Complications After Systematic, Random, and Image-guided Prostate Biopsy

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Abstract

Context: Prostate biopsy (PB) represents the gold standard method to confirm the presence of cancer. In addition to traditional random or systematic approaches, a magnetic resonance imaging (MRI)-guided technique has been introduced recently.

Objective: To perform a systematic review of complications after transrectal ultrasound (TRUS)-guided, transperineal, and MRI-guided PB.

Evidence acquisition: We performed a systematic literature search of Web of Science, Embase, and Scopus databases up to October 2015, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Complications and mortality following random, systematic, and image-guided PBs were reviewed. Eighty-five references were included.

Evidence synthesis: The most frequent complication after PB was minor and self-limiting bleeding (hematuria and hematospermia), regardless of the biopsy approach. Occurrence of rectal bleeding was comparable for traditional TRUS-guided and image-guided PBs. Almost 25% of patients experienced lower urinary tract symptoms, but only a few had urinary retention, with higher rates after a transperineal approach. Temporary erectile dysfunction was not negligible, with a return to baseline after 1–6 mo. The incidence of infective complications is increasing, with higher rates among men with medical comorbidities and older age. Transperineal and in-bore MRI-targeted biopsy may reduce the risk of severe infectious complications. Mortality after PB is uncommon, regardless of biopsy technique.

Conclusions: Complications after PB are frequent but often self-limiting. The incidence of hospitalization due to severe infections is continuously increasing. The patient's general health status, risk factors, and likelihood of antimicrobial resistance should be carefully appraised before scheduling a PB.

Patient summary: We reviewed the variety and incidence of complications after prostate biopsy. Even if frequent, complications seldom represent a problem for the patient. The most troublesome complications are infections. To minimize this risk, the patient's medical condition should be carefully evaluated before biopsy.

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1. Introduction

Prostate biopsy (PB), often guided by transrectal ultrasound (TRUS), is the gold standard technique to confirm the presence of cancer in men with suspicion for prostate malignancy. It is estimated that >2 million procedures are carried out in the United States and Europe every year [1,2]. Although PB is often performed transrectally in an outpatient setting, it also can be performed by a transperineal approach, avoiding the rectum. Magnetic resonance imaging (MRI) was proposed recently for targeting biopsies toward suspicious areas to improve detection of clinically significant prostate cancer (PCa) [3]. The opportunity to perform a lesion-targeted biopsy could reduce the number of biopsy cores taken and thus lower complications rates without compromising detection rates. Our objective was to perform an updated systematic review of complication profiles after TRUS-guided systematic, transperineal, and MRI-targeted PB.

2. Evidence acquisition

A PubMed search for English-language publications up to October 2015 with the search terms prostate biopsy AND complications was performed. This initial search identified 7000 records. Another 60 contributions were retrieved through hand and free-text searches, including Web of Science, Embase, and Scopus databases, using the following search terms: fusion prostate biopsy AND complications; in-bore prostate biopsy; prostate biopsy AND erectile dysfunction OR erectile function; image-guided prostate biopsy. All available reports containing data on complications after systematic, random, and image-guided PB were considered for eligibility.

Studies were finally included based on the following criteria: (1) Complications after PB were appropriately reported, including, if available, the tools used to measure the adverse events; (2) randomized controlled trials (RCTs) were considered first; (3) in the absence of RCTs, prospective cohort studies, series from national databases, and retrospective studies were included; (4) in case of overlapping study design, only the report with the most comprehensive information or the largest population was included. Studies were excluded if they were editorials, abstracts, or case reports; if they lacked sufficient data on complications and rates of adverse events; or if the publication date was before 2002. The rates and types of complications after PB were assessed and recorded for all contributions. The first author (M.B.) screened all abstracts and full-text articles. A flowchart of the systematic search process is shown in Figure 1. Based on the above-mentioned criteria, 85 unique references were ultimately included in this qualitative synthesis.

3. Evidence synthesis

3.1. Bleeding

PB is generally performed as a transrectal procedure under local anesthesia in an outpatient setting and is usually well tolerated. Postprocedural bleeding, voiding dysfunctions, and pain are common [1] but are not clinically significant and are seldom troublesome. Both patient-related factors (eg, use of anticoagulant medications, coagulopathies, medical comorbidities, prostate volume, obstructive symptoms, and anxiety) and procedure-related factors (eg, biopsy indication, technique, number of cores taken, type of anesthesia) may affect occurrence of these complications.

3.1.1. Hematuria

Hematuria following PB is common, with a reported incidence of 2–84% [1,4–11] depending on the technical approach, definition, duration of follow-up, and method of data collection. Patient-related factors, such as prostate volume and medical comorbidities, also influence the risk of hematuria. In a large prospective cohort of 1147 men undergoing TRUS-guided PB, hematuria was reported by 65.8% of patients within 35 d, but only 6.2% of them considered it bothersome [7]. In the European Randomized Study of Screening for Prostate Cancer (ERSPC), hematuria lasting >3 d occurred in 22.6% of cases and was significantly correlated with higher prostate and transition zone volumes (p < 0.001) [11]. The impact of the number of biopsy cores on hematuria is controversial, regardless of the technique (TRUS-guided or transperineal). Ghani et al found that the prevalence of hematuria did not vary with the number of TRUS-guided PB cores (44% with 6 cores, 41% with 8 cores, 39% with 12 cores) [4], whereas others reported higher rates of bleeding with increased sampling [12]. Among 3000 patients undergoing transperineal biopsy, Pepe et al reported hematuria in 10.4% of cases, regardless of the number of cores [10]. Higher rates of hematuria (73.4%) after transperineal PB were observed by others, although multivariate analysis did not reveal any predictive factors [13].

