Non-antibiotic strategies for the prevention of infectious complications following prostate biopsy: A Systematic Review and Meta-analysis

Running head: How can technical interventions reduce infections after prostate biopsy?

Benjamin Pradere[a*], Rajan Veeratterapillay[b*], Konstantinos Dimitropoulos[c], Yuhong Yuan[d], Muhammad Imran Omar[e], Steven MacLennan[f], Tommaso Cai[g], Franck Bruyère[a], Riccardo Bartoletti[h], Bela Köves[i], Florian Wagenlehner[j], Gernot Bonkat[k], Adrian Pilatz[j]

[a]Urologie, CHRU Bretonneau, Tours, France; Université Francois Rabelais, PRES Centre Val de Loire, Tours, France, f.bruyere@chu-tours.fr, benjaminpradere@gmail.com
[b]Freeman Hospital, Newcastle Upon Tyne, UK, Rajan.Veeratterapillay@nuth.nhs.uk
[c]Department of Urology, Aberdeen Royal Infirmary, Aberdeen, Scotland, UK, k.dimitropoulos@nhs.net
[d]Department of Medicine, Division of Gastroenterology, McMaster University, Hamilton, Canada, yyuan@mcmaster.ca
[e]Guidelines Office, European Association of Urology, Arnhem, The Netherlands, m.i.omar@abdn.ac.uk
[f]Academic Urology Unit, University of Aberdeen, Aberdeen, United Kingdom, steven.maclennan@abdn.ac.uk
[g]Department of Urology, Santa Chiara, Reg. Hospital, Trento, Italy, ktommy@libero.it
[h]Department of Translational Research and New Technologies, University of Pisa, Italy, riccardo.bartoletti@hotmail.com
[i]Department of Urology, South-Pest Teaching Hospital, Budapest, Hungary, bkoves@gmail.com
[j]Department of Urology, Pediatric Urology and Andrology, Justus-Liebig-University Giessen, Giessen, Germany, adrian.pilatz@chiru.med.uni-giessen.de, florian.wagenlehner@chiru.med.uni-giessen.de
[k]alta uro AG, Merian Iselin Klinik, Center of Biomechanics & Calorimetry, University Basel, Basel, Switzerland, bonkat@alta-uro.com
[*]Shared first authorship

Key Words: prostate biopsy; infection, prophylaxis

Text word count: 3,311; Abstract: 272; Tables: 1; Figures: 8; Appendix in supplement: 5; Tables in supplement: 3; Figures in supplement: 8

Corresponding author: PD Dr. med. A. Pilatz, Department of Urology, Pediatric Urology and Andrology, Justus Liebig University Giessen, Rudolf-Buchheim-Str. 7, 35392 Giessen, Germany; E-mail: adrian.pilatz@chiru.med.uni-giessen.de, Tel.:+49-641-985-56362, Fax: +49-641-985-44577

Abstract

Purpose

To identify which non-antibiotic strategies could reduce the risk of infectious complications following prostate biopsy.

Materials and Methods

We performed a literature search on MEDLINE, Embase, and Cochrane Database for randomized controlled trials (RCTs) (Inception to May 2020) assessing non-antibiotic interventions in prostate biopsy. Primary outcome was pooled infectious complications (fever, sepsis and symptomatic UTI) and secondary outcome was hospitalization. Cochrane risk of bias tool and GRADE approach were used to assess the bias and the certainty of evidence. Protocol was registered with PROSPERO (CRD42015026354).

Results

90 RCTs (16,941 participants) were included in the analysis with 83 RCTs being categorized into one of ten different interventions. Transperineal biopsy was associated with significantly reduced infectious complications as compared to transrectal biopsy (RR 0·55, 95% CI 0·33-0·92, p=0·02, I^2=0%, participants=1330, studies=7). Rectal preparation with povidone-iodine was also shown to reduce infectious complications (RR 0·50, 95% CI 0·38-0·65, p<0·000001, I^2=27%, participants=1686, studies=8) as well as hospitalization (RR 0·38, 95% CI 0·21-0·69, p=0·002, I^2=0%, participants=620; studies=4). We found no difference in infectious complications/hospitalization for six other interventions: number of biopsy cores, periprostatic nerve block (PPNB), number of injections for PPNB, needle guide type, needle type, and rectal preparation with enema. In two interventions (needle diameter, rectal preparation with chlorhexidine) meta-analysis was not possible. Finally, seven studies had unique interventions. The certainty of evidence was rated as low/very low for all interventions.

Conclusions

Transperineal biopsy significantly reduces infectious complications compared to transrectal biopsy and should therefore be preferred. If transrectal biopsy is performed, rectal preparation with povidone-iodine is highly recommended. The other investigated non-antibiotic strategies did not significantly influence infection and hospitalization after prostate biopsy.

Introduction

In 2019 more than 190,000 new cases of prostate cancer (PCa) are diagnosed in the USA causing more than 33,000 deaths[1]. Worldwide prostate cancer accounts for a significant proportion of male cancer and mortality. PCa diagnosis is based on biopsies following patient evaluation for an elevated PSA or abnormal digital rectal examination and there is an increasing role for pre-biopsy MRI.[2,3] Prostatic biopsy remains the keystone for diagnosis and management of PCa and the most commonly performed diagnostic procedure in urology with more than 2 million per year.[4] Therefore, many efforts have been made to prevent infectious complications which account for the major adverse events with up to 7% of infections and 3.1% of sepsis depending of antibiotic prophylaxis regimens.[3] Even if an antibiotic prophylaxis is recommended by every guideline, the incidence of infectious complications is not negligible and its prevention of utmost importance.[2,3] In addition, both the induction of resistance through the use of antibiotics and side effects must be considered.[5] Post-biopsy infections have been increasing over the last few years.[6,7] Thus, antibiotic interventions such as targeted antibiotic prophylaxis based on rectal swab culture as well as augmented antibiotic prophylaxis applying more than one antibiotic were introduced to reduce infectious complications.[8,9] In a comprehensive meta-analysis we have recently compiled the evidence of various interventions for antibiotic prophylaxis.[10] In addition to antibiotics different aspects and modalities of biopsy techniques have been investigated with a view to minimizing adverse events. Among them, biopsy route, enema, and number of cores have been already suggested as potential factors to reduce the infectious risk.[11,12] Nevertheless, no systematic analysis is available evaluating various technical aspects of prostate biopsy for reducing post-biopsy infections.

