COMMENTARY

Pokes, Pathogens, and Primum Non Nocere: Prudent Prophylaxis Protocols for Prostate Biopsy

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(See the article by Suwantarat et al, on pages 973–976.)

Infectious complications following transrectal ultrasound-guided biopsy of the prostate (TRUBP)—including urinary tract infections, prostatitis, epididymo-orchitis, and bacteremia—have increased dramatically in recent years.[1,2] Traditionally, fluoroquinolones have been the mainstay for perioperative prophylaxis.[3] Likely as a result of a combination of this selective pressure and temporal shifts in the clonal composition of the rectal microbiota, most post-TRUBP infections today are caused by fluoroquinolone-resistant *Escherichia coli*, especially those from sequence type 131 (ST131), an emerging multidrug-resistant strain that is highly prevalent among pre-TRUBP rectal isolates.[4-6] Clinicians need improved approaches for preventing these complications. Fortunately, helpful guidance is beginning to appear.

In this issue, Suwantarat et al[7] report their promising results from a quality improvement intervention designed to decrease post-TRUBP complications. In 2010, a cluster of serious post-TRUBP infections occurred at the Cleveland Veterans Affairs Medical Center. In response, Suwantarat et al[7] developed a multicomponent protocol that included identifying fluoroquinolone-resistant gram-negative organisms from routine prebiopsy rectal cultures. Antimicrobial prophylaxis was then tailored according to the cultured organism's susceptibility profile.

These authors found that the rate of TRUBP-associated fluoroquinolone-resistant *E. coli* infections was significantly lower during the 18-month intervention period than during the 18-month preintervention period (1.6% vs 4.3%; $P = .01$). Additionally, during the first 12 months of the intervention period, patients who completed prebiopsy screening were significantly less likely to develop post-TRUBP infections—and specifically fluoroquinolone-resistant infections—compared with unscreened patients who received standard empirical ciprofloxacin therapy ($P < .01$ for both comparisons). These encouraging results suggest a feasible protocol for reducing the serious negative sequelae of TRUBP. However, important questions remain regarding both this study and how its findings should impact future practice.

Suwantarat et al's[7] results agree with those of recent similar studies by Duplessis et al[8] and Taylor et al,[9] in which targeted prophylaxis likewise appeared to reduce the frequency of post-TRUBP fluoroquinolone-resistant *E. coli* infections. However, since these studies involved relatively few subjects, were observational, and lacked optimal control groups, they require cautious interpretation. Taylor et al[9] left the decision to culture individual patients to the clinicians' discretion; Duplessis et al[8] required culture on all pre-TRUBP patients but used historical controls; and Suwantarat et al[7] compared their intervention group with both historical controls and, as concurrent controls, the 39% of intervention period TRUBP patients who, for various reasons, did not undergo the protocol pre-TRUBP screening. Although these patients resembled the screened patients across a broad range of epidemiological characteristics, the possibility of unrecognized confounders threatens the validity of the infection rate comparison. Additionally, the authors' statistical analysis of pre- versus postintervention includes only fluoroquinolone-resistant *E. coli* infections and not the equally or more relevant rates of all-cause infections and hospitalizations due to post-TRUBP infections.

Pre-post comparisons present well-recognized challenges for assessing causality. Although larger studies have documented climbing rates of post-TRUBP infections in Medicare and Canadian populations, short-term trends at single institutions are less well defined.[1,2] Conceivably, the observed decline in post-TRUBP infections at the Cleveland Veterans Affairs Medical Center may have resulted from a spontaneous return to baseline complication rates following the described outbreak—the "regression to the mean" phenomenon. Alternatively, the institution's post-TRUBP infection rate may have been generally declining already, independent of the screening intervention. Use of a larger (ideally, randomly assigned) concurrent control group or of more sophisticated statistical methods for analyzing observational data can help avoid confounding from such trends. The most appropriate next step for assessment of targeted prophylaxis is a large

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randomized controlled trial. We eagerly await the results of such studies.

