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. Besides traditional random or systematic approach, magnetic resonance imaging (MRI)-guided technique has been recently introduced.

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 Review and Meta-analysis (PRISMA) statement. Complications and mortality following random, systematic and image-guided PB were reviewed. Eighty-four references were included.

Evidence Synthesis: The most frequent complication after PB is minor and self-limiting bleeding (hematuria and hematospermia), irrespective of the biopsy approach. Occurrence of rectal bleeding was comparable among traditional TRUS-guided and image-guided PB. Almost 25% of patients experience lower urinary tract symptoms, but only a few have urinary retention, with higher rates after transperineal approach. Temporary erectile dysfunction is not negligible, with a return to baseline after 1-6 months. The incidence of infective complications is being 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, irrespective of biopsy technique.

Conclusions: Complications after PB are frequent but often self-limiting. The incidence of hospitalization due to severe infections is continuously increasing. Still, a careful appraisal of

patient's general health status, risk factors and likelihood of antimicrobial resistance should be done before scheduling a PB.

Patient Summary: In this paper we reviewed the variety and incidence of complications after prostate biopsy. Even if frequent, seldom represent a problem for the patient. The most troublesome complications are infections. In order to minimize this risk, a careful evaluation of patient's medical condition must be done before biopsy.

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 more than 2 million procedures are carried out in the United States and Europe every year[1,2]. Although prostate biopsy is often performed transrectally in an outpatient setting, they can also be performed via a transperineal approach, avoiding the rectum. Recently, magnetic resonance imaging (MRI) has been proposed in targeting biopsies towards suspicious areas, to improve the detection of clinically significant prostate cancer [3]. The opportunity to perform a lesion-targeted biopsy could reduce the number of biopsy cores taken and, therefore 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 prostate biopsy.

2. Evidence Acquisition

A PubMed search for English-language publications up to October 2015, with the search terms *prostate biopsy AND complications* was firstly performed. By this initial search 7000 records were identified. Furthermore, 60 additional contributions were retrieved through hand and free-text search, including Web of Science, Embase and Scopus databases, by 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 prostate biopsy were considered for eligibility. Studies were finally included basing on the following criteria: (1) appropriate reporting of complications after PB, including, whenever available, the tools used to measure the adverse events; (2) randomized

controlled trials (RCTs) were firstly considered; (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 in case of: (1) editorials, abstracts or case reports; (2) absence of sufficient data on complications and rates of adverse events (3) publication date before 2002. The rate and type of complications after prostate biopsies was 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 Prostate biopsy is generally performed as a transrectal procedure in an outpatient setting, under local anesthesia, and is usually well-tolerated. Post-procedural bleeding, voiding dysfunctions and pain are common[1], but are not clinically significant and seldom troublesome. Both patient-related (i.e. use of anticoagulant medications, coagulopathies, medical comorbidities, prostate volume, obstructive symptoms, and anxiety) and procedure-related (i.e. biopsy indication, technique, number of cores taken, and type of anesthesia) factors may impact on the occurrence of these complications.

3.1.1 Hematuria

Hematuria following prostate biopsy 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 days, but only 6.2% of them considered it bothersome[7]. In the European Randomized Study for Prostate Cancer (ERSPC), hematuria lasting more than 3 days 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, irrespective of the technique (TRUS-guided or transperineal). Ghani et al. found that the prevalence of hematuria did not vary with the number of TRUS-PB core (44% [6 cores], 41% [8 cores], 39% [12 cores])[4], while 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 prostate biopsies have been associated with lower rates of overall complications compared to TRUS-guided PB, including bleeding. Egbers et al, in a prospective non-randomized study of 54 patients, recently reported hematuria in 51% of MRI-guided in-bore biopsy compared to 79% of transrectal PB ($p=0.006$), as well as a longer bleeding duration for the latter technique[14]. Moreover, a recent systematic review evaluating outcomes of MRI 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 to 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. Indeed, 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 a significantly higher rates of rectal bleeding in men undergoing more biopsy cores (17% vs. 26% vs. 27% after six, eight and 12-core biopsy, respectively)[4]. Berger et al reported an overall bleeding rate of 2.3%. 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 in-bore prostate biopsy 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 prostate biopsy, ranging from 1.1%-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 days after PB, and 26.6% perceived it as a moderate/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-core, 10-core and 15-core biopsies, respectively; p<0.001). Similarly, Pepe et al. found that hematospermia significantly correlated with the number of cores following transperineal PB (30.4% and 10.7% following >/=24 cores vs. 12 cores, respectively; p=0.001)[10]. Conversely, in a recent MRI in-bore PB series with a median of 4 cores, the rate of hematospermia was similar to TRUS-guided prostate biopsies 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 ICUD (International Consultation on Urological Disease)/AUA (American Urological Association) on anticoagulant and antiplatelet (AC/AP) therapy in urological practice[18] stated that the risk of bleeding after PB in men using AC/AP must always be balanced against the hazard of cardiovascular or thromboembolic events when stopping such therapies, especially in high-risk patients (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, replace it with low molecular-weight heparin or 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%, 69.7%, and 81.5%, respectively; 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 results of 930 men undergoing TRUS-guided PB with increasing sampling number (up to 10), without stopping warfarin or aspirin[12]. The type of bleeding complication, duration and severity significantly increased with an increasing number of cores in all patents. 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 symptoms and acute urinary retention