The aim of our comprehensive systematic review and meta-analysis was to investigate whether and to what extent any non-antibiotic interventions reduce the risk of infectious complications following prostate biopsy.

Materials and Methods

Evidence acquisition

We followed the PRISMA guidance and the Cochrane Handbook for systematic reviews of interventions.[13,14] The protocol was registered at PROSPERO (CRD42015026354). The detailed PICO (Population, Intervention, Comparison and Outcomes) is provided in supplementary appendix 1.

Literature search

The Medline, Embase, LILACS, CENTRAL, Cochrane Database of Systematic reviews databases and clinicaltrial.gov were searched for randomized controlled trials (RCTs) (last search 27th May 2020). The grey literature was searched through opengrey.eu and oclc.org. Potentially-eligible trials were also identified by searching the reference lists of trials, reviews, and health technology assessment reports (Y.Y). There were no date or language restrictions. In order to avoid publication bias, abstracts characterized as RCTs, but for which published manuscripts were not yet available, were included in this systematic review with meta-analysis, as were funnel plots for interventions involving more than 10 studies. The search strategy is included in supplementary appendix 2.

Types of outcome measures

Primary outcome:

- Pooled infectious complications (calculated by summing all types of infectious complications reported i.e. fever, sepsis, symptomatic UTI). This approach was chosen since in many studies investigating post-biopsy complications, a distinction between severe infections (e.g. sepsis) and mild infections (e.g. cystitis) is not reported in detail (supplementary table 1).

Secondary outcome:

- Hospitalization due to infectious complications.

Data collection and analysis

Abstract screening, full-text screening, and data extraction was independently performed by two reviewers (A.P., B.P., or R.V.). For each disagreement, another reviewer (M.I.O., S.M.) was consulted. All the study authors were contacted to provide missing information if

necessary. Eight non-English articles were evaluated in the corresponding languages by members of the author team with appropriate language skills (4×Chinese: Y.Y., 1×French: B.P., F.B., 1×Spanish: A.P., B.P., 2×Turkish: Mete Cek, former EAU Guideline panel member). One Japanese article and two Korean articles were translated into English by professional translators. Among the 90 RCTs there are also eight studies that have so far only been published as abstracts. The risk of bias (RoB) was independently assessed by two reviewers (R.V., K.D.), by using the Cochrane RoB assessment tool.[14,15] Any disagreements were resolved via discussion or consultation with another reviewer (M.I.O., S.M.). The GRADE approach was used to assess the certainty of evidence for each comparison (M.I.O., S.M.).[14]

Statistical analysis

The meta-analysis was performed using Review Manager (RevMan) version 5.3. A fixed-effects model was used to calculate pooled estimates of treatment effects across similar studies and their 95% confidence intervals (CIs). We used risk ratio (RR) for dichotomous outcomes. We identified heterogeneity by visually inspecting forest plots and using a standard x^2 test with a significance level of $\alpha=0.1$. We also considered the I^2 statistic, which quantifies inconsistency across trials to assess the impact of heterogeneity on the meta-analysis. Where there was evidence of heterogeneity, we attempted to determine possible reasons by examining individual trial, subgroup characteristics, or by using a random-effects model.[14]

Results

Literature search and characteristics of the included studies

We identified 3111 citations, of those 284 were selected for full-text screening. Reasons for exclusion are provided in supplementary table 2. A total of 90 RCTs were included in the SR (supplementary appendix 3). The inclusion process is graphically illustrated in a PRISMA diagram (figure 1). For all included studies we provide detailed study characteristics in supplementary table 3. Of the 90 RCTs 83 studies could be categorized into one of ten different interventions, while 7 studies had unique interventions. Sensitivity analyses for the individual interventions showed that no changes occurred with or without the data of the eight included abstracts, which have not yet been published as full-text.

Risk of Bias (RoB) assessment

The RoB assessment is graphically illustrated in figure 2. It is noticeable that the majority of studies have an unclear RoB regarding random sequence generation, allocation concealment and blinding of outcome assessment. Furthermore, most studies have been conducted without blinding patients or personnel, which is certainly also due to the type of technical intervention. A funnel plot from the interventions with more than 10 studies (PPNB) showed no asymmetry (details in supplementary appendix 4).

Study heterogeneity

The I^2 statistic was 0% in all cases except Intervention 8 (povidone-iodine) where it was 27%. Since the p-values changed only marginally when using random-effect models for all interventions and endpoints, we used fixed-effect models throughout.

GRADE

The certainty of evidence was mainly downgraded due to study design, imprecision and risk of bias (details in supplementary appendix 5).

Intervention 1: Impact of biopsy route

A total of seven RCTs including 1330 patients compared the impact of biopsy route on infectious complications (supplementary appendix 3). There were significantly lower infectious complications when the transperineal route was performed (22 events among 673 men) compared to the transrectal route (37 events among 657 men) (RR 0.55, 95 CI: 0.33 to 0.92; participants=1330; studies=7; I^2=0%; low certainty; figure 3).

Data on hospitalization were reported in three studies with a total of 685 patients. While two hospitalizations were necessary in 346 patients in the transperineal group, hospitalization was reported in six cases out of 339 patients undergoing transrectal biopsy without any statistical difference (RR 0.38, 95 CI: 0.09 to 1.61; participants=685; studies=3; I^2=0%; very low certainty; supplementary figure 1).

Intervention 2: Impact of number of biopsy cores

The impact of the number of cores was evaluated in 11 studies including 2626 men undergoing prostate biopsy (supplementary appendix 3). While ten studies performed transrectal biopsy one study used the transperineal approach. MA showed 38 infectious complications in 1320

men randomized to standard and 47 in those 1306 randomized to extended number of cores. The comparison was not significant (RR 0.80, 95% CI: 0.53 to 1.22; participants=2230; studies=9; I^2=0%; low certainty; figure 4).

Of those studies, only five studies presented data on hospitalization following prostate biopsy. There was one case of hospitalization among 415 men in the standard group, while four cases occurred among 411 men in the extended biopsy scheme group. The comparison was not significant (RR 0.34, 95% CI: 0.05 to 2.13; participants=306; studies=2; I^2=0%; very low certainty; supplementary figure 2).