MRI-guided in-bore PBs have been associated with lower rates of overall complications compared with TRUS-guided PB, including bleeding. In a prospective nonrandomized study of 54 patients, Egbers et al recently reported hematuria in 51% of MRI-guided in-bore biopsies compared with 79% of transrectal PBs (p = 0.006), as well as a longer bleeding duration for the latter technique [14]. Moreover, in a recent systematic review evaluating outcomes of MRI-guided in-bore PB performed transrectally, transient hematuria occurred in 1–24% of patients [3]. Hospital admissions rates for severe hematuria have been reported in <1% of cases [1,2,15,16], and despite a higher average number of biopsy cores taken in recent years compared with historical data, the rate of bleeding complications has not changed over time.

3.1.2. Rectal bleeding

Transrectal PB could lead to transient hematochezia, with reported rates of 1.3–45% [1]. As with hematuria, in the vast majority of men, rectal bleeding is self-limiting and rarely bothersome. In a large prospective study, rectal bleeding was common (36.8%), but only 2.5% of all patients found it a major or moderate problem, according to the National Cancer Institute’s criteria [7]. Lower rates were reported
within the ERSPC study (1.3%), with no correlation between hematochezia and other clinical parameters [11]. Ghani et al reported significantly higher rates of rectal bleeding in men undergoing more biopsy cores (17%, 26%, and 27% after 6-, 8-, and 12-core biopsy, respectively) [4]. Berger et al reported an overall bleeding rate of 2.3% [5]. In this TRUS-guided series, only 0.6% of patients experienced prolonged hematochezia or required surgical intervention for bleeding control, with no significant correlation with the number of cores taken [5]. The occurrence of hematochezia after MRI-guided in-bore PB ranged from 11% to 17% [3], with no significant advantages offered by this approach over traditional TRUS-guided PB in terms of incidence and duration of bleeding in this population [14]. Massive rectal bleeding is uncommon, and management options include rectal balloon tamponade, endoscopic adrenaline injection or sclerotherapy, or direct endoscopic vessel clipping or ligation [1].

3.1.3. Hematospermia
The presence of visible blood in the ejaculate is the most variably reported complication after PB, ranging from 1.1% to 92.6% [1,5,7,11,13,17]. Unlike hematuria or rectal bleeding, hematospermia could have a transient detrimental effect on sexual activity or trigger anxiety [7,17]. In a large prospective cohort from the UK screening study, Rosario et al reported hematospermia in 92.6% of patients within 35 d after PB, and 26.6% perceived it as a moderate or serious and bothersome problem [7]. In the ERSPC study, hematospermia was reported in 50.4%, and was inversely correlated with age \((p < 0.001)\), previous transurethral resection of the prostate \((p < 0.001)\), and prostate volume \((p < 0.001)\) [11]. Regardless of the procedural approach, the number of cores can influence incidence of hematospermia. In a retrospective study by Berger et al, hematospermia was the most frequently reported complication after TRUS-guided PB (36.3%) and was significantly higher with more cores taken (31.8%, 37.4%, and 38.4% after 6-, 10-, and 15-core biopsy, respectively; \(p < 0.001\)) [5]. Similarly, Pepe et al found that hematospermia significantly correlated with the number of cores following transperineal PB (30.4% and 10.7% following ≥24 and 12 cores, respectively; \(p = 0.001\)) [10]. Conversely, in a recent MRI-guided in-bore PB series with a median of four cores, the rate of hematospermia was similar to TRUS-guided PB with 10 median cores (36% vs 33%, \(p > 0.05\)) [14].

3.1.4. Use of anticoagulants and bleeding complications
A recent consensus-based recommendation from the International Consultation on Urological Disease and the American Urological Association on anticoagulant and antiplatelet (AC/AP) therapy in urologic practice [18] stated that the risk of bleeding after PB in men using AC/AP therapy must always be balanced against the hazard of cardiovascular or thromboembolic events when stopping such therapies, especially in high-risk patients (eg, metal heart valves, drug-eluting coronary stent, atrial fibrillation). Giannarini et al randomly assigned 196 men undergoing
TRUS-guided PB to continue low-dose aspirin, to replace it with low-molecular-weight heparin, or to discontinue aspirin without replacement [19]. They found no significant difference in the overall bleeding rate (hematuria, rectal bleeding, and hematospermia) among the three groups (78.5% with aspirin, 69.7% with heparin, and 81.5% without aspirin; \( p = 0.26 \)), and no severe bleeding occurred; however, the median duration of hematuria and rectal bleeding was significantly longer in men under AC/AP therapy than in those who stopped antiplatelet therapy (\( p < 0.001 \)) [19].

Comparable results have been reported by other authors [20]. Chowdhury et al compared the results of 930 men undergoing TRUS-guided PB with increasing sampling numbers (up to 10) without stopping warfarin or aspirin [12]. Type of bleeding complication, duration, and severity increased significantly with increasing numbers of cores in all patients. Interestingly, warfarin use, once controlled for core number and patient age, was not associated with bleeding events, duration, or severity. Conversely, low-dose aspirin significantly increased the incidence of hematuria and both incidence and duration of rectal bleeding. No severe hemorrhagic complications were reported [12]. Similarly, Ihezue et al reported no difference in incidence, duration, or severity of bleeding in men using warfarin before TRUS-guided PB [21]. Accordingly, high-risk patients on low-dose aspirin or warfarin may have greater risk from AC/AP withdrawal than the risk of a serious bleeding complication. Consultation with the AP/AC-prescribing physician can help balance risks and benefits of discontinuing AP/AC therapy to prevent biopsy-related hemorrhage.

### 3.2. Lower urinary tract symptoms and acute urinary retention

A common side effect after transrectal PB is short-term exacerbation of urinary symptoms, with reported rates of lower urinary tract symptoms (LUTS) from 6% to 25% [1,13,22]. The reported incidence of acute urinary retention after transrectal biopsy is substantially lower, ranging from 0.4% to 6% [1,9,11,23,24]. Urinary retention is usually transient, and most patients do not require more invasive treatments than temporary placement of a urethral catheter.

