrials.gov NCT04081636). It was designed as a multilocation, single-center RCT for leveraging the resources of a unified health system (including 4 affiliated hospitals and 5 nonaffiliated hospitals over a 23-county region), eg, use of a single institutional review board, identification of potential study participants, and accelerated enrollment.[18,19] Both biopsy procedures were centralized due to COVID-19–related constraints and performed by 3 urologists experienced in the fusion TR-Bx and/or TP-Bx. In line with the PRagmatic-Explanatory Continuum Indicator Summary–2 criteria (www.precis-2.org), our trial design adopted a highly pragmatic approach, utilizing existing procedural protocols, usual practice setting, enrolling a broad range of participants, and clinical indications (Supplementary Table, https://www.jurology.com).[20] The trial was funded by the Capital Region Medical Research Institute through the School of Public Health at State University of New York, who had no role in the study. This study was approved by the Committee on Research Involving Human Subjects at Albany Medical College (protocol No. 5479). The data and safety monitoring committee oversaw the trial, amendments (Supplementary Appendix 1, https://www.jurology.com), and the interim analysis.

Participants and Randomization

From September 5, 2019, to September 9, 2022, all men undergoing initial or repeat prostate biopsy for clinical suspicion of PCa at one of the affiliated centers were invited to participate in the study, regardless of indications or baseline characteristics (age, PSA, comorbidities, or genitourinary history). The only exclusion criteria at screening was surgically absent rectum (3 patients). Prebiopsy mpMRI of prostate was encouraged but not required for study participation. Participants who were eligible to undergo either TR-Bx or TP-Bx under local anesthesia were randomly assigned 1:1 to either the TR-Bx or the TP-Bx procedure by one of several nonurologist research staff.[10] The simple, unrestricted randomization approach using coin flip method was utilized, which is highly effective in preventing selection bias since the randomizing staff remains unaware of previous participants' allocation.[21] Allocation concealment was further maintained by separating the clinical and research visits and storing the data in a password protected computers (Supplementary Appendix 2, https://www.jurology.com).

Procedures

Both biopsy procedures were performed using existing protocols, instruments, and preparations that were in place prior to the study. This included standard single-day antibiotic prophylaxis for TR-Bx without rectal cultures and without routine prophylaxis for TP-Bx (Table 1).[22] The TP-Bx was performed using an ultrasound probe-mounted needle guide (Precision Point). For participants with mpMRI demonstrating suspicious lesions (Prostate Imaging Reporting and Data System [PI-RADS] score 3-5), MRI-targeted biopsy was performed (3 cores/lesion) using an image fusion platform (UroNav 3.0, In Vivo Phillips, Gainesville, Florida), followed by a 12-core systematic biopsy. Systematic-only samples were taken in both groups when mpMRI was negative or not performed.

Outcomes and Follow-up

The primary outcomes were 30-day composite infectious complication rates defined as any 1 or more of the following: fever (including undocumented), genitourinary infection (any UTI, prostatitis, epididymoorchitis), perineal abscess/cellulitis, antibiotic prescriptions (for suspected or confirmed infection), sepsis, infection-related emergency room (ER) visits, hospital admission, office visits, or phone calls. Sepsis was defined using the Sepsis-3 task force criteria.[23] Secondary outcomes included 30-day composite noninfectious complications, including urinary retention; hemorrhage requiring any intervention; and related ER visits, hospital admissions, office visits, or phone calls.

Outcome data were collected by research staff during the follow-up office/virtual visit at 2 weeks and follow-up phone contact at 30 days. Additionally, electronic health records were reviewed after 30 days to identify clinic visits, phone calls, ER visits, hospital admissions, and antibiotic prescriptions. For the 48 participants (6.6%) who did not respond, medical records were obtained from referring urologists, and the Health Information Exchange of New York (HIXNY) was queried to identify all prescriptions, urine cultures, and clinic or hospital visits. HIXNY is a

Table 1. *Prostate Biopsy Protocols*[a]