A common side effect after transrectal PB is a short-term exacerbation of urinary symptoms, with reported rates of lower urinary tract symptoms (LUTS) from 6% -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 prostate biopsy-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]. For example, in 5802 men from the Rotterdam section of the ERSPC, prostate volume, transition zone

volume/total prostate volume ratio, and a higher IPSS score 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 transrectal ultrasound guided biopsy. The main limitations of this study are small sample size (92 men) and short follow-up (7 days) [24]. Less data are available on urinary side effects of transperineal PB. Namekawa et al, recently reported on 2.086 men undergoing an initial PB under lumbar spinal anesthesia: PSA , IPSS score, prostate volume, abnormal DRE and history of α-blocker use were independent predictors of LUTS and urinary retention [13]. When compared to TRUS-guided PB, the occurrence of acute urinary retention after 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 a severe worsening of urinary symptoms with urinary retention in 6%, with a return to baseline within 6 weeks[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 prostate biopsy with or without peri-prostatic nerve block (PPNB). Overall IPSS score was significantly increased in all at 1 week, which persisted at 1 and 3 months only in those men submitted to repeated saturation biopsy (p=0.007). Conversely, patients who underwent 10-core prostate biopsy with PPNB had a higher IPSS score at 1 and 3 months compared to those without PPNB, but this was not statistically significant[23]. There are limited data on the impact of serial biopsies during active surveillance (AS) on voiding symptoms and risk of acute urinary retention, although limited evidence suggests no significant correlation between number of prostate biopsies 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 peri-procedural tamsulosin or no tamsulosin. 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 retentions were found in those patients using Tamsulosin[30]. In summary, although almost 25% of patients experience transient LUTS, only a small proportion of these individuals experience urinary retention. The administration of alpha-blockers after PB could have a beneficial impact.

3.3 Erectile dysfunction

Prostate biopsies may lead to transient erectile dysfunction (ED), with complete recovery after 1-3 months[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 34% of patients with no ED at baseline had a decrease in IIEF score at 1 week; 20% and 24% continued to have lower scores at 1 and 3 months, respectively. Age ≥60 years or above, the first biopsy setting and a diagnosis of PCa were the main predictors of IIEF score impairment at 1 and 3 months[31]. It has been hypothesized that extensive sampling during saturation PB could affect erectile function, but in multiple series the IIEF score impairment resolved within 6 months after biopsy, and no correlation was found between number of cores and IIEF scores[28,32]. Several anatomical 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, the peri-prostatic nerve blockade (PPNB) could affect EF, due to the direction of anesthetic into the neurovascular bundles; however, the changes in IIEF seem to be similar

among the different analgesia techniques [22,23]. Significant anxiety regarding the possibility of cancer may also have an impact on erectile function. One study found a reduction in all IIEF domains only among men diagnosed with prostate cancer on biopsy, while no significant decrease was found in their counterparts with negative biopsy results[22]. With expanded use of active surveillance for clinically localized low risk PCa, many men with a diagnosis of prostate cancer 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. A history of 3 or more biopsies was correlated to a greater EF impairment than 2 or fewer biopsies (p=0.02) [28]. Another prospective AS study of 342 patients undergoing TRUS-PB found that EF decreased by 1-point every year for the first 4 years [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 month post-procedure and it is unclear whether these changes are due to the biopsy itself versus psychological impact of the event or other confounders.