However, even with use of a targeted prophylaxis protocol—and certainly without one—empirical prophylaxis will still be necessary for many (as observed by Suwantarat et al)[7] or all TRUBP recipients. Choice of an appropriate empirical regimen in this era of widespread antimicrobial resistance requires careful consideration of spectrum of activity, prostate penetration, and route of administration. Unfortunately, empirical data to guide evidence-based regimen selection are lacking.

Reliance on fluoroquinolones for single-agent empirical TRUBP prophylaxis clearly is unwise. Fluoroquinolone-resistant *E. coli* are overrepresented as the cause of post-TRUBP bacteremia compared with non-TRUBP-related bacteremia (62% vs 14%; $P < .001$).[6] A consistent risk factor for developing a fluoroquinolone-resistant postbiopsy infection is recent (6 months) fluoroquinolone exposure.[10,11] Regarding alternate/supplemental agents, reliance on gentamicin to cover for fluoroquinolone-resistant organisms may be risky, since 30% or more of fluoroquinolone-resistant rectal *E. coli* can be coresistant to aminoglycosides.[5] Additionally, prophylactic gentamicin does not reliably prevent even gentamicin-susceptible *E. coli* from causing post-TRUBP sepsis.[12] If the local prevalence of resistance to extended-spectrum cephalosporins is low enough, oral cefuroxime or cefixime—or intramuscular ceftriaxone—can be used either alone or with ciprofloxacin. The January 2012 update to the American Urological Association's Best Practice Policy Statement on Urologic Surgery Antimicrobial Prophylaxis recognizes the need to diversify antimicrobial regimens and allows for intramuscular administration.[13]

Concerning treatment duration, both a Cochrane review[14] and a retrospective study by Zaytoun et al[15] found no benefit of 3-day over 1-day prophylaxis for post-TRUBP infections. Notably, the protocol described by Suwantarat et al[7] involved 3-day antimicrobial administration, which may have intensified selection for resistant organisms without providing greater efficacy than shorter treatment. Selection of pre-TRUBP prophylactic protocols provides an important opportunity for antimicrobial stewardship. Future studies should consider as endpoints resistance selection, adverse drug effects, and *Clostridium difficile* infection, in addition to post-TRUBP urinary tract infection and sepsis. The proper role for antimicrobial-sparing alternatives—such as a transperineal route or use of preparatory rectal enemas and disinfectants—is undefined, but these approaches may attract further attention if, as is likely, the pre-TRUBP rectal microbiota becomes even more extensively antimicrobial resistant.[14]

The cost effectiveness of culture-guided prophylaxis versus routine use of broader empirical therapy will be an important consideration as organizations choose among alternative prophylaxis approaches for TRUBP. Although Suwantarat et al[7] did not perform such calculations, they noted that the low cost of screening, the modest number needed to test to prevent an infection (estimated at 38 by Taylor et al),[9] and the substantial savings per hospitalization averted might make a screening program cost neutral or even cost saving compared with routine ciprofloxacin prophylaxis. Comparisons with a more relevant alternative—that is, routine broader empirical therapy—are needed, especially since the (imagined or real) logistical complexities of implementing a culture-guided prophylaxis pathway may deter some institutions from this approach.

This year, both the American Urological Association and the US Preventive Task Force published strong recommendations against routine prostate-specific antigen–guided screening for prostate cancer.[16,17] Although the full impact of these guideline changes remains to be seen, reductions in prostate-specific antigen screening will likely reduce the number of patients referred for TRUBP. More selective screening practices and fewer reflexive biopsies, combined with rising antimicrobial resistance rates, may change the perception that pre-TRUBP cultures are too cumbersome or costly.

In summary, Suwantarat et al[7] report the use of a seemingly effective intervention for an increasingly important clinical problem. These investigators' apparent success in achieving improved patient outcomes is to be commended. Nonetheless, more data are needed to clarify the best practice for preventing post-TRUBP infections, whether through culture-guided prophylaxis, broader empirical prophylaxis, or other approaches. Prophylaxis for TRUBP likely will remain a moving target requiring the integration of local antibiograms, clinical laboratory and infection prevention service capabilities, prostate cancer screening guidelines, and biopsy referral procedures. The challenge will be to devise approaches broad enough for the majority, flexible enough for the minority, and capable of adapting quickly in response to inevitable shifts in the rectal microbiota.

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