	Transrectal	Transperineal
Bowel prep	Enema (saline, sodium phosphate)	Enema (saline, sodium phosphate)
Anticoagulants and antiplatelet medications	Hold for a few d (medication dependent), except aspirin 81 mg	Hold for a few d (medication dependent), except aspirin 81 mg
Antibiotic prophylaxis	Standard, oral: ciprofloxacin 500 mg and SMZ-TMP 800 mg-160 mg, 1 h before and 12 h after, or risk adjusted[b]: ceftriaxone 1 g, intramuscular, 1 h prior	None, or risk adjusted,[b] based on surgeon's assessment
Skin prep	None	Povidone-iodine
Prebiopsy analgesics	Optional: acetaminophen tablets, 650-1000 mg, 1-2 h prior	Optional: acetaminophen tablets, 650-1000 mg, 1-2 h prior
Position	Left lateral decubitus	Lithotomy
Local anesthetic type	Lidocaine 1% inj, 9 mL plus sodium bicarbonate inj, 1 mL	Lidocaine 1% inj, 27 mL plus sodium bicarbonate inj, 3 mL
Local anesthetic injection site	Prostate base/seminal vesical junction (bilaterally)	Perineal skin, soft tissues, muscles, and prostate apex (bilaterally)
Postbiopsy analgesics	Optional: acetaminophen tablets, 1000 mg, Q8H, PRN	Optional: acetaminophen tablets, 1000 mg, Q8H, PRN

Abbreviations: inj, injection; PRN, as needed; Q8H, every 8 hours; SMZ-TMP, sulfamethoxazole and trimethoprim.
[a] The Bard MaxCore 1825 disposable, spring-loaded 18-gauge core biopsy needle was used for both biopsy procedures. All biopsy procedures were performed using BK Flex Focus 400 ultrasound machine and BK8818 or BK8848 transducers.
[b] For those with recent exposure to antibiotics (within 6 months) or overseas travel, or recent history of prostatitis or allergies to standard antibiotics, indwelling Foley catheter. For ceftriaxone allergy, gentamicin 160 mg intramuscular was used. Rectal cultures were not performed in any participant.

secure health information network that allows physicians to access > 5 million people's health care records from New York and neighboring states (www.HIXNY.org).

Statistical Analysis

The statistical analysis plan was informed by cumulative evidence from observational studies of TR-Bx and TP-Bx procedures.[12,24,25] The sample size calculation was based on the anticipated infectious complication rates of 4% and 0.8% after TR-Bx and TP-Bx, respectively, which are in line with the data used in the current clinical guidelines.[14,26] To demonstrate the superiority of TP-Bx over TR-Bx for the primary outcome (infectious complications), with a statistical power of 80% and type I error of 0.05, 716 participants needed to complete the procedure. Continuous variables are presented as mean (SD) or as median and interquartile range (IQR: 25th, 75th percentile). Categorical variables are presented as frequencies and percentages. Odds ratios (ORs) are calculated using binary logistic regression to assess the effect of the biopsy procedure (TR-Bx vs TP-Bx) on the occurrence of composite infectious and composite noninfectious complication rates. ORs for infectious and noninfectious complication outcomes are estimated for each variable (unadjusted OR). The confidence intervals for the secondary outcomes are 2-sided at 95% and have not been adjusted for multiplicity, so these may not be used in place of hypothesis testing. Statistical significance was set at $P < .05$. Statistical analysis was performed by one of us (P.J.F.) using R (version 4.3.0) and Minitab (V19).

RESULTS

Participants

Of the 763 consecutive randomized participants, 718 completed the procedure, with 351 and 367 participants undergoing TR-Bx and TP-Bx procedures, respectively. Overall, 93% of participants were White and the mean (SD) age was 65 (6.9) years. Forty-five participants (36 during the peak of the COVID-19 pandemic) did not undergo prostate biopsy for various reasons (Figure). The baseline characteristics of the participants in each group are presented in Table 2.

The primary indication for biopsy was an elevated PSA level (587 [82%]). Prebiopsy mpMRI of the prostate was performed in 687 (96%) participants, of whom 527 (73%) had a lesion prompting a combined MRI-targeted plus systematic sampling of the prostate. In the TR-Bx group, antibiotic prophylaxis included standard oral agents or intramuscular injections in 272 (78%) and 79 (23%) participants, respectively. Four participants in the TP-Bx group received prophylaxis at the surgeon's discretion due to urinary catheters or mechanical heart valves.