The exact pathophysiology of PB-related voiding impairment is unclear, although it may be related to iatrogenic trauma from placing needles into the prostate that could affect bladder outlet resistance and voiding symptoms. Prostate volume, in particular, the transition zone volume, is a well-documented and significant factor associated with subjective voiding impairment and acute urinary retention in most studies [22]. In 5802 men from the Rotterdam section of the ERSPC, for example, prostate volume, ratio of transition zone volume to total prostate volume, and a higher International Prostate Symptom Score (IPSS) were all predictors of urinary retention [11]. Similarly, Aktas et al found that patients with a prostate volume >38.8 ml were more prone to voiding difficulty after TRUS-guided biopsy. The main limitations of this study were small sample size (92 men) and short follow-up (7 d) [24].

Fewer data are available on urinary side effects of transperineal PB. Namekawa et al recently reported on 2086 men undergoing an initial PB under lumbar spinal anesthesia: Prostate-specific antigen, IPSS, prostate volume, abnormal digital rectal examination, and history of alpha blocker use were independent predictors of LUTS and urinary retention [13]. Compared with TRUS-guided PB, the occurrence of acute urinary retention after a transperineal approach is slightly higher, ranging from 1.7% to 11.1% [8–10,25,26]. Pepe et al reported 11.1%, which was significantly correlated with the number of cores taken [10,27]. Tsivian et al showed severe worsening of urinary symptoms with urinary retention in 6%, with a return to baseline within 6 wk [9].

There are conflicting data on the association between number of cores and type of anesthesia with voiding symptoms after PB. Klein et al evaluated 198 patients randomized to undergo PB with or without periprostatic nerve block (PPNB) [23]. Overall IPSS was significantly increased in all patients at 1 wk but persisted at 1 and 3 mo only in those men submitted to repeated saturation biopsy (\( p = 0.007 \)). Conversely, patients who underwent 10-core PB with PPNB had a higher IPSS at 1 and 3 mo compared with those without PPNB, but this result was not statistically significant [23].

There are limited data on the impact of serial biopsies during active surveillance (AS) on voiding symptoms and the risk of acute urinary retention, although limited evidence suggests no significant correlation between number of PBs and IPSS [28]. Based on the currently available data, the reported incidence of acute urinary retention after MRI-guided PB is sporadic, from 0% to 1% [3,14,29]. Voiding symptoms and risk of acute urinary retention after PB might be mitigated using alpha blockers, although results are conflicting. Chung et al randomized 88 patients undergoing TRUS-guided PB to periprocedural tamsulosin or no tamsulosin [30]. Patients treated with tamsulosin had better flow rates (\( p < 0.01 \)) and lower postvoid residual urine volume (\( p < 0.05 \)) than controls on postbiopsy days 1 and 7. No acute urinary retention was found in those patients using tamsulosin [30]. In summary, although almost 25% of patients experience transient LUTS, only a small proportion of these patients experience urinary retention. The administration of alpha blockers after PB could have a beneficial impact.

### 3.3. Erectile dysfunction

PBs may lead to transient erectile dysfunction (ED), with complete recovery after 1–3 mo [28]. Notably, currently available data are heterogeneous with respect to patient populations and ED classifications, and significant confounders could impair the reliability of results. Murray et al showed that 34% of patients with no ED at baseline had a decrease in International Index of Erectile Function (IIEF) at 1 wk; 20% and 24% continued to have lower scores at 1 and 3 mo, respectively [31]. Age ≥60 yr, the first biopsy setting, and a diagnosis of PCs were the main predictors of IIEF-measured impairment at 1 and 3 mo [31]. It has been
hypothesized that extensive sampling during saturation PB could affect erectile function (EF), but in multiple series, the IIEF-measured impairment resolved within 6 mo after biopsy, and no correlation was found between number of cores and IIEF [28,32]. Several anatomic hypotheses have been postulated, such as a compression on the neurovascular bundle by edema or hematoma and neuropraxia caused by laterally directed biopsy needles. Moreover, PPNB could affect EF, due to the direction of anesthetic into the neurovascular bundles; however, the changes in IIEF seem to be similar for the different analgesia techniques [22,23]. Significant anxiety regarding the possibility of cancer may also have an impact on EF. One study found a reduction in all IIEF domains only among men diagnosed with PCa on biopsy, whereas no significant decrease was found in their counterparts with negative biopsy results [22]. With expanded use of AS for clinically localized low-risk PCa, many men with a diagnosis of PCa are also undergoing repeated PB during follow-up. Considering the effect of serial TRUS-guided biopsy in 231 patients from an AS program, Fujita et al demonstrated a significant correlation between number of biopsy sessions and decrease in EF [28]. A history of three or more biopsies was correlated to greater EF impairment than two or fewer biopsies (p = 0.02) [28]. Another prospective AS study of 342 patients undergoing TRUS-guided PB found that EF decreased by 1 point every year for the first 4 yr [33]. However, the impact of repeated PB itself on EF cannot be separated from the natural aging process and other potential confounders. In 427 men in an AS program, Hilton et al showed that sexual activity level changed in >20% of respondents; however, no significant association between EF and increasing biopsy exposure was found after adjusting for age, sexual activity status, clinical stage, and diagnostic period [34]. In summary, a non-negligible proportion of men undergoing biopsy experience ED; however, they usually return to baseline EF by 1–6 mo after the procedure, and it is unclear whether these changes are due to the biopsy itself, to the psychological impact of the event, or to other confounders.

### 3.4. Pain

Although PB is well tolerated by most of patients, techniques to reduce pain and discomfort are routinely used in clinical practice. Different steps may cause pain during biopsy, such as probe insertion, periprostatic infiltration, and biopsy sampling, and pain may last up to several hours afterward. Previously reported predictors of pain include anorectal compliance, younger age, prostate volume, number of biopsy cores, and lateral decubitus position that could affect blood flow within the prostate [1]. Anxiety is also an important factor that should be considered, especially in younger patients. PPNB, which consists of injecting lidocaine between the prostate base and the seminal vesicle on each side (where the neurovascular bundles are anatomically positioned), is the most widely used anesthetic for transrectal PB and has been shown to reduce pain compared with no anesthetic [1,35]. However, PPNB does not alleviate the discomfort related to TRUS probe insertion and manipulation, and periprostatic anesthetic infiltration itself is among the most painful parts of the procedure [35]. Consequently, non-infiltrative topical anesthesia (eg, creams, gels, and suppositories) represent potential alternatives to reduce discomfort.