Intervention 3: Impact of periprostatic nerve block

Pain after periprostatic nerve block (PPNB) during biopsy was evaluated in 41 RCTs and infectious outcomes were reported in a total of 5540 men (supplementary appendix 3). There were 61 infectious complications among 2633 patients randomized to periprostatic nerve block and 73 among 2907 patients randomized to no nerve block/control. The comparison was not significant (RR 1.07, 95% CI: 0.77 to 1.48; participants=3857; studies=26; I^2=0%; very low certainty; figure 5).

Among these studies, only 14 reported hospitalization with 13 cases of hospitalization among 971 men in the PPNB group, while 15 cases occurred among 1128 men in the group without PPNB. The comparison was not significant (RR 1.13, 95% CI: 0.59 to 2.16; participants=1469; studies=9; I^2=0%; very low certainty; supplementary figure 3).

Intervention 4: Impact of number of injections for periprostatic nerve block

Six studies compared the number of injections applied for PPNB and assessed post-biopsy infections (supplementary appendix 3). MA showed five infections among 459 men randomized to standard number of injections and four among 468 men randomized to extended PPNB. The difference was not statistically significant (RR 1.30, 95 CI: 0.35 to 4.76; participants=478; studies=3; I^2=0%; low certainty; supplementary figure 4).

Two studies reported hospitalization with two patients being hospitalized among 147 men randomized to standard PPNB and two men among 153 randomized to extended PPNB. The difference was not statistically significant (RR 1.05, 95 CI: 0.15 to 7.32; participants=300; studies=2; I^2=0%; low certainty; supplementary figure 5).

Intervention 5: Impact of disposable needle guides

Two RCTs evaluated the use of disposable needle guides compared to reusable guides in a total of 253 patients (supplementary appendix 3).

There were nine events among 113 men randomized to disposable needle guides and 22 events among 140 men randomized to reusable needle guides. The difference was not statistically significant (RR 0.51, 95% CI: 0.24 to 1.06; participants=253; studies=2; I^2=0%; very low certainty; supplementary figure 6).

Both studies evaluated the impact on hospitalization. While four events occurred in 113 men randomized to the disposable needle guide group, nine events were recorded in 140 men of the reusable needle guide group. The difference was not statistically significant (RR 0.55, 95% CI: 0.17 to 1.74; participants=253; studies=2; I^2=0%; very low certainty; supplementary figure 7).

Intervention 6: Impact of needle type

Only two studies investigated the impact of a coaxial needle versus a non-coaxial needle and reported on infectious complications (supplementary appendix 3). Data analysis revealed no infections in 171 men in the coaxial needle arm, while one case occurred among 171 men in the group randomized to the non-coaxial biopsy needles. MA was not possible, because of zero events in one study. Hospitalization was reported in only one of the two studies and did not occur in any among the 240 patients.

Intervention 7: Impact of needle diameter

The impact of needle diameter was investigated in two studies (supplementary appendix 3). Data analysis revealed no infections in 133 men randomized to the smaller needle diameter, while one case occurred among 163 men in the group randomized to the larger needle diameter. MA was not possible, because of zero events in one study. Hospitalization was not reported as an endpoint in any study.

Intervention 8: Impact of rectal preparation with enema

Four RCTs evaluated rectal preparation with enema (supplementary appendix 3). Among 336 men randomized to enema 30 events were recorded, while among 335 men in control group 31

events were reported. The difference was not statistically significant (RR 0.96, 95% CI: 0.60 to 1.53; participants=671; studies=4; I^2=0%; low certainty; figure 6).

Only two studies with each 231 patients per group reported on hospitalization with nine events in the enema and eight events in the control group. This comparison was not statistically significant (RR 1.13, 95% CI: 0.44 to 2.86; participants=462; studies=2; I^2=0%; low certainty; supplementary figure 8).

Intervention 9: Impact of rectal preparation with chlorhexidine

Two studies investigated the influence of rectal preparation with chlorhexidine (supplementary appendix 3). Although both studies report infectious complications separately for the intervention and control groups, the primary outcome cannot be meta-analyzed due to a possible double case count in one of the studies.

Intervention 10: Impact of rectal preparation with povidone-iodine

Nine studies evaluated the use of rectal preparation with povidone-iodine (supplementary appendix 3) in a total of 1936 patients. MA showed 61 infections among 930 men in the povidone-iodine group and 131 among 1006 in the control group. The difference was statistically significant (RR 0.50, 95% CI: 0.38 to 0.65; participants=1686; studies=8; I^2=27%; low certainty; figure 7).

Four studies reported on hospitalization with a total of 12 men hospitalized among 285 men randomized to povidone iodine preparation and 37 men among 335 randomized to the control group. The difference was statistically significant (RR 0.38, 95% CI: 0.21 to 0.69; participants=620; studies=4; I^2=0%; low certainty; figure 8).

Different unique interventions

Seven RCTs with unique technical interventions (e.g. needle disinfection, needle size, perineal cleansing) were identified. Of those, only one study investigating the timepoint of rectal preparation with povidone-iodine showed significantly reduced infectious complications when applied before vs. after biopsy (table 1).

Discussion

To our knowledge this meta-analysis is the first to assess all the different technical aspects of prostate biopsy that can possibly reduce the risk of infectious complications. Therefore, it complements our comprehensive previous meta-analysis on antibiotic prophylaxis of prostate biopsy.[10] In the current analysis we have reported a total of 90 RCTs exploring non-antibiotic prophylactic strategies including the risk of peri-prostatic nerve block, prostate biopsy route, number of cores, rectal preparation, and type of needle used. Among the different strategies assessed in our analysis, transperineal prostate biopsy route and rectal preparation with povidone-iodine were found as the best interventions (low certainty of evidence) to reduce both post-biopsy infections and hospitalization.