Infectious Complications

A composite infectious complication event occurred in 9 participants (2.6%) in the TR-Bx group and 10 participants (2.7%) in the TP-Bx group (OR, 1.06; 95% CI, 0.43 to 2.65; $P = .89$; Table 3). There were no episodes of sepsis following either biopsy procedure. Fever (including undocumented) was the most frequent infectious component, reported by 6 participants in each group. Additional antibiotic prescriptions for suspected GU infections were provided to 6 and 5 participants in the TR-Bx and TP-Bx groups, respectively. Of these, a positive urine culture was noted in only 1 participant per group. Three participants in each group presented to 4 different ERs due to fever and suspected infection. Two participants in the TR-Bx group and 1 in the TP-Bx group were hospitalized for overnight observation. Of note, 5 of the 7 phone calls related to a potential infection were also associated with another infectious component (antibiotics, fever, ER visit). Complications were classified as Clavien-Dindo grade II in 6 and 5 participants in the TR-Bx and TP-Bx groups, respectively. For reference, regional patterns of antibiotic-resistant *Escherichia coli* are presented in the Supplementary Figure (https://www.jurology.com).

CONSORT
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Figure1. CONSORT 2010 flow diagram.

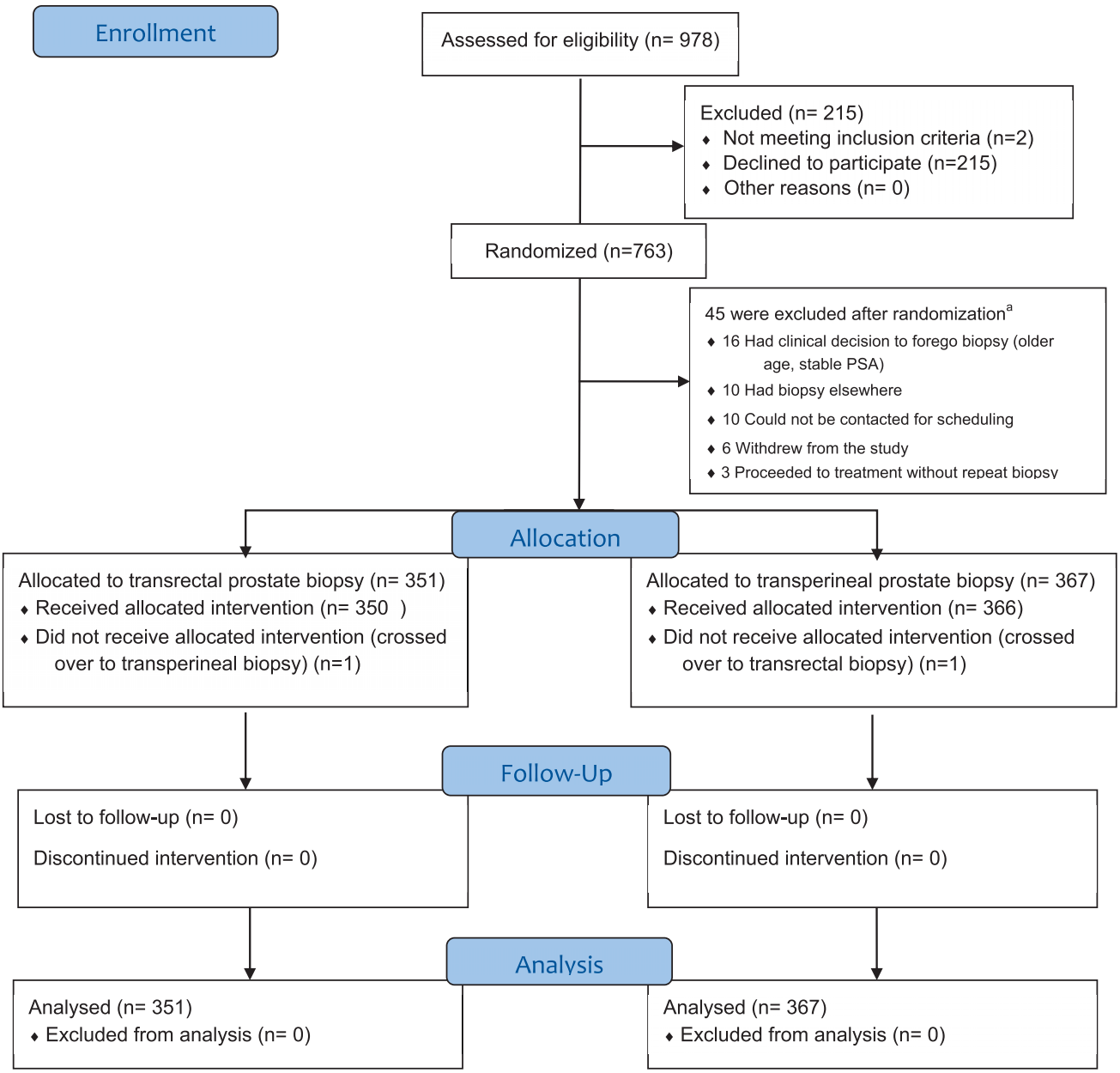

Figure. Randomization and enrollment. Participants undergoing prostate biopsy procedure were invited to participate in the study. Participants were randomized in a 1:1 ratio to undergo either transrectal or transperineal prostate biopsy procedure using the existing standard protocols. Participant withdrawal after randomization (45 participants: 27 from transrectal and 18 from transperineal group) was largely due to COVID-19 pandemic–related limitations and delays in health care access for nonurgent health care.