Lidocaine gel was among the first and most used local anesthetic agents due to its low cost and safety. Reports showed significantly less pain with probe insertion and manipulation compared with placebo [36], but it did not reduce pain related to anesthetic infiltration and needle biopsy. A combination of 2.5% lidocaine and 2.5% prilocaine (EMLA cream; Actavis Pharma, Buena, NJ, USA) was found to be superior to other topical anesthetic agents, possibly due to its longer duration (2–5 h) and deeper tissue infiltration [37]. Furthermore, suppositories based on nonsteroidal anti-inflammatory drugs (eg, diclofenac) can be used to reduce the local and systemic anti-inflammatory effect but do not significantly reduce pain from probe manipulation and biopsy sampling [38]. Comparing lidocaine gel with lidocaine–ketorolac gel and lidocaine–prilocaine cream, the latter was the most effective on probe-related pain, whereas lidocaine–ketorolac gel was most useful for sampling-related pain [39].

Another alternative form of anesthesia is pelvic plexus block (administration of lidocaine in the area of the pelvic plexus, lateral to the tip of seminal vesicles on each side) [40] and a combination of intracapsular anesthesia and PPNB [41], which was found to provide superior analgesia to PPNB alone. Interestingly, Iremashvili et al reported that patients receiving combined PPNB and bilateral pudendal block during transperineal PB had significantly better pain control throughout probe insertion and biopsy sampling and at 1 h after the procedure compared with PPNB alone [42].

There is also increasing interest in combining topical and infiltrating anesthesia. Consequently, Raber et al showed that a combination of intrarectal local analgesia using a lidocaine–prilocaine cream and PPNB was superior to PPNB alone in controlling pain during TRUS-guided PB and may have maximum benefit for younger patients [43]. Similarly, Giannarini et al found that the combination of perianal–intrarectal lidocaine–prilocaine cream and PPNB was able to provide better pain control than the two modalities alone, with no increase in the complication rate. The magnitude of this effect was higher in younger men, especially with an enlarged prostate and lower anorectal compliance [44]. A recent meta-analysis confirmed that the combination of local analgesia and PPNB significantly reduced pain associated with probe manipulation, anesthesia, infiltration, and needle biopsy. Subgroup analyses suggested that lidocaine–prilocaine cream provided the most effective pain control regardless of the origin of pain [38]. Moreover, Cormio et al compared the efficacy of topical anesthesia (combined lidocaine–prilocaine cream with lidocaine–ketorolac gel) with the combination of topical and infiltrating anesthesia (lidocaine–prilocaine cream plus PPNB): Both anesthetic regimens provided...
almost comparable pain at probe insertion, movement, and during sampling, but patients receiving the second regimen reported significantly greater maximal procedural pain scores ($p < 0.001$) [37,39].

With MRI-guided in-bore PB, some patients now undergo prostate sampling limited to suspicious lesions, resulting in significantly less pain intensity and duration compared with the traditional transrectal procedure. In the study by Egbers et al, pain intensity was significantly lower for MRI-guided in-bore PB compared with TRUS-guided PB ($p = 0.005$), and similarly, pain duration was shorter after the former technique [14]. Table 1 summarizes the outcomes of the most relevant randomized trials evaluating pain during and after PB.

In conclusion, optimal pain control is essential to reduce discomfort and improve patients’ acceptance of biopsy. Although the best clinical practice consists of combined local analgesia with PPNB, proper patient selection for higher level analgesia is crucial to achieve individualized pain control.

3.5. Infectious complications and hospitalization rates after prostate biopsy

Infections are well-established adverse events after TRUS-guided PB. Asymptomatic bacteriuria, febrile urinary tract infections (UTIs), acute bacterial prostatitis, orchitis, epididymitis, and urinary sepsis represent the broad spectrum of possible infectious complications [1,45,46]. Accordingly, antibiotic prophylaxis is recommended as the standard of care [1,47,48]. Fluoroquinolones were the drug of choice since the introduction of PB because they achieve high concentrations in prostatic tissue and have broad-spectrum activity against common urogenital pathogens; however, growing fluoroquinolone resistance has recently led to increasing rates of infective complications. Fluoroquinolone-resistant (FQR) organisms have been identified in 10–30% of patients undergoing rectal swab culture before PB [47,49–52], although rates of clinical infectious complications are lower, at approximately 1–17.5% [7,45,46,48,53–57]. Most infections are self-limiting and can be managed in the outpatient setting [7,45]; however, the incidence of more serious infectious complications requiring hospitalization has dramatically increased over time [2,15,58–60], with FQR *Escherichia coli* as the most recognized risk factor [2,45,47,49–51,53]. In this scenario, patients with biopsy-related bacterial acute prostatitis have a higher risk of sepsis compared with those with spontaneous acute prostatitis, probably due to a different pathogenic bacterial strain among the two groups [61]. Furthermore, medical comorbidities (particularly diabetes or metabolic syndrome) and older age are independent predictors increasing the risk of infections and sepsis [45,58,60,62]. A previous history of prostatitis, use of antibiotics within 6 mo before PB, and nonadherence to antibiotic prophylaxis represent other risk factors [46].