This meta-analysis is the most comprehensive and recent one evaluating specifically infectious complications in the head-to-head comparison between transperineal and transrectal route. The two approaches have been highly debated in recent years with the introduction of MRI targeted biopsy and diagnostic accuracy.[16-20] In addition, there is increasing evidence that MRI diagnostics can be used to avoid unnecessary prostate biopsies - and thus the corresponding complications.[21,22] Until now, the different MRI targeted biopsy methods have not proved a real significant difference in terms of PCa detection.[23,24] The most recent studies were designed to assess the PCa detection rates between the two techniques and the potential risk for adverse events was only a secondary criterion.[25,26] Hence, study size of the aforementioned studies was not calculated to reveal differences in post-biopsy infection, but to investigate diagnostic accuracy. Thus, two older meta-analyses evaluating also infections complications in dependence of the biopsy route did not report a significant difference.[12,27] On the other hand, a recent meta-analysis suggested a benefit of transperineal biopsy, which significantly protected patients from postoperative fever (RR 0.26, 95% CI: 0.14 to 0.28).[28] However, all three of these meta-analyses are limited because they combined estimates from RCTs with those from case-control studies and double counted one study published in duplicate which has a very low number of post-biopsy infections in both groups.[29,30]

In the largest systematic review on infectious complications following prostate biopsy (165 studies including 162,577 patients) the standardized prevalence of sepsis was 0.8% in transrectal and 0.1% in transperineal biopsy and the standardized prevalence of hospitalization was 1.1% vs. 0.9%, respectively.[31] These data are not surprising, as they reinforce the classical principle for a surgical procedure to choose the lowest possible contamination category in order

to reduce the rate of infectious complications.[32] Our meta-analysis based on 7 RCTs confirmed this important aspect and showed a significantly lower infection rate using the transperineal route (RR 0.55, 95% CI: 0.33 to 0.92). Despite the potential logistic challenges attached to the widespread introduction of the local anesthetic transperineal technique, our findings support the "TREXIT 2020" approach to abandon transrectal prostate biopsy.[17]

Another important aspect is the number of biopsy cores taken. Over the years, the number has increased with the aim of improving diagnostic accuracy. Since one passes repeatedly through the rectal mucosa by an increased number of biopsy cylinders, one would expect a higher infection rate. Various cohort studies addressed this important point and were mainly able to show that the number of biopsy cylinders obtained is independent of postoperative infections.[33-35] Our meta-analysis including 11 RCTs shows that the number of cores is not associated with the risk of infection. This confirms the current guidelines which recommend standard biopsies in addition to targeted biopsies.[2,3]

In this context, the question of local anesthesia in the sense of a periprostatic nerve block arises. Various meta-analyses could impressively show that the periprostatic nerve block significantly contributes to perioperative pain control compared to an anesthetic gel applied intrarectally/control.[36-39] However, this requires further passages of a needle through the rectum and the injection of an anesthetic might be associated with the risk of distribution of possible pathogens. Previous meta-analyses on this topic reported sporadically on post-biopsy infections, but never primarily investigated the impact of periprostatic nerve block on infection.[38,39] Our analysis including 41 RCTs could show, that there is no increased risk of infection using periprostatic nerve block. In addition, the number of injections used for the periprostatic nerve block has no impact on the rate of post-biopsy infections. This is absolutely consistent with the number of biopsy cores taken as discussed above, which had no influence on the infection rate.

Since the passage of the needle leads through the contaminated rectal mucosa, there are several studies that have investigated different parameters of the needle. The diameter, shape, disinfection and the nature of the needle guide were each investigated in one or two studies, but no significant advantage in preventing post-biopsy infection was ever detected.[40-45]

Rectal preparation is a heterogenous practice when transrectal biopsies are planned with some urologists using enema, chlorhexidine, povidone-iodine applications, full bowel preparation, or no preparation at all. Here, we found that enema had no impact on postoperative infectious complications. However, rectal preparation with povidone-iodine prior to prostate biopsy significantly reduced the risk of infection (RR 0.50, 95% CI: 0.38-0.65), and hospitalization

(RR 0.38, 95% CI: 0.21-0.69). This is fully in line with a previous meta-analysis.[11] The advantages of rectal povidone-iodine preparation are its simple implementation to daily practice without largely increasing the cost of the procedure.[46] Despite the clear recommendation in guidelines,[2] the value still needs to be spread among urologists.[47]

The major strengths of this SR are that, i) it is the most comprehensive analysis on non-antibiotic prophylaxis strategies to prevent infectious complications after prostate biopsy, ii) we included only RCTs without any language and publication date restriction, iii) it includes studies also with patients being at higher risk for post-biopsy infection, and iv) it reports with post-biopsy infections and hospitalization due to infection the two most important adverse events after prostate biopsy.

Our study has some limitations which should be acknowledged: i) all infections were summed, since in many included studies a distinction between severe infections (e.g. sepsis) and mild infections (urinary tract infection) is not reported in detail, ii) many RCTs were not designed for the evaluation of postoperative complications particularly regarding peri-prostatic nerve block, which might underestimate infections and leads to a possible bias, iii) our analysis has been done without taking the individual antibiotic prophylaxis regimes used in each study into account, since I^2 was low or very low in all interventions, and iv) since it was the evaluation of non-antibiotic measures, the geographical origin of the included RCTs was not considered.

Conclusions

In this systematic review and meta-analysis we evaluated all published non-antibiotic prophylaxis regimens to reduce infectious complications following prostate biopsy. We show with low certainty of evidence, that both transperineal biopsy and rectal preparation with povidone iodine in transrectal biopsy significantly reduce the risk of infection. Whereas many concerns are rising to reduce antibiotic resistance and side effects, these non-antibiotic procedures should be favored in daily practice.

Funding

None

Acknowledgments

The authors would like to thank Emma Smith from the EAU Guidelines Office for her assistance with the systematic review.