Noninfectious Complications

A composite noninfectious complication event occurred in 6 (1.7%) and 8 (2.2%) participants in the TR-Bx and TP-Bx groups, respectively (OR, 1.28; 95% CI, 0.44 to 3.73; $P = .65$; Table 3). Of these, phone calls to the office were the most frequent component events noted in 3 participants and 7 participants in the TR-Bx and TP-Bx group (0.9% vs 1.9%, $P = .34$), respectively. Urinary retention requiring a Foley catheter was developed in 1 participant in each group. Two

Table 2. *Baseline Characteristics*

Characteristic	Transrectal prostate biopsy (n = 351)	Transperineal prostate biopsy (n = 367)
Age, y		
Median (IQR)	66 (61, 70)	65 (60, 70)
>75, No. (%)	55 (15.0)	25 (7.1)
Race, No. (%)[a]		
Asian	4 (1.1)	0 (0.0)
Black	18 (5.1)	25 (6.8)
Hispanic	1 (0.3)	0 (0.0)
Unknown	2 (0.6)	3 (0.8)
White	326 (92.9)	339 (92.4)
BMI, median (IQR)	28.3 (25.3, 31.7)	28.2 (25.8, 31.5)
Diabetes, No. (%)	46 (13.1)	36 (9.8)
Anticoagulation, No. (%)	16 (4.6)	16 (4.4)
Antiplatelet, No. (%)		
Aspirin 81 mg	62 (17.7)	58 (15.8)
Aspirin 325 mg	48 (13.7)	35 (9.5)
Clopidogrel	3 (0.9)	7 (1.9)
PSA level, ng/mL	7.0 (5.0, 10.1)	6.9 (5.0, 10.3)
Median (IQR)	90 (25.6)	97 (27.6)
>10, No. (%)		
Prostate volume, median (IQR), mL	47 (35, 65)	47 (36, 65)
PSA density, median (IQR)	0.14 (0.09, 0.22)	0.14 (0.09, 0.22)
Family history of prostate cancer, No. (%)	101 (29.3)	94 (25.9)
Clinical stage, No. (%)[b]		
T1c	280 (80.0)	307 (83.7)
T2	61 (17.4)	52 (14.2)
T3	9 (2.6)	8 (2.2)
Postvoid residual urine, mL		
Median (IQR)[c]	15 (2, 48)	13 (1, 44)
>100, No. (%)	37 (10.5)	35 (9.5)
IPSS		
Median (IQR)[d]	7 (4, 12)	7 (4, 12)
Moderate-severe symptoms, No. (%)	96 (27.4)	100 (27.2)
History of previous biopsy, No. (%)	152 (43.3)	181 (49.3)
Antibiotics used in last 6 mo, No. (%)[e]	25 (7.1)	13 (3.5)
Prebiopsy multiparametric MRI performed, No. (%)	339 (96.6)	348 (94.8)
Positive MRI, No. (%)	259 (76.4)	264 (75.9)
PIRADS		
Median (IQR)		
Score, No. (%)[f]	4 (3, 5)	4 (3, 5)
3	74 (28.7)	75 (28.5)
4	115 (44.6)	105 (39.9)
5	69 (26.7)	83 (31.6)
Prebiopsy prep, No. (%)		
Antibiotics (used for 1 d)		
Oral	272 (77.5)	1 (0.3)
Intramuscular	79 (22.5)	1 (0.3)
Enema, sodium phosphate	348 (99.2)	365 (99.5)
Biopsy technique, No. (%)		
MRI targeted and systematic	260 (74.1)	267 (72.3)
Systematic only	91 (25.9)	100 (27.2)
Biopsy cores taken, median (IQR)	13 (12, 13)	14 (12, 15)

