EDITORIAL

Clinical

TRexit is going one step further

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"*Habit is habit, and not to be flung out of the window by any man, but coaxed downstairs a step at a time*", so states a quote attributed to Mark Twain and such may be the eventual fate of the habit of choosing the transrectal route for prostate biopsy (TR-Bx), which is lately facing mounting criticism. Indeed, several experts are advocating for an abandonment of the TR-Bx approach in favour of the "cleaner" transperineal (TP-Bx) route. The shift aims to decrease infectious complications and the development of resistant microbial strains without compromising diagnostic accuracy; this movement has been denominated "TRexit" [1, 2]. Discontinuation of TR-Bx could significantly impact centres traditionally offering only this approach, as it would imply procurement of novel equipment and surgeon retraining. In view of the absence of level 1 evidence comparing TR-Bx vs TP-Bx post-procedural infectious complications, two randomised controlled trials (RCT) were recently published.

Prostate Biopsy Efficacy and Complications (ProBE-PC), a trial characterised by a real-word pragmatic design, randomised 763 patients and reported 30-day composite infectious complication rates of 2.6% for TR-Bx and 2.7% for TP-Bx [3]. Patients allocated to the TR-Bx arm received one-day antibiotic prophylaxis without rectal cultures while no prophylaxis was administered in 98.9% (362/366) of the patients undergoing TP-Bx. It is worth noting that the study protocol allowed liberal criteria to define an infectious complication including any fever occurring within a month of the procedure or antibiotics prescription for suspected infection [4]. By applying stricter definitions of infectious complications, reported rates were in favour of TP-Bx with 1.4%, against 1.7% for TR-Bx. Composite non-infectious complications rates were very low and comparable among approaches, aside for a higher rate of biopsy-related phone calls for TP-Bx.

The PReclude infection EVEnts with No prophylaxis Transperineal (PREVENT) study, a superiority RCT comparing infectious complications of TP-Bx vs. TR-Bx as its primary outcome, reported no events in the TP-Bx arm against 4 (1.4%) in the TR-Bx arm ($p = 0.059$) [5]. Patients undergoing a TP-Bx did not receive antibiotic prophylaxis also in this study; rectal cultures and targeted antibiotic prophylaxis were administered to each patient in the TR-Bx arm in adherence to antimicrobial stewardship recommendations. The trial established restrictive definitions of infectious complications, limited to urinary tract infections (UTI) or urosepsis, in addition to a cut-off of seven days after biopsy to adequately capture post-procedural morbidity [6].

Several noteworthy considerations can be inferred from the results of these trials. Primarily, that TP-Bx, a procedure not requiring antibiotic prophylaxis according to the NORAPP RCT [7], appears to be safer compared to TR-Bx, which mandates antibiotic prophylaxis. These results further support the use of TP-Bx as a mean to interrupt the development of antimicrobial resistance related to prostate biopsy [8], adhering to antimicrobial stewardship recommendations. Nonetheless, the infectious complications rates of TP-Bx in ProBE-PC equal those of TR-Bx in PREVENT; protocol differences could explain these findings. 46.4% of the patients enrolled in ProBE-PC had a history of previous biopsy, a factor which has been variously associated to a higher risk of colonisation by resistant bacterial strains and consequently infection [9]. Furthermore pre-procedural microbial cultures were not performed in any of the patients enrolled in ProBE-PC, these features collectively increase the risk of infection in patients receiving a prostate biopsy without prophylaxis, irrespective of the chosen route, possibly explaining the episodes documented in ProBE-PC TP-Bx arm. This hypothesis is also corroborated by PREVENT, which included exclusively biopsy naïve patients and showed a better safety profile for both approaches. Comparison of PREVENT results with those of the germane PREVENT2 trial (NCT04815876), currently enrolling only non-biopsy naïve patients, may provide definitive answers to the risk of infectious complications associated to previous biopsy history.

Both studies failed to elicit statistically significant differences for infection rates among arms, this outcome was attributed to the high anticipated infection rates for TR-Bx used to determine sample sizes. However, the planned extension of enrolment of 200 further cases for PREVENT may provide sufficient statistical power for the results to reach statistical significance [10]. These RCTs showed that infectious events for TR-bx range between 1 and 2% within the confines of a well-designed trial. We recommend utilising these more conservative rates for the design of future studies on this topic, as they may facilitate adequate enrolment and appropriate estimation of the risk of urosepsis in both approaches. Additionally, we acknowledge that such rates would imply very high sample sizes, thus encouraging collaborative multicentre RCTs.

The adjusted differences of infectious rates derived from these trials may appear relatively small at −0.3% and −1.4% in favour of TP-Bx, respectively. These results should be contextualised within the considerable number of biopsies performed annually, estimated at two million procedures in the United States of America and Europe alone [5]. If all these biopsies were conducted as TP-bx, the aforementioned reduction in risk would entail between 6000 and 28,000 fewer infectious episodes per year, some of which would have ineluctably led to urosepsis. These figures, already striking, represent only a fraction of the potential benefits that discontinuation of TR-Bx may offer to healthcare systems worldwide.

Infectious complications are not the sole factor to consider when comparing the approaches. The assumption of increased non-infectious complications in TP-Bx was also refuted by these RCTs. Our extensive experience with in-office TP-Bx, focusing lately

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on local anaesthesia techniques, demonstrated, differently from PREVENT, high tolerability and reported pain levels comparable with historical data on TR-Bx (data to be published shortly) [11]. However, we advocate for further research as high-level evidence in this area is still lacking. In-office TP-Bx also demonstrated negligible rates of bleeding and acute urinary retention. Meanwhile, the upcoming results of TRANSLATE [12] and PERFECT [13], two trials primarily comparing the diagnostic yield of TR-Bx and TP-Bx, may soon provide valuable data to inform the debate on clinically significant prostate cancer detection and differences in accuracy among approaches based on prostate zone sampling.

We recognise that the findings of both ProBE-PC and PREVENT do not support a recent claim to consider TR-Bx as medical malpractice [14], infectious rates following TR-Bx were overall low and no urosepsis was documented. Nevertheless, these RCTs also demonstrate that TR-Bx currently lacks any discernible clinical advantage over TP-Bx. This holds considerable significance for urology residents who are currently learning TR-Bx over TP-Bx. We advocate for training program directors to ensure that residents are exposed to both approaches, enabling them to break the habit of solely relying on the transrectal route for prostate sampling. We expect upcoming scientific evidence in favour of TP-Bx to steer the process further towards widespread adoption of this approach.

Roberto Miano [1,2,4]✉, Guglielmo Manenti [3] and Luca Orecchia [1,4]

[1]Urology Unit, AOU Policlinico Tor Vergata, Rome, Italy. [2]Department of Surgical Sciences, University of Rome Tor Vergata, Rome, Italy. [3]Department of Diagnostic and Interventional Radiology, Molecular Imaging and Radiotherapy, AOU Policlinico Tor Vergata, University of Rome Tor Vergata, Rome, Italy. [4]These authors contributed equally: Roberto Miano, Luca Orecchia. ✉email: mianor@virgilio.it

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COMPETING INTERESTS

The authors declare no competing interests.