Whether a repeated biopsy protocol, including those done for AS, could increase the risk of infection is unclear. In a recent study by Ehdaie et al, the risk of infection significantly increased for each additional previous biopsy (odds ratio [OR]: 1.33; 95% confidence interval [CI], 1.01–1.74; $p = 0.04$), up to a rate of 15% for patients who had undergone five or more biopsies [6]. Similarly, Loeb et al reported a cumulative increase in the risk of having a complication for which each additional biopsy was associated with a 1.7-fold increase in overall hospitalizations and a 1.7-fold increase in serious infectious complications [59]. In a biopsy-based multivariable analysis, however, the repeat biopsy procedure itself was not associated with a greater risk of serious complications requiring hospital admission compared with the initial biopsy session [59]. In patients undergoing transperineal PB, the reported incidence of infections and sepsis is close to zero (0–0.2%), given the avoidance of bacterial contamination (which is common during transrectal access) and the limited number of cores taken when performing transperineal MRI-guided in-bore biopsy [8–10,13,25–27,29,63–67]. Although data are currently limited, it is unclear whether the lower incidence of infectious complications after MRI-targeted PB could be related to the sampling route (ie, transperineal) or the low number of cores taken. In a comparative series of patients undergoing transrectal MRI-targeted PB and TRUS-guided PB, the authors found a lower incidence of infective complications in the former group (the rate of infections was halved compared with the latter), even if not statistically significant [14]. Conversely, the infectious complication rate after in-bore transperineal MRI-targeted biopsy appears to be virtually absent, with a hospitalization rate of 0% [29,64].

A minority of patients require hospitalization for the management of serious biopsy-related adverse events or the exacerbation of underlying medical conditions. Data on hospital admissions following PB were recently reported by Anastasiadis et al from the English national cancer registry [58]. Of the 198 361 men who underwent PB between 2000 and 2008, 3.7% required hospitalization because of biopsy-related complications (UTI or sepsis, hematuria, and urinary retention in 1.1%, 1.4%, and 1.3% of men, respectively). Independent predictors of complications requiring hospitalization were age and comorbidities, with a roughly fourfold increased risk of admission at age $\geq$85 yr compared with ages 45–54 yr and more than threefold increased risk in those men with two or more comorbidities. Remarkably, hospitalization increased during the study period (20% greater incidence, $p = 0.03$), predominantly due to UTI or sepsis (70% higher incidence in 2008 than in 2000), whereas rates of hematuria and urinary retention remained stable [58]. Nam et al were the first to report rising rates of hospitalization over time in a retrospective analysis of 75 190 biopsied men from Canada [15]. They reported an overall hospitalization rate of 1.4% within 30 d from TRUS-guided PB, with an increasing occurrence from 1996 to 2005 for both PCA-positive and -negative patients. Infections dramatically increased over time (from 0.6% in 1996 to 3.6% in 2005), with no significant differences based on age. Those men undergoing systematic repeated biopsy experienced a complication rate similar to those undergoing
Table 1 – Randomized controlled trials reporting pain during transrectal and transperineal prostate biopsy