Abbreviations: BMI, body mass index; IPSS, International Prostate Symptom Score; IQR, interquartile range; MRI, magnetic resonance imaging; PIRADS, Prostate Imaging Reporting and Data System; PSA, prostate-specific antigen.
Data were missing for PSA level in 1 patient, IPSS in 288, and postvoid residual in 44.
[a] Race was collected from each participant's electronic medical records.
[b] Clinical stages of prostate cancer: T1c, organ confined, detected via PSA screening; T2, palpable, organ confined; T3: palpable, extending past the capsule.
[c] Measured with a postvoid bladder scan.
[d] IPSS: 0-7, mild symptoms; 8-19, moderate symptoms; 20-35, severe symptoms.
[e] Use of any antibiotics for any reason in the 6 months before biopsy.
[f] In case of multiple lesions, the highest PIRADS score was used.

participants visited primary care offices following TR-Bx for testicular pain and/or voiding symptoms. One participant required an ER visit following TP-Bx for urinary symptoms, but no participant required hospitalization in either group. Of the noninfectious events, grade II complications were noted in 1 and 2 participants in the TR-Bx and TP-Bx groups, respectively.

No participants in either group required postbiopsy interventions (cystoscopy, irrigation, fulguration, colonoscopy, etc) due to bleeding. A vasovagal reaction during the procedure was recorded for 1 participant in each group that resolved spontaneously after a short observation period. No procedures were aborted because of intraoperative complications. One

Table 3. *Infectious and Noninfectious Complication Rates Following Prostate Biopsy Procedures*

	Transrectal prostate biopsy (n = 351)	Transperineal prostate biopsy (n = 367)	Odds ratio[a] (95% CI)
Composite infectious complications, No. (%)[b]	9 (2.6)	10 (2.7)	1.06 (0.43, 2.65)
Components, No. (%) (Clavien-Dindo grade)[c]			
Fever (I)	6 (1.7)	6 (1.6)	0.96 (0.31, 2.99)
Documented UTI (II)	1 (0.3)	2 (0.5)	1.92 (0.17, 21.23)
Antibiotic prescription (II)	6 (1.7)	5 (1.4)	0.79 (0.24, 2.63)
Prostatitis (I)	0 (0.0)	0 (0.0)	—
Epididymoorchitis (II)	0 (0.0)	1 (0.3)	—
Sepsis (IV)	0 (0.0)	0 (0.0)	—
Emergency room visit (II)	3 (0.9)	3 (0.8)	0.96 (0.19, 4.77)
Hospital admission (II)	2 (0.6)	1 (0.3)	0.48 (0.31, 5.28)
Phone calls (I, II)[d]	3 (0.9)	4 (1.1)	1.28 (0.28, 5.75)
Composite noninfectious complications, No. (%)[b]	6 (1.7)	8 (2.2)	1.28 (0.44, 3.73)
Components, No. (%) (Clavien-Dindo grade)[c]			
Urinary retention (II)	1 (0.3)	1 (0.3)	0.96 (0.15, 15.34)
Bleeding requiring intervention (III)	0 (0.0)	0 (0.0)	—
Primary physician visit (I, II)	3 (0.9)	2 (0.5)	0.64 (0.11, 3.83)
Emergency room visit (II)	0 (0.0)	1 (0.3)	—
Hospital admission (II)	0 (0.0)	0 (0.0)	—
Phone calls (I, II)[d]	3 (0.9)	7 (1.9)	2.26 (0.58, 8.80)

Abbreviations: CI, confidence interval; UTI, urinary tract infection.
[a] Odds ratios for complications with empty cells (0 events) not calculated due to quasicomplete separation. The confidence intervals for the secondary (component) outcomes are 2-sided 95% and have not been adjusted for multiplicity, so these may not be used in place of hypothesis testing.
[b] The composite represents the number of participants experiencing any 1 or more of the component events, with each component weighted equally within the composite. Multiple component events in 1 participant, such as a phone call to the office followed by an emergency room visit, are counted as 1 composite event.
[c] Complications are classified as Clavien-Dindo grade I, II, III, or IV. A higher grade represents more severe complication.
[d] All incoming phone calls were scrutinized, but these data represent only those phone calls that were related to the biopsy procedure and specifically mentioned one of the potential side effects or complications. Of the 7 phone calls related to a potential infection, 5 participants had another infectious component (antibiotics, fever, emergency room visit), and 2 were just reassured.

participant, who was asymptomatic, died 14 days after TP-Bx while actively engaged in physical activity. An autopsy request to determine the cause was not granted.