3.4 Pain

Although PB is well-tolerated in most of patients, techniques to reduce pain and discomfort are routinely employed in clinical practice. Different steps may cause pain during biopsy, such as probe insertion, periprostatic infiltration and biopsy sampling, extending 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 may affect blood flow within the prostate [1]. Anxiety is also an important factor that should be considered, especially in younger patients. Periprostatic nerve block (PPNB), which consists of injecting Lidocaine between the prostate base and seminal vesicle on each side (where the neurovascular bundles are anatomically positioned), is the most widely used anethetic for transrectal PB and has been shown to reduce pain compared to no anesthetic [1,35]. However, PPNB does not alleviate the discomfort related to TRUS probe insertion and manipulation, and peri-prostatic anaesthetic infiltration itself is among the most painful parts of the procedure[35]. Consequently, non-infiltrative topical anaesthesia (e.g., creams, gels, and suppositories) represent potential alternatives to reduce discomfort. Lidocaine gel was among the first and most used local anaesthetic agents due to its low cost and safety. Reports showed significantly less pain with probe insertion and manipulation compared to placebo[36], but it did not reduce pain related to anaesthetic infiltration and needle biopsy. A combination of 2.5% lidocaine and 2.5% prilocaine (EMLA© cream) was found to be superior to other topical anaesthetic agents, possibly due to its longer duration (2–5 hours) and deeper tissue infiltration[37]. Furthermore, suppositories based on non-steroidal anti-inflammatories (e.g., diclofenac) can be used to reduce the local and systematic anti-inflammatory effect, but do not significantly reduce pain from probe manipulation and biopsy sampling[38]. Comparing lidocaine gel with lidocaine-ketorolac 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 intra-capsular 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 the probe insertion, biopsy sampling, and at 1 hour post-procedure, compared to PPNB alone[42]. There is also increasing interest in combining topical and infiltrating anaesthesia. As consequence, Raber at al. showed that a combination of intra-rectal 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 if 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 suggest that lidocaine-prilocaine cream proved 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 anaesthetic 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 ($p<0.001$). With MRI in-bore PB, some patients now undergo prostate sampling limited to suspicious lesions, resulting in significantly less pain intensity and duration compared to the traditional transrectal procedure. In the study by Egbers et al, pain intensity was significantly lower for MRI-in bore PB compared with TRUS-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 in order 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 in order 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 (UTI), 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 the 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 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 fluoroquinolone-resistant (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 when compared to 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, antibiotics within 6 months before PB, and non- adherence to antibiotic prophylaxis represent other risk factors[46]. Whether a repeated biopsy protocol, including those done in active surveillance (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 (OR: 1.33; 95% CI: 1.01-1.74, p=0.04), up to a rate of 15% for patients who had undergone ≥5 biopsies [6]. Similarly, Loeb et al, reported a cumulative increase in the risk of having a complication where each additional biopsy was associated with a 1.7-fold increase in overall hospitalizations, and a 1.7-fold increase in serious infectious complications. However, in a biopsy-based multivariable analysis, the repeat biopsy procedure itself was not associated with a greater risk of serious complications requiring hospital admission compared to 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), as well as 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 uncertain whether the lower incidence of infectious complications after MRI-targeted PB could be related to the sampling route (i.e. 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 to the latter), even if not statistically significant[14]. Conversely, the infectious complication rate after in-bore transperineal MRI-targeted biopsy appears 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 Anastadiasis 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/sepsis, haematuria 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 ≥ 85 years compared to ages 45-54, and more than threefold increased risk in those men with two or more comorbidities. Remarkably, the hospitalization increased during the study period (20% greater incidence, p=0.03), predominantly due to urinary tract infections or sepsis (70% higher incidence in 2008 than in 2000), while rates of hematuria and urinary retention remained stable [58]. Nam et al was the first to report rising rates of hospitalization over time in a retrospective analysis of 75,190 biopsied men from Canada. They reported an overall hospitalization rate of 1.4% within 30 days from TRUS-guided PB, with an increasing occurrence from 1996 to 2005 for both prostate cancer-positive and negative patients. Infections dramatically increased over time (from 0.6% in 1996 to 3.6% in 2005), with no significant differences