References

1. Siegel RL, Miller, KD, Jemal, A: Cancer statistics, 2020. CA Cancer J Clin 2020; **70:** 7.
2. Guidelines E. Arnhem, The Netherlands: EAU Guidelines Office, 2019
3. Liss MA, Ehdaie, B, Loeb, S et al: An Update of the American Urological Association White Paper on the Prevention and Treatment of the More Common Complications Related to Prostate Biopsy. Journal of Urology 2017; **198:** 329.
4. Loeb S, Vellekoop, A, Ahmed, HU et al: Systematic review of complications of prostate biopsy. European Urology 2013; **64:** 876.
5. Roberts MJ, Bennett, HY, Harris, PN et al: Prostate Biopsy-related Infection: A Systematic Review of Risk Factors, Prevention Strategies, and Management Approaches. Urology 2017; **104:** 11.
6. Johansen TEB, Zahl, PH, Baco, E et al: Antibiotic resistance, hospitalizations, and mortality related to prostate biopsy: first report from the Norwegian Patient Registry. World J Urol 2020; **38:** 17.
7. Borghesi M, Ahmed, H, Nam, R et al: Complications After Systematic, Random, and Image-guided Prostate Biopsy [figure presented]. European Urology 2017; **71:** 353.
8. Yang L, Tang, Z, Gao, L et al: The augmented prophylactic antibiotic could be more efficacious in patients undergoing transrectal prostate biopsy: a systematic review and meta-analysis. International Urology and Nephrology 2016; **48:** 1197.
9. Scott S, Harris, PN, Williamson, DA et al: The effectiveness of targeted relative to empiric prophylaxis on infectious complications after transrectal ultrasound-guided prostate biopsy: a meta-analysis. World journal of urology 2018; **36:** 1007.
10. Pilatz A, Dimitropoulos, K, Veeratterapillay, R et al: Antibiotic Prophylaxis for the Prevention of Infectious Complications following Prostate Biopsy: A Systematic Review and Meta-Analysis. J Urol 2020; 101097JU0000000000000814.
11. Pu C, Bai, Y, Yuan, H et al: Reducing the risk of infection for transrectal prostate biopsy with povidone-iodine: A systematic review and meta-analysis. International Urology and Nephrology 2014; **46:** 1691.
12. Xue J, Qin, Z, Cai, H et al: Comparison between transrectal and transperineal prostate biopsy for detection of prostate cancer: A meta-analysis and trial sequential analysis. Oncotarget 2017; **8:** 23322.
13. Moher D, Liberati, A, Tetzlaff, J et al: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; **6:** e1000097.
14. Knoll T, Omar, MI, Maclennan, S et al: Key Steps in Conducting Systematic Reviews for Underpinning Clinical Practice Guidelines: Methodology of the European Association of Urology. Eur Urol 2018; **73:** 290.
15. Higgins JP, Altman, DG, Gotzsche, PC et al: The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Bmj 2011; **343:** d5928.
16. Wegelin O, Exterkate, L, van der Leest, M et al: The FUTURE Trial: A Multicenter Randomised Controlled Trial on Target Biopsy Techniques Based on Magnetic Resonance Imaging in the Diagnosis of Prostate Cancer in Patients with Prior Negative Biopsies. European Urology 2019; **75:** 582.
17. Grummet J, Gorin, MA, Popert, R et al: "TREXIT 2020": why the time to abandon transrectal prostate biopsy starts now. Prostate Cancer Prostatic Dis 2020; **23:** 62.
18. Kasivisvanathan V, Rannikko, AS, Borghi, M et al: MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. N Engl J Med 2018; **378:** 1767.
19. Rouviere O, Puech, P, Renard-Penna, R et al: Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naive patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. Lancet Oncol 2019; **20:** 100.
20. van der Leest M, Cornel, E, Israel, B et al: Head-to-head Comparison of Transrectal Ultrasound-guided Prostate Biopsy Versus Multiparametric Prostate Resonance Imaging with Subsequent Magnetic Resonance-guided Biopsy in Biopsy-naive Men with Elevated Prostate-specific Antigen: A Large Prospective Multicenter Clinical Study. Eur Urol 2019; **75:** 570.
21. Donato P, Morton, A, Yaxley, J et al: Improved detection and reduced biopsies: the effect of a multiparametric magnetic resonance imaging-based triage prostate cancer pathway in a public teaching hospital. World J Urol 2020; **38:** 371.