DISCUSSION

In this randomized study comparing TR-Bx and TP-Bx procedures, no difference was noted in the overall composite infectious or noninfectious complication rates between the 2 procedures. The postbiopsy incidence of possible infection-related components such as fever, antibiotic prescriptions, ER visits, and/or hospital admissions were also not different between the 2 groups. We defined infectious complications to include events that may appear less consequential (related phone calls or subjective fever) to ensure that all potential infection data were captured. However, phone calls had minimal impact on the composite infections data since only 2 phone calls were without an additional infection component. Of the 11 participants receiving antibiotic prescriptions, a clear indication could not be ascertained in 5 participants, and hospitalization in 3 participants was limited to overnight observation only. Most importantly, no participants experienced sepsis or needed intensive care following either of the biopsy procedures.

Infectious complications following TR-Bx are often cited as the major indication for adopting the TP-Bx approach. Previous studies comparing the 2 prostate biopsy procedures have largely consisted of observational cohorts with highly variable protocols, antibiotic prophylaxis, and procedural techniques. While the frequently cited infectious complication rates after TR-Bx are in the range of 4% to 6%, there is considerable variation in definitions and results between the studies. Interestingly, recent European studies of TR-Bx report infection rates of 1% to 1.5%, which are similar to our study.[27,28] Similarly, observational studies of infectious complications following TP-Bx demonstrate variable results. A recent single arm study of men undergoing TP-Bx with antibiotic prophylaxis reported fever and additional antibiotic prescriptions in 4.7% and 4.3%, respectively.[29] In a population study, Berry et al reported that for every infection-related hospitalization prevented with the use of TP-Bx, 3 additional hospitalizations occurred due to urinary complications.[25] A systematic review by Pradere et al reported the composite infectious complication rates of 5.6% and 3.2% after TR-Bx and TP-Bx, respectively. This pooled analysis consisted of small studies designed to evaluate the feasibility of TP-Bx, without prespecified infectious or diagnostic outcomes.[24] If the more restrictive

definition used in the aforementioned studies (UTI, antibiotics, hospitalization, sepsis) was applied to our RCT, our infectious complication rates were 1.4% and 1.7% after TP-Bx and TR-Bx, respectively. Further, we did not observe the reportedly high rate of urinary retention after TP-Bx, which is likely related to sedation/anesthesia, number of cores, and technique.[13]

This trial was conducted against the backdrop of a high rate of fluoroquinolone-resistant *E coli* (30%-35%) in our region. Although several centers have adopted enhanced antibiotic prophylaxis (longer duration, multiagent, intravenous, rectal culture-guided), we have maintained our standard single-day prophylaxis (in use since 2011) for TR-Bx without escalating antibiotic usage. TP-Bx were primarily performed without antibiotic prophylaxis, which could be clinically important in terms of side effects and workflow. Although any antibiotic exposure (prescriptions or food chain) can alter the intestinal flora, the contribution of a single-day antibiotic prophylaxis alone in promoting antibiotic-resistant infections remains unclear and requires further study.[30] It is possible that factors other than antibiotic resistance and prophylaxis play an important role in the development of postbiopsy infections. Future studies may critically assess the technical aspects of the procedure that can potentially increase the risk of postbiopsy infections.

This study represents the first randomized comparative study of the 2 biopsy procedures designed to include contemporary features (local anesthesia, office based, free hand) and predefined outcomes. It is sufficiently powered to evaluate the differences in infectious complication rates. The sample size calculation was guided by the published average infection rates that are often used to draw distinction between the 2 procedures. A different power analysis based on lower infection rates or severe infections would require an impractically large sample size to demonstrate statistical significance, and the differences may be too small to be clinically significant enough to justify a major paradigm shift. Our study has some limitations. The number of non-Caucasian participants was low, and the results may not be applicable to other ethnic groups. Second, a single-center design can limit generalizability to some other settings, although centralization is likely to remain important. These concerns are partially balanced by the pragmatic trial domains that support generalizability, such as enrollment from varied locations (urban, rural, academic, community) and real-world inclusion criteria (regardless of infection history, age, PSA, or MRI findings), using existing procedural techniques.

CONCLUSIONS

This randomized study was unable to demonstrate a difference in the infectious and noninfectious complications following transperineal or transrectal prostate biopsy. Both procedures appear safe and viable options for clinical practice. These findings can inform future research, current practice, and clinical guidelines regarding the safety of prostate biopsy procedures.