<table>
<thead>
<tr>
<th>Author</th>
<th>No. cases</th>
<th>Type of biopsy</th>
<th>No. biopsy cores</th>
<th>Type of anesthesia</th>
<th>Global pain, mean</th>
<th>Pain related to insertion/ manipulation of transrectal probe, mean</th>
<th>Pain related to infiltrating anesthesia, mean</th>
<th>Pain related to biopsy sampling, mean</th>
<th>Pain after procedure, mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akpinar et al [40]</td>
<td>n = 80</td>
<td>TRUS-guided</td>
<td>12</td>
<td>RCT:</td>
<td>NR</td>
<td>1: 2.27</td>
<td>1: 3.12</td>
<td>1: 4.97</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1: PPNB</td>
<td></td>
<td>2: 2.2</td>
<td>2: 2.05</td>
<td>2: 2.7</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>2: Pelvic plexus block</td>
<td></td>
<td>p = 0.7</td>
<td>p = 0.007</td>
<td>p = 0.001</td>
<td>p = 0.001</td>
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<tr>
<td>Cantiello et al [35]</td>
<td>n = 180</td>
<td>TRUS-guided</td>
<td>12</td>
<td>RCT:</td>
<td>NR</td>
<td>1: 1.36</td>
<td>1: 1.32</td>
<td>1: 2.28</td>
<td>1: 2.02</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td>1: Intrarectal local anesthesia (lidocaine 1.5%-nifedipine 0.3% cream) plus pelvic plexus block</td>
<td></td>
<td>2: 1.22</td>
<td>2: 1.34</td>
<td>2: 3.37</td>
<td>2: 2.41</td>
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<td></td>
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<td></td>
<td>2: Intrarectal local anesthesia (lidocaine 1.5%-nifedipine 0.3% cream) plus PPNB</td>
<td></td>
<td>p = 0.2</td>
<td>p = 0.8</td>
<td>p = 0.001</td>
<td>p = 0.001</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1: Intrarectal 5 g 2.5% lidocaine gel</td>
<td></td>
<td>2: 1.67</td>
<td>3: 0.39</td>
<td>1: 1.97</td>
<td>2: 0.76</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2: Intrarectal 5 g 2.5% lidocaine gel and 0.3% ketorolac tromethamine solution</td>
<td></td>
<td>p ≤ 0.001</td>
<td>(1 vs 2 and 3)</td>
<td>p ≤ 0.001</td>
<td>p ≤ 0.001</td>
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<td></td>
<td></td>
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<td></td>
<td>3: Intrarectal 2.5% prilocaine cream</td>
<td></td>
<td>p ≤ 0.001</td>
<td>(3 vs 2 vs 1)</td>
<td>p ≤ 0.001</td>
<td>p ≤ 0.001</td>
</tr>
<tr>
<td>Cormio et al [37]</td>
<td>n = 200</td>
<td>TRUS-guided</td>
<td>18</td>
<td>RCT:</td>
<td>1: 0.68</td>
<td>2: 1.53</td>
<td>3: 0.37</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1: Intrarectal lidocaine-prilocaine cream and lidocaine-ketorolac gel</td>
<td></td>
<td>2: 0.37</td>
<td>3: 0.52</td>
<td>1: –</td>
<td>2: 1.35</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2: Intrarectal lidocaine-prilocaine cream and PPNB</td>
<td></td>
<td>p ≤ 0.001</td>
<td>p = 0.7</td>
<td>2: 0.51</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p ≤ 0.001</td>
<td>(2 vs 1 and 3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goluza et al [36]</td>
<td>n = 80</td>
<td>TRUS-guided</td>
<td>12</td>
<td>RCT:</td>
<td>1: 3.0</td>
<td>2: 4.0</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1: Intrarectal lidocaine suppository</td>
<td></td>
<td>p ≤ 0.001</td>
<td>2: Placebo (glycerin suppository)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2: Placebo (glycerin suppository)</td>
<td></td>
<td>p = 0.001</td>
<td>p = 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iremashvili et al [42]</td>
<td>n = 150</td>
<td>Transperineal</td>
<td>12</td>
<td>RCT:</td>
<td>NR</td>
<td>1: 3.15</td>
<td>2: 2.16</td>
<td>1: 3.63</td>
<td>2: 1.13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1: PPNB</td>
<td></td>
<td>2: 2.16</td>
<td>3: 2.38</td>
<td>2: 2.07</td>
<td>2: 0.72</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2: PPNB combined with pudendal block</td>
<td></td>
<td>p ≤ 0.001</td>
<td>p = 0.06</td>
<td>p ≤ 0.001</td>
<td>p ≤ 0.001</td>
</tr>
<tr>
<td>Lee et al [41]</td>
<td>n = 152</td>
<td>TRUS-guided</td>
<td>12</td>
<td>RCT:</td>
<td>NR</td>
<td>1: 3.7</td>
<td>2: 4.1</td>
<td>1: 4.3</td>
<td>2: 4.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1: Intraprostatic local anesthesia with 2 ml 1% lidocaine and periprostatic injection of 2 ml saline later</td>
<td></td>
<td>3: 3.9</td>
<td>3: 4.9</td>
<td>3: 2.7</td>
<td>3: 0.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2: Intraprostatic injection of 2 ml saline, and periprostatic local anesthesia with 2 ml 1% lidocaine</td>
<td></td>
<td>p = NS</td>
<td>p = 0.003</td>
<td>p = 0.003</td>
<td>p = NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p = 0.003</td>
<td>p = 0.003</td>
<td>p = 0.003</td>
<td>p = NS</td>
</tr>
<tr>
<td>Raber et al [43]</td>
<td>n = 300</td>
<td>TRUS-guided</td>
<td>14</td>
<td>RCT:</td>
<td>NR</td>
<td>1: 1.48</td>
<td>2: 2.39</td>
<td>1: 0.43</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1: PPNB</td>
<td></td>
<td>2: 2.09</td>
<td>3: 1.06</td>
<td>2: 0.37</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2: Intrarectal lidocaine-prilocaine cream and PPNB</td>
<td></td>
<td>3: Placebo</td>
<td>p ≤ 0.001</td>
<td>p ≤ 0.001</td>
<td>p = 0.8</td>
</tr>
</tbody>
</table>
initial biopsy [15]. In a study from the Surveillance Epidemiology and End Results (SEER) database, Loeb et al reported a 6.9% 30-d overall hospitalization rate after PB [2]. More medical comorbidities, nonwhite race, and later year were significant risk factors [2]. A Canadian retrospective study of 5798 PB patients reported a hospitalization rate of 0.5%, with all hospitalizations due to infection [60]. Independent predictors were more recent year of biopsy (OR: 4.74; \( p < 0.001 \)), diabetes (OR: 4.78; \( p = 0.01 \)), chronic obstructive pulmonary disease (OR: 5.66; \( p = 0.005 \)), and history of recent hospitalization (OR: 8.83; \( p = 0.03 \)) [60]. In men from the Rotterdam section of the ERSPC, the hospitalization rate within 14 d after biopsy was 0.8%, primarily due to infection (81%). Similar to previously reported studies, year of biopsy was an independent predictor of hospital admissions, with a 10% increase over time, likely related to rising fluoroquinolone resistance. Fluoroquinolones have been widely used as prophylaxis for TRUS-guided PB and for the treatment of urologic infections for the last two decades, but the number of FQR bacteria have increased over time [47,49,53]. Other relevant studies [7,11,16,48,49,59,68–70] reporting similar hospitalization rates are summarized in Table 2.

A recent statewide study from the Michigan Urological Surgery Improvement Collaborative (MUSIC) group, reported a reduction in hospitalization rates for infectious complications from 1.19% to 0.56% when adopting a specific protocol for antibiotic prophylaxis (by shifting from a monotherapy to multidrug prophylaxis or performing culture-directed prophylaxis) [51]. Although a transperineal approach for PB is infrequently used in many parts of the world, largely for logistical reasons, the incidence of readmissions for urinary infection or sepsis is lower, ranging from 0% to 0.7% in published reports [9,10,25,26] (Table 2).

Despite the currently limited available literature, the lower incidence of infections and hospitalizations among patients undergoing MRI-targeted PB appears mostly related to transperineal access rather than the number of cores taken [29,64].

In summary, the occurrence of serious major complications after transrectal PB requiring hospital admission ranges from 0.5% to 6.9% and has increased over time. In the absence of grade 1 evidence, based on the currently available data, transperineal and limited sampling with in-bore MRI targeted biopsy seems to be associated with a reduced risk of severe infectious complications.