22. Venderink W, van Luijtelaar, A, van der Leest, M et al: Multiparametric magnetic resonance imaging and follow-up to avoid prostate biopsy in 4259 men. BJU Int 2019; **124:** 775.
23. Jambor I, Kahkonen, E, Taimen, P et al: Prebiopsy multiparametric 3T prostate MRI in patients with elevated PSA, normal digital rectal examination, and no previous biopsy. J Magn Reson Imaging 2015; **41:** 1394.
24. Mendhiratta N, Rosenkrantz, AB, Meng, X et al: Magnetic Resonance Imaging-Ultrasound Fusion Targeted Prostate Biopsy in a Consecutive Cohort of Men with No Previous Biopsy: Reduction of Over Detection through Improved Risk Stratification. J Urol 2015; **194:** 1601.
25. Zhu K, Qin, Z, Xue, J et al: Comparison of prostate cancer detection rates between magnetic resonance imaging-targeted biopsy and transrectal ultrasound-guided biopsy according to Prostate Imaging Reporting and Data System in patients with PSA >/=4 ng/mL: a systematic review and meta-analysis. Transl Androl Urol 2019; **8:** 741.
26. Drost FH, Osses, D, Nieboer, D et al: Prostate Magnetic Resonance Imaging, with or Without Magnetic Resonance Imaging-targeted Biopsy, and Systematic Biopsy for Detecting Prostate Cancer: A Cochrane Systematic Review and Meta-analysis. Eur Urol 2020; **77:** 78.
27. Shen PF, Zhu, YC, Wei, WR et al: The results of transperineal versus transrectal prostate biopsy: a systematic review and meta-analysis. Asian J Androl 2012; **14:** 310.
28. Xiang J, Yan, H, Li, J et al: Transperineal versus transrectal prostate biopsy in the diagnosis of prostate cancer: a systematic review and meta-analysis. World J Surg Oncol 2019; **17:** 31.
29. Hara R, Jo, Y, Fujii, T et al: Optimal approach for prostate cancer detection as initial biopsy: prospective randomized study comparing transperineal versus transrectal systematic 12-core biopsy. Urology 2008; **71:** 191.
30. Takenaka A, Hara, R, Ishimura, T et al: A prospective randomized comparison of diagnostic efficacy between transperineal and transrectal 12-core prostate biopsy. Prostate Cancer Prostatic Dis 2008; **11:** 134.
31. Bennett HY, Roberts, MJ, Doi, SA et al: The global burden of major infectious complications following prostate biopsy. Epidemiol Infect 2016; **144:** 1784.
32. Grabe M: Antibiotic prophylaxis in urological surgery, a European viewpoint. International Journal of Antimicrobial Agents 2011; **38:** 58.
33. Wagenlehner FME, Van Oostrum, E, Tenke, P et al: Infective complications after prostate biopsy: Outcome of the Global Prevalence Study of Infections in Urology (GPIU) 2010 and 2011, A prospective multinational multicentre prostate biopsy study. European Urology 2013; **63:** 521.
34. Seo YE, Ryu, H, Oh, JJ et al: Clinical importance of antibiotic regimen in transrectal ultrasound-guided prostate biopsy: A single center analysis of nine thousand four hundred eighty-seven cases. Surgical Infections 2018; **19:** 704.
35. Simsir A, Kismali, E, Mammadov, R et al: Is it possible to predict sepsis, the most serious complication in prostate biopsy? Urologia Internationalis 2010; **84:** 395.
36. Kim DK, Lee, JY, Jung, JH et al: What is the most effective local anesthesia for transrectal ultrasonography-guided biopsy of the prostate? A systematic review and network meta-analysis of 47 randomized clinical trials. Sci Rep 2019; **9:** 4901.
37. Garcia-Perdomo HA, Mejia, NG, Fernandez, L et al: Effectiveness of periprostatic block to prevent pain in transrectal prostate biopsy: A systematic review and a network meta-analysis. Central European Journal of Urology 2019; **72:** 121.
38. Tiong HY, Liew, LCH, Samuel, M et al: A meta-analysis of local anesthesia for transrectal ultrasound-guided biopsy of the prostate. Prostate Cancer and Prostatic Diseases 2007; **10:** 127.
39. Yang Y, Liu, Z, Wei, Q et al: The Efficiency and Safety of Intrarectal Topical Anesthesia for Transrectal Ultrasound-Guided Prostate Biopsy: A Systematic Review and Meta-Analysis. Urologia Internationalis 2017; **99:** 373.
40. Gurbuz C, Canat, L, Atis, G et al: Reducing infectious complications after transrectal prostate needle biopsy using a disposable needle guide: is it possible? In: International braz j urol : official journal of the Brazilian Society of Urology, vol. 37, pp. 79, 2011
41. Tuncel A, Aslan, Y, Sezgin, T et al: Does disposable needle guide minimize infectious complications after transrectal prostate needle biopsy? In: Urology, vol. 71, pp. 1024, 2008
42. Babaei Jandaghi A, Habibzadeh, H, Falahatkar, S et al: Transperineal Prostate Core Needle Biopsy: A Comparison of Coaxial Versus Noncoaxial Method in a Randomised Trial. CardioVascular and Interventional Radiology 2016; **39:** 1736.
43. Novella G, Ficarra, V, Galfano, A et al: Pain assessment after original transperineal prostate biopsy using a coaxial needle. Urology 2003; **62:** 689.

44. Inal GH, Oztekin, VC, Ugurlu, O et al: Sixteen gauge needles improve specimen quality but not cancer detection rate in transrectal ultrasound-guided 10-core prostate biopsies. Prostate Cancer and Prostatic Diseases 2008; **11:** 270.
45. Koc G, Un, S, Filiz, DN et al: Does washing the biopsy needle with povidone-iodine have an effect on infection rates after transrectal prostate needle biopsy? Urologia Internationalis 2010; **85:** 147.
46. Raman JD, Lehman, KK, Dewan, K et al: Povidone Iodine Rectal Preparation at Time of Prostate Needle Biopsy is a Simple and Reproducible Means to Reduce Risk of Procedural Infection. J Vis Exp 2015;
47. Wagenlehner FM, van Oostrum, E, Tenke, P et al: Infective complications after prostate biopsy: outcome of the Global Prevalence Study of Infections in Urology (GPIU) 2010 and 2011, a prospective multinational multicentre prostate biopsy study. Eur Urol 2013; **63:** 521.

Tables

Table 1 - Showing unique RCTs

Legends

Figure 1 – Preferred Reporting Items for Systematic Reviews and Meta-analyses flow chart.

Figure 2 – Risk of bias assessment. (A) Risk of bias summary according to the judgment of the review authors on each risk of bias item for each study included. (B) Risk of bias graph according to the judgment of the review authors for each risk of bias item presented as a percentage across all the studies included.

Figure 3 – Comparison of transperineal to transrectal biopsy on infections complications following prostate biopsy. CI = confidence interval; df = degrees of freedom.

Figure 4 – Comparison of standard to extended biopsy cores on infections complications following prostate biopsy. CI = confidence interval; df = degrees of freedom. Note: Emilozzi 2004 reports transperineal biopsy, while all other studies performed transrectal biopsy.

Figure 5 - Effect of periprostatic nerve block on infections complications following prostate biopsy. CI = confidence interval; df = degrees of freedom.

Figure 6 – Effect of rectal preparation with enema on infections complications following prostate biopsy. CI = confidence interval; df = degrees of freedom.

Figure 7 – Effect of rectal preparation with povidone-iodine on infections complications following prostate biopsy. CI = confidence interval; df = degrees of freedom.

Figure 8 – Effect of rectal preparation with povidone-iodine on hospitalization following prostate biopsy. CI = confidence interval; df = degrees of freedom.

Non-antibiotic strategies for the prevention of infectious complications following prostate biopsy: A Systematic Review and Meta-analysis

Running head: How can technical interventions reduce infections after prostate biopsy?