REFERENCES

1. Ahdoot M, Wilbur AR, Reese SE, et al. MRI-targeted, systematic, and combined biopsy for prostate cancer diagnosis. *N Engl J Med.* 2020;382(10):917-928.
2. Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-targeted or standard biopsy for prostate-cancer diagnosis. *N Engl J Med.* 2018;378(19):1767-1777.
3. Redgrave LS, Sutton SB, Webber MA, Piddock LJV. Fluoroquinolone resistance: mechanisms, impact on bacteria, and role in evolutionary success. *Trends Microbiol.* 2014;22(8):438-445.
4. Borghesi M, Ahmed H, Nam R, et al. Complications after systematic, random, and image-guided prostate biopsy. *Eur Urol.* 2017;71(3):353-365.
5. Loeb S, Carter HB, Berndt SI, Ricker W, Schaeffer EM. Complications after prostate biopsy: data from SEER-Medicare. *J Urol.* 2011;186(5):1830-1834.
6. Xiang J, Yan H, Li J, Wang X, Chen H, Zheng X. Transperineal versus transrectal prostate biopsy in the diagnosis of prostate cancer: a systematic review and meta-analysis. *World J Surg Oncol.* 2019;17(1):31.
7. Loy LM, Lim GH, Leow JJ, Lee CH, Tan TW, Tan CH. A systematic review and meta-analysis of magnetic resonance imaging and ultrasound guided fusion biopsy of prostate for cancer detection—comparing transrectal with transperineal approaches. *Urol Oncol.* 2020;38(8):650-660.
8. Pepdjonovic L, Tan GH, Huang S, et al. Zero hospital admissions for infection after 577 transperineal prostate biopsies using single-dose cephazolin prophylaxis. *World J Urol.* 2017;35(8):1199-1203.
9. Vyas L, Acher P, Kinsella J, et al. Indications, results and safety profile of transperineal sector biopsies (TPSB) of the prostate: a single centre experience of 634 cases. *BJU Int.* 2014;114(1):32-37.
10. Mian BM, Kaufman RP Jr, Fisher HAG. Rationale and protocol for randomized study of transrectal and transperineal prostate biopsy efficacy and complications (ProBE-PC study). *Prostate Cancer Prostatic Dis.* 2021;24(3):688-696.
11. Lenfant L, Barret E, Rouprêt M, Rozet F, Ploussard G, Mozer P. Transperineal prostate biopsy is the new Black: what are the next targets?. *Eur Urol.* 2022;82(1):3-5.
12. Stefanova V, Buckley R, Flax S, et al. Transperineal prostate biopsies using local anesthesia: experience with 1,287 participants. Prostate cancer detection rate, complications and participant tolerability. *J Urol.* 2019;201(6):1121-1126.
13. Miah S, Eldred-Evans D, Simmons LAM, et al. Participant reported outcome measures for transperineal template prostate mapping biopsies in the PICTURE study. *J Urol.* 2018;200(6):1235-1240.
14. European Association of Urology. *Guidelines: Prostate Cancer.* 2022. Accessed October 1, 2023. https://uroweb.org/guidelines/prostate-cancer/chapter/diagnostic-evaluation
15. Kum F, Elhage O, Maliyil J, et al. Initial outcomes of local anaesthetic freehand transperineal prostate biopsies in the outpatient setting. *BJU Int.* 2020;125(2):244-252.
16. Günzel K, Magheli A, Baco E, et al. Infection rate and complications after 621 transperineal MRI-TRUS fusion biopsies in local anesthesia without standard antibiotic prophylaxis. *World J Urol.* 2021;39(10):3861-3866.

17. Grummet J, Gorin MA, Popert R, et al. "TREXIT 2020": why the time to abandon transrectal prostate biopsy starts now. *Prostate Cancer Prostatic Dis.* 2020;23(1):62-65.

18. Stevenson C, Catalano AD, Cho L. The use of a single center, multi-location research structure for participation in large clinical trials: the Cleveland Clinic model. 2014. https://www.appliedclinicaltrialsonline.com/view/use-single-center-multi-location-research-structure-participation-large-clinical-trials-cleveland-cl

19. Kernan W, Viscoli C, Brass L, et al. Boosting enrolment in clinical trials: validation of a regional network model. *Clin Trials.* 2011;8(5):645-653.

20. Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. *BMJ.* 2015;350:h2147.

21. Schulz KF, Grimes DA. Generation of allocation sequences in randomised trials: chance, not choice. *Lancet.* 2002;359(9305):515-519.

22. Ahmad AE, Sorokin I, Aggarwal H, Bosukonda A, Khalid A, Mian B. MP53-06 Controlling the prostate biopsy related infectious complications through vigilant screening and enhanced antibiotic prophylaxis. *J Urol.* 2016;195(4S):e698.

23. Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA.* 2016;315(8):801-810.

24. Pradere B, Veeratterapillay R, Dimitropoulos K, et al. Nonantibiotic strategies for the prevention of infectious complications following prostate biopsy: a systematic review and meta-analysis. *J Urol.* 2021;205(3):653-663.

25. Berry B, Parry MG, Sujenthiran A, et al. Comparison of complications after transrectal and transperineal prostate biopsy: a national population-based study. *BJU Int.* 2020;126(1):97-103.

26. Wei JT, Barocas D, Carlsson S, et al. Early detection of prostate cancer: AUA/SUO guideline Part II: considerations for a prostate biopsy. *J Urol.* 2023;210(1):54-63.

27. Hugosson J, Månsson M, Wallström J, et al. Prostate cancer screening with PSA and MRI followed by targeted biopsy only. *N Engl J Med.* 2022;387(23):2126-2137.

28. Wenzel M, Welte MN, Theissen LH, et al. Comparison of complication rates with antibiotic prophylaxis with cefpodoxime versus fluoroquinolones after transrectal prostate biopsy. *Eur Urol Focus.* 2021;7(5):980-986.

29. Lopez JF, Campbell A, Omer A, et al. Local anaesthetic transperineal (LATP) prostate biopsy using a probe-mounted transperineal access system: a multicentre prospective outcome analysis. *BJU Int.* 2021;128(3):311-318.

30. Cohen ME, Salmasian H, Li J, et al. Surgical antibiotic prophylaxis and risk for postoperative antibiotic-resistant infections. *J Am Coll Surg.* 2017;225(5):631-638.e3.

EDITORIAL COMMENT

The randomized controlled trial by Mian et al provides the first contemporary level 1 evidence directly comparing rates of infectious complications between transrectal (TR) and transperineal (TP) prostate biopsy.[1] Contrary to prior reports, they found no difference between the biopsy approaches, challenging the belief that TP biopsy is associated with lower infection risk. Surprisingly, the rate of infections in the TR biopsy group was relatively low compared to what has been reported in prior observational studies. Further, the infection rate with TP biopsies was higher than in a recently published trial.[2]

While no difference was seen regarding infectious complications, it is important to note that the TR biopsy group received prophylactic antibiotics, while the TP group did not (except for select circumstances). These results build on prior evidence that antibiotics can likely be safely avoided for TP biopsy in most cases,[2] which has important implications for antibiotic stewardship.

We look forward to the results of ongoing studies to provide additional data, including a large multicenter trial comparing infectious complications between TP and TR biopsy.[3] In addition, the superiority of diagnostic performance has yet to be confirmed for either of the 2 biopsy approaches. Two ongoing European multicenter randomized controlled trials—PERFECT and TRANSLATE—are designed to compare clinically significant prostate cancer detection rates between TP and TR biopsy.[4,5]

Despite a lack of robust evidence for superiority, some have advocated that TP biopsy should completely replace TR biopsy. Given the similar safety profiles based on this trial, perhaps TR biopsy should not be discarded altogether but used selectively in cases where it may be helpful. For example, TR biopsy may provide better sampling in obese men, larger prostates, or for lesions located at the base of the prostate. These hypotheses should be tested in future studies.

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REFERENCES

1. Mian BM, Feustel PJ, Aziz A, et al. Complications following transrectal and transperineal prostate biopsy: results of the ProBE-PC randomized clinical trial. *J Urol.* 2024;211(2):205-213.

2. Jacewicz M, Günzel K, Rud E, et al. Antibiotic prophylaxis versus no antibiotic prophylaxis in transperineal prostate biopsies (NORAPP): a randomised, open-label, non-inferiority trial. *Lancet Infect Dis.* 2022;22(10):1465-1471.

3. Hu J, Zhu A, Vickers A, et al. Protocol of a multicentre randomised controlled trial assessing transperineal prostate biopsy to reduce infectious complications. *BMJ Open.* 2023;13(5):e071191.

4. Touzani A, Fiard G, Barret E, et al. Clinical trial protocol for PERFECT: a randomised controlled trial comparing the efficiency and tolerance of transperineal fusion versus transrectal imaging-targeted prostate biopsies (CCAFU-PR1 study). *Eur Urol Open Sci.* 2022;45:76-80.

5. Bryant RJ, Yamamoto H, Eddy B, et al. Protocol for the TRANSLATE prospective, multicentre, randomised clinical trial of prostate biopsy technique. *BJU Int.* 2023;131(6):694-704.