based upon age. Those men undergoing systematic repeated biopsy experienced a similar complication rate compared to those undergoing initial biopsy [15]. In a study from the SEER database, Loeb et al. reported a 6.9% 30-day overall hospitalization rate after PB. More medical comorbidities, non-white race and later year were significant risk factors [2]. A Canadian, retrospective study of 5798 PB patients reported a hospitalization rate of 0.5%, all due to infection. Independent predictors were a 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 a 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 days 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 the rising FQR. Fluoroquinolones, indeed, have been widely used as prophylaxis for TRUS-guided PB and for the treatment of urological infections for the last two decades but the number of FQR bacteria have been increased over time [47,49,53]. Other relevant studies [7,11,16,48,49,59,68–70] reporting a similar hospitalization rate 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 mono-therapy to a multi-drug prophylaxis or performing culture-directed prophylaxis) [51]. Although transperineal approach for PB is infrequently used in many parts of the world largely due to logistical reasons, the incidence of re-admissions 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 body of literature, the lower incidence of infections and hospitalizations among patients undergoing MRI-targeted PB appears mostly related to the 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 I evidences, 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]. Pre-biopsy rectal enemas, either with glycerin/saline or povidone-iodine (PI), are one first-line option. Kam et al. reported a significantly lower rate of complications by administering glycerin/saline enema one hour 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 to no cleanse, although it was not statistically significant (2.6% vs. 4.5%, p=0.15)[56]. A recent systematic review and meta-analysis showed that rectal PI enemas significantly reduced the risk of fever, bacteriuria and bacteremia compared to no cleansing (Risk Ratio: 0.3; 95% CI 0.21-0.45), while the combination of PI enemas and antibiotics was superior in 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 by many studies to prevent severe infectious complications. Adibi et al. showed that the addition of 1 dose of intramuscular gentamicin before transrectal PB to the standard ciprofloxacin or trimethoprim/sulfometoxazole 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 have 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 gram of ceftriaxone into the periprostatic lidocaine injection[79] or by combining intramuscular cephalosporin with povidone-iodine suppositories[57]. A growing body of non-randomized 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 to 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 previously reported, bleeding and infections represent the two most frequent adverse events which may be severe enough to require hospitalization, but rarely lead to death. To date, most PB-related deaths are due to septicemia and septic shock. Gallina and co-workers reported a large population-based study evaluating the mortality in men undergoing PB between 1989-2000 in Canada. [83]. A higher overall 120-day mortality rate was observed in the 22,175 patients who underwent biopsy compared to 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 subjected to only one PB (1.4%), compared to those with 3 or more biopsies (0.6%). Contrasting results have been reported by two other large reports from the ERSPC [84] and PLCO [85] screening trials. Screen-positive patients undergoing PB experienced a similar 120-day mortality rate compared to 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 days, albeit not significant, was observed in men who had undergone PB compared to 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 (e.g. ischemic heart disease, pancreatitis, cancer, pneumonia). Thus, the use of 120-day mortality rates may over-estimate mortality rates from PB since other competing causes may confound the results. Indeed, Nam et al reported a 30-day mortality rate of 0.09% among the non-cancer group who had a PB – the healthiest screened group of men[15]. Also, a low 30-day mortality rate was reported in men undergoing PB compared to 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-day 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-day mortality rate of 1%, and a 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 prostate biopsy 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, irrespective of the biopsy approach or technique. Some men also experience transient lower urinary symptoms or erectile dysfunction. While less common, acute urinary retention does occur particularly after transperineal biopsy in patients with an enlarged prostate or with more biopsy cores. Optimal pain control, either by topical or infiltrative anaesthesia, reduces discomfort and improves biopsy acceptance. When compared to transrectal or transperineal systematic PB, MRI-guided biopsies have shown to reduce the rate of lower urinary symptoms and pain. Hospital admissions after PB have increased over time, mainly because of infectious complications. Older age, pre-existing 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 hospitalizations after MRI-guided PB is marginal. Mortality after PB is uncommon.

Overall, a careful appraisal of patient's general health status and risk factors for antimicrobial resistance should be done before scheduling a prostate biopsy.

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