Benjamin Pradere[a*], Rajan Veeratterapillay[b*], Konstantinos Dimitropoulos[c], Yuhong Yuan[d], Muhammad Imran Omar[e], Steven MacLennan[f], Tommaso Cai[g], Franck Bruyère[a], Riccardo Bartoletti[h], Bela Köves[i], Florian Wagenlehner[j], Gernot Bonkat[k], Adrian Pilatz[j]

[a]Urologie, CHRU Bretonneau, Tours, France; Université Francois Rabelais, PRES Centre Val de Loire, Tours, France, f.bruyere@chu-tours.fr, benjaminpradere@gmail.com
[b]Freeman Hospital, Newcastle Upon Tyne, UK, Rajan.Veeratterapillay@nuth.nhs.uk
[c]Department of Urology, Aberdeen Royal Infirmary, Aberdeen, Scotland, UK, k.dimitropoulos@nhs.net
[d]Department of Medicine, Division of Gastroenterology, McMaster University, Hamilton, Canada, yyuan@mcmaster.ca
[e]Guidelines Office, European Association of Urology, Arnhem, The Netherlands, m.i.omar@abdn.ac.uk
[f]Academic Urology Unit, University of Aberdeen, Aberdeen, United Kingdom, steven.maclennan@abdn.ac.uk
[g]Department of Urology, Santa Chiara, Reg. Hospital, Trento, Italy, ktommy@libero.it
[h]Department of Translational Research and New Technologies, University of Pisa, Italy, riccardo.bartoletti@hotmail.com
[i]Department of Urology, South-Pest Teaching Hospital, Budapest, Hungary, bkoves@gmail.com
[j]Department of Urology, Pediatric Urology and Andrology, Justus-Liebig-University Giessen, Giessen, Germany, adrian.pilatz@chiru.med.uni-giessen.de, florian.wagenlehner@chiru.med.uni-giessen.de
[k]alta uro AG, Merian Iselin Klinik, Center of Biomechanics & Calorimetry, University Basel, Basel, Switzerland, bonkat@alta-uro.com
[*]Shared first authorship

Key Words: prostate biopsy; infection, prophylaxis

Text word count: 3,311; Abstract: 272; Tables: 1; Figures: 8; Appendix in supplement: 5; Tables in supplement: 3; Figures in supplement: 8

Corresponding author: PD Dr. med. A. Pilatz, Department of Urology, Pediatric Urology and Andrology, Justus Liebig University Giessen, Rudolf-Buchheim-Str. 7, 35392 Giessen, Germany; E-mail: adrian.pilatz@chiru.med.uni-giessen.de, Tel.:+49-641-985-56362, Fax: +49-641-985-44577

Abstract

Purpose

To identify which non-antibiotic strategies could reduce the risk of infectious complications following prostate biopsy.

Materials and Methods

We performed a literature search on MEDLINE, Embase, and Cochrane Database for randomized controlled trials (RCTs) (Inception to May 2020) assessing non-antibiotic interventions in prostate biopsy. Primary outcome was pooled infectious complications (fever, sepsis and symptomatic UTI) and secondary outcome was hospitalization. Cochrane risk of bias tool and GRADE approach were used to assess the bias and the certainty of evidence. Protocol was registered with PROSPERO (CRD42015026354).

Results

90 RCTs (16,941 participants) were included in the analysis with 83 RCTs being categorized into one of ten different interventions. Transperineal biopsy was associated with significantly reduced infectious complications as compared to transrectal biopsy (RR 0·55, 95% CI 0·33-0·92, p=0·02, I^2=0%, participants=1330, studies=7). Rectal preparation with povidone-iodine was also shown to reduce infectious complications (RR 0·50, 95% CI 0·38-0·65, p<0·000001, I^2=27%, participants=1686, studies=8) as well as hospitalization (RR 0·38, 95% CI 0·21-0·69, p=0·002, I^2=0%, participants=620; studies=4). We found no difference in infectious complications/hospitalization for six other interventions: number of biopsy cores, periprostatic nerve block (PPNB), number of injections for PPNB, needle guide type, needle type, and rectal preparation with enema. In two interventions (needle diameter, rectal preparation with chlorhexidine) meta-analysis was not possible. Finally, seven studies had unique interventions. The certainty of evidence was rated as low/very low for all interventions.

Conclusions

Transperineal biopsy significantly reduces infectious complications compared to transrectal biopsy and should therefore be preferred. If transrectal biopsy is performed, rectal preparation with povidone-iodine is highly recommended. The other investigated non-antibiotic strategies did not significantly influence infection and hospitalization after prostate biopsy.

Introduction

In 2019 more than 190,000 new cases of prostate cancer (PCa) are diagnosed in the USA causing more than 33,000 deaths[1]. Worldwide prostate cancer accounts for a significant proportion of male cancer and mortality. PCa diagnosis is based on biopsies following patient evaluation for an elevated PSA or abnormal digital rectal examination and there is an increasing role for pre-biopsy MRI.[2,3] Prostatic biopsy remains the keystone for diagnosis and management of PCa and the most commonly performed diagnostic procedure in urology with more than 2 million per year.[4] Therefore, many efforts have been made to prevent infectious complications which account for the major adverse events with up to 7% of infections and 3.1% of sepsis depending of antibiotic prophylaxis regimens.[3] Even if an antibiotic prophylaxis is recommended by every guideline, the incidence of infectious complications is not negligible and its prevention of utmost importance.[2,3] In addition, both the induction of resistance through the use of antibiotics and side effects must be considered.[5] Post-biopsy infections have been increasing over the last few years.[6,7] Thus, antibiotic interventions such as targeted antibiotic prophylaxis based on rectal swab culture as well as augmented antibiotic prophylaxis applying more than one antibiotic were introduced to reduce infectious complications.[8,9] In a comprehensive meta-analysis we have recently compiled the evidence of various interventions for antibiotic prophylaxis.[10] In addition to antibiotics different aspects and modalities of biopsy techniques have been investigated with a view to minimizing adverse events. Among them, biopsy route, enema, and number of cores have been already suggested as potential factors to reduce the infectious risk.[11,12] Nevertheless, no systematic analysis is available evaluating various technical aspects of prostate biopsy for reducing post-biopsy infections.

The aim of our comprehensive systematic review and meta-analysis was to investigate whether and to what extent any non-antibiotic interventions reduce the risk of infectious complications following prostate biopsy.

Materials and Methods

Evidence acquisition

We followed the PRISMA guidance and the Cochrane Handbook for systematic reviews of interventions.[13,14] The protocol was registered at PROSPERO (CRD42015026354). The detailed PICO (Population, Intervention, Comparison and Outcomes) is provided in supplementary appendix 1.

Literature search

The Medline, Embase, LILACS, CENTRAL, Cochrane Database of Systematic reviews databases and clinicaltrial.gov were searched for randomized controlled trials (RCTs) (last search 27th May 2020). The grey literature was searched through opengrey.eu and oclc.org. Potentially-eligible trials were also identified by searching the reference lists of trials, reviews, and health technology assessment reports (Y.Y). There were no date or language restrictions. In order to avoid publication bias, abstracts characterized as RCTs, but for which published manuscripts were not yet available, were included in this systematic review with meta-analysis, as were funnel plots for interventions involving more than 10 studies. The search strategy is included in supplementary appendix 2.