### 3.6. Biopsy protocol modification to reduce the risk of infectious complications

Several strategies have been proposed to reduce the risk of infectious complications in men undergoing PB [1]. Prebiopsy rectal enemas, either with glycerin or saline or with povidone–iodine (PI), are a first-line option. Kam et al reported a significantly lower rate of complications by administering a glycerin or saline enema 1 h before TRUS-guided PB (4.7% vs 8.9%, \( p = 0.007 \)) [71]. Abughosh and collaborators reported fewer infections in men randomized to PI cleansing compared with no cleanse, although the
Table 2 – Studies reporting hospital admission rates and reasons for and predictors of hospitalization after prostate biopsy

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of biopsy</th>
<th>No. of patients undergoing biopsy</th>
<th>Hospital admission rate</th>
<th>Reason for hospitalization</th>
<th>Independent predictors of hospitalization</th>
<th>Follow-up interval, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anastasiadis et al, 2015 [58]</td>
<td>NA</td>
<td>198 361</td>
<td>3.7%</td>
<td>UTI/sepsis Hematuria Urinary retention</td>
<td>Patient age Medical comorbidities Recent biopsy year</td>
<td>30</td>
</tr>
<tr>
<td>Nam et al, 2013 [15]</td>
<td>TRUS-guided</td>
<td>75 190</td>
<td>1.4%</td>
<td>UTI/sepsis Hematuria Urinary retention</td>
<td>Recent biopsy year</td>
<td>30</td>
</tr>
<tr>
<td>Carignan et al, 2012 [60]</td>
<td>NA</td>
<td>5798</td>
<td>0.5%</td>
<td>UTI/sepsis</td>
<td>Recent biopsy year</td>
<td>30</td>
</tr>
<tr>
<td>Loeb et al, 2012 [53]</td>
<td>TRUS-guided</td>
<td>9198</td>
<td>0.8%</td>
<td>UTI/sepsis (81% of cases) Hematuria Urinary retention</td>
<td>Recent biopsy year</td>
<td>14</td>
</tr>
<tr>
<td>Luong et al, 2015 [68]</td>
<td>TRUS-guided</td>
<td>2093</td>
<td>0.6%</td>
<td>UTI/sepsis</td>
<td>Diabetes</td>
<td>2</td>
</tr>
<tr>
<td>Pinkhasov et al, 2012 [16]</td>
<td>TRUS-guided</td>
<td>1000</td>
<td>2.5%</td>
<td>UTI/sepsis Hematuria Urinary retention Transient ischemic attack</td>
<td>No significant predictors</td>
<td>30</td>
</tr>
<tr>
<td>Ganeswaran et al, 2014 [69]</td>
<td>TRUS-guided</td>
<td>715</td>
<td>1.95%</td>
<td>UTI/sepsis Hematuria Urinary retention</td>
<td>NA</td>
<td>30</td>
</tr>
<tr>
<td>Roth et al, 2015 [70]</td>
<td>TRUS-guided</td>
<td>35 501</td>
<td>3.7%</td>
<td>UTI/sepsis</td>
<td>NA</td>
<td>7</td>
</tr>
<tr>
<td>Loeb et al, 2013 [59]</td>
<td>TRUS-guided</td>
<td>13 883 (initial) 3640 (repeat)</td>
<td>6.9% 4%</td>
<td>Infectious Noninfectious</td>
<td>–</td>
<td>30</td>
</tr>
<tr>
<td>Raaijmakers et al, 2002 [11]</td>
<td>TRUS-guided</td>
<td>5802</td>
<td>0.5%</td>
<td>UTI/sepsis Septic shock</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Liss et al, 2014 [49]</td>
<td>TRUS-guided</td>
<td>2673</td>
<td>1.6% overall, 0.9% in patients without FQR, 4.4% in patients with FQR</td>
<td>UTI/sepsis</td>
<td>FQR</td>
<td>30</td>
</tr>
<tr>
<td>Lundström et al, 2014 [45]</td>
<td>TRUS-guided</td>
<td>51 321</td>
<td>1%</td>
<td>UTI/sepsis</td>
<td>Medical comorbidities</td>
<td>30</td>
</tr>
<tr>
<td>Wagenlehner et al, 2013 [48]</td>
<td>TRUS-guided</td>
<td>521</td>
<td>3.1%</td>
<td>UTI/sepsis</td>
<td>No significant predictors</td>
<td>14</td>
</tr>
<tr>
<td>Womble et al, 2015 [51]</td>
<td>TRUS-guided</td>
<td>4087</td>
<td>1.19% (without implementation), 0.56% with implementation</td>
<td>UTI/sepsin</td>
<td>NA</td>
<td>30</td>
</tr>
<tr>
<td>Grummet et al, 2014 [26]</td>
<td>Transperineal</td>
<td>244</td>
<td>0%</td>
<td>–</td>
<td>–</td>
<td>NA</td>
</tr>
<tr>
<td>Pepe and Aragona, 2013 [10]</td>
<td>Transperineal</td>
<td>3000</td>
<td>1.2% (0.7% for UTI)</td>
<td>Acute urinary retention UTI</td>
<td>NA</td>
<td>20</td>
</tr>
<tr>
<td>Vyas et al, 2014 [25]</td>
<td>Transperineal</td>
<td>634</td>
<td>1.4% (0% for UTI/sepsin)</td>
<td>Acute urinary retention Hematuria and blood clots</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Tsivian et al, 2013 [9]</td>
<td>Transperineal</td>
<td>84</td>
<td>1.1% (0% for UTI/sepsin)</td>
<td>Hematuria</td>
<td>NA</td>
<td>30</td>
</tr>
<tr>
<td>Penzkofer et al, 2015 [64]</td>
<td>MRI-guided</td>
<td>90</td>
<td>0%</td>
<td>–</td>
<td>–</td>
<td>NA</td>
</tr>
<tr>
<td>Panebianco et al, 2015 [29]</td>
<td>MRI-guided</td>
<td>23</td>
<td>0%</td>
<td>–</td>
<td>–</td>
<td>NA</td>
</tr>
</tbody>
</table>

COPD = chronic obstructive pulmonary disease; FQR = fluoroquinolone resistance; MRI = magnetic resonance imaging; NA = not available; TRUS = transrectal ultrasound; UTI = urinary tract infection.
A recent systematic review and meta-analysis showed that rectal PI enemas significantly reduced the risk of fever, bacteriuria, and bacteremia compared with no cleansing (risk ratio: 0.3; 95% CI, 0.21–0.45), whereas the combination of PI enemas and antibiotics was superior for reducing fever and bacteremia versus antibiotics alone in men undergoing transrectal PB (risk ratio: 0.23; 95% CI, 0.10–0.54) [72]. Even though short-term ciprofloxacin prophylaxis may still be adequate in a non-FQR population [54,73], antibiotic prophylaxis augmentation or switching have been proposed in many studies to prevent severe infectious complications. Adibi et al showed that the addition of one dose of intramuscular gentamicin before transrectal PB to standard ciprofloxacin or trimethoprim/sulfamethoxazole significantly reduced infection rates (0.6% vs 3.8%, p < 0.001) and costs related to hospitalization [74]. Similarly, adding intramuscular amikacin [75], gentamicin [76], ceftriaxone [68], or amoxicillin-clavulanate [77] to fluoroquinolones has been shown to reduce infectious complications after TRUS-guided PB. Others have reported favorable results by switching from ciprofloxacin 500 mg plus aminoglycosides to levofloxacin 750 mg plus aminoglycosides [78] by mixing 1 g ceftriaxone into the periprostatic lidocaine injection [79] or by combining intramuscular cephalosporin with PI suppositories [57].

A growing body of nonrandomized studies support rectal swab–targeted prophylaxis for transrectal PB. Duplessis et al showed no infectious complications in men receiving targeted prophylaxis in contrast with those using standard ciprofloxacin [80]. Similarly, Cook and collaborators reported a significant drop in infections after the introduction of rectal swab–targeted prophylaxis in routine clinical practice compared with a retrospective cohort receiving standard fluoroquinolones (0.41% vs 2.65%, p < 0.05) [81]. Dai et al recently reported clinically fewer infections (1.9% vs 2.9%) in men managed with targeted antibiotic prophylaxis, although the difference was not statistically significant (p = 0.53) [82].

3.7. Mortality following prostate biopsy

Despite the rates of minor and major complications, mortality after PB is uncommon. As reported previously, bleeding and infections are the two most frequent adverse events that may be severe enough to require hospitalization but that rarely lead to death. To date, most PB-related deaths are due to septicemia and septic shock. Gallina and coworkers reported a large population-based study evaluating mortality in men undergoing PB between 1989 and 2000 in Canada [83]. A higher overall 120-d mortality rate was observed in the 22 175 patients who underwent biopsy compared with the 1778 controls (1.3% vs 0.3%, respectively; p < 0.001). Increasing age and comorbidity were independent predictors of mortality on multivariable analysis, but interestingly, the rate of fatal events was found to be higher in patients who underwent only one PB (1.4%) compared to those with three or more biopsies (0.6%).

Contrasting results have been reported in two other large studies from the ERSPC [84] and Prostate, Lung, Colorectal and Ovarian Cancer Screening (PLCO) [85] trials. Screen-positive patients undergoing PB experienced a similar 120-d mortality rate compared with screen-negative patients in the ERSPC (0.24% vs 0.24%, p = 0.96) [84]. In the PLCO, a lower rate of deaths after 120 d, albeit not significant, was observed in men who had undergone PB compared with controls (0.095% vs 0.18%, respectively) [85]. It must be noted that in both studies, almost all reported deaths were related to the deterioration of underlying chronic medical conditions (eg, ischemic heart disease, pancreatitis, cancer, pneumonia). Consequently, the use of 120-d mortality rates may overestimate mortality rates from PB because other competing causes may confound the results.

Nam et al reported a 30-d mortality rate of 0.09% among the noncancer group that had a PB—the healthiest screened group of men [15]. In addition, a low 30-d mortality rate was reported in men undergoing PB compared with controls (0.31% vs 1.09%) in a US report from the SEER–Medicare database by Loeb et al, after adjusting for age, race, region, year, and comorbidity (OR: 0.29; 95% CI, 0.22–0.38; p < 0.001); however, men who were hospitalized for infectious complications had a 12-fold higher 30-d mortality rate in comparison to those who were not (95% CI, 8.59–16.80; p < 0.0001) [2]. Similar results were reported in a recent Swedish nationwide population-based study with a 90-d mortality rate of 1% and significantly higher odds of dying for hospitalized patients than those not admitted to the hospital (OR: 12.6; 95% CI, 2.4–61.8; p = 0.002) [45]. Repeat biopsy is not associated with a higher overall mortality rate [59]. Based on the currently available evidence, fatal events after PB are uncommon, and the risk has remained relatively stable over time. Older age, the deterioration of underlying medical conditions, and severe septic events represent the most important risk factors for death after biopsy.

4. Conclusions

The most frequently reported complication after PB is minor and self-limiting bleeding, regardless of the biopsy approach or technique. Some men also experience transient LUTS or ED. Although less common, acute urinary retention occur particularly after transperineal biopsy in patients with enlarged prostate or with more biopsy cores. Optimal pain control, either by topical or infiltrative anesthesia, reduces discomfort and improves biopsy acceptance. Compared with transrectal or transperineal systematic PB, MRI-guided biopsies have been shown to reduce the rate of LUTS and pain. Hospital admissions after PB have increased over time, mainly because of infectious complications. Older age, preexisting comorbidities, and the development of antimicrobial resistance represent the most important risk factors for infection after biopsy. Despite the paucity of data and the absence of comparative studies, the incidence of serious infections, sepsis, or hospitalization after MRI-guided PB is marginal. Mortality after PB is uncommon. A patient’s general health status and risk
factors for antimicrobial resistance should be carefully appraised before scheduling a PB.

Author contributions: Marco Borghesi had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Borghesi, Loeb.

Acquisition of data: Borghesi.

Analysis and interpretation of data: Borghesi, Loeb, Ahmed, Nam, Schaeffer, Weidner, Schiavina, Taneja.

Drafting of the manuscript: Borghesi, Loeb, Ahmed, Nam, Schaeffer, Weidner.

Critical revision of the manuscript for important intellectual content: Loeb, Borghesi, Ahmed, Nam, Schaeffer, Schiavina, Weidner.

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Supervision: Loeb.

Other (specify): None.

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References