Types of outcome measures

Primary outcome:

- Pooled infectious complications (calculated by summing all types of infectious complications reported i.e. fever, sepsis, symptomatic UTI). This approach was chosen since in many studies investigating post-biopsy complications, a distinction between severe infections (e.g. sepsis) and mild infections (e.g. cystitis) is not reported in detail (supplementary table 1).

Secondary outcome:

- Hospitalization due to infectious complications.

Data collection and analysis

Abstract screening, full-text screening, and data extraction was independently performed by two reviewers (A.P., B.P., or R.V.). For each disagreement, another reviewer (M.I.O., S.M.) was consulted. All the study authors were contacted to provide missing information if

necessary. Eight non-English articles were evaluated in the corresponding languages by members of the author team with appropriate language skills (4×Chinese: Y.Y., 1×French: B.P., F.B., 1×Spanish: A.P., B.P., 2×Turkish: Mete Cek, former EAU Guideline panel member). One Japanese article and two Korean articles were translated into English by professional translators. Among the 90 RCTs there are also eight studies that have so far only been published as abstracts. The risk of bias (RoB) was independently assessed by two reviewers (R.V., K.D.), by using the Cochrane RoB assessment tool.[14,15] Any disagreements were resolved via discussion or consultation with another reviewer (M.I.O., S.M.). The GRADE approach was used to assess the certainty of evidence for each comparison (M.I.O., S.M.).[14]

Statistical analysis

The meta-analysis was performed using Review Manager (RevMan) version 5.3. A fixed-effects model was used to calculate pooled estimates of treatment effects across similar studies and their 95% confidence intervals (CIs). We used risk ratio (RR) for dichotomous outcomes. We identified heterogeneity by visually inspecting forest plots and using a standard x^2 test with a significance level of $\alpha=0.1$. We also considered the I^2 statistic, which quantifies inconsistency across trials to assess the impact of heterogeneity on the meta-analysis. Where there was evidence of heterogeneity, we attempted to determine possible reasons by examining individual trial, subgroup characteristics, or by using a random-effects model.[14]

Results

Literature search and characteristics of the included studies

We identified 3111 citations, of those 284 were selected for full-text screening. Reasons for exclusion are provided in supplementary table 2. A total of 90 RCTs were included in the SR (supplementary appendix 3). The inclusion process is graphically illustrated in a PRISMA diagram (figure 1). For all included studies we provide detailed study characteristics in supplementary table 3. Of the 90 RCTs 83 studies could be categorized into one of ten different interventions, while 7 studies had unique interventions. Sensitivity analyses for the individual interventions showed that no changes occurred with or without the data of the eight included abstracts, which have not yet been published as full-text.

Risk of Bias (RoB) assessment

The RoB assessment is graphically illustrated in figure 2. It is noticeable that the majority of studies have an unclear RoB regarding random sequence generation, allocation concealment and blinding of outcome assessment. Furthermore, most studies have been conducted without blinding patients or personnel, which is certainly also due to the type of technical intervention. A funnel plot from the interventions with more than 10 studies (PPNB) showed no asymmetry (details in supplementary appendix 4).

Study heterogeneity

The I^2 statistic was 0% in all cases except Intervention 8 (povidone-iodine) where it was 27%. Since the p-values changed only marginally when using random-effect models for all interventions and endpoints, we used fixed-effect models throughout.

GRADE

The certainty of evidence was mainly downgraded due to study design, imprecision and risk of bias (details in supplementary appendix 5).

Intervention 1: Impact of biopsy route

A total of seven RCTs including 1330 patients compared the impact of biopsy route on infectious complications (supplementary appendix 3). There were significantly lower infectious complications when the transperineal route was performed (22 events among 673 men) compared to the transrectal route (37 events among 657 men) (RR 0.55, 95 CI: 0.33 to 0.92; participants=1330; studies=7; I^2=0%; low certainty; figure 3).

Data on hospitalization were reported in three studies with a total of 685 patients. While two hospitalizations were necessary in 346 patients in the transperineal group, hospitalization was reported in six cases out of 339 patients undergoing transrectal biopsy without any statistical difference (RR 0.38, 95 CI: 0.09 to 1.61; participants=685; studies=3; I^2=0%; very low certainty; supplementary figure 1).

Intervention 2: Impact of number of biopsy cores

The impact of the number of cores was evaluated in 11 studies including 2626 men undergoing prostate biopsy (supplementary appendix 3). While ten studies performed transrectal biopsy one study used the transperineal approach. MA showed 38 infectious complications in 1320

men randomized to standard and 47 in those 1306 randomized to extended number of cores. The comparison was not significant (RR 0.80, 95% CI: 0.53 to 1.22; participants=2230; studies=9; I^2=0%; low certainty; figure 4).

Of those studies, only five studies presented data on hospitalization following prostate biopsy. There was one case of hospitalization among 415 men in the standard group, while four cases occurred among 411 men in the extended biopsy scheme group. The comparison was not significant (RR 0.34, 95% CI: 0.05 to 2.13; participants=306; studies=2; I^2=0%; very low certainty; supplementary figure 2).

Intervention 3: Impact of periprostatic nerve block

Pain after periprostatic nerve block (PPNB) during biopsy was evaluated in 41 RCTs and infectious outcomes were reported in a total of 5540 men (supplementary appendix 3). There were 61 infectious complications among 2633 patients randomized to periprostatic nerve block and 73 among 2907 patients randomized to no nerve block/control. The comparison was not significant (RR 1.07, 95% CI: 0.77 to 1.48; participants=3857; studies=26; I^2=0%; very low certainty; figure 5).

Among these studies, only 14 reported hospitalization with 13 cases of hospitalization among 971 men in the PPNB group, while 15 cases occurred among 1128 men in the group without PPNB. The comparison was not significant (RR 1.13, 95% CI: 0.59 to 2.16; participants=1469; studies=9; I^2=0%; very low certainty; supplementary figure 3).

Intervention 4: Impact of number of injections for periprostatic nerve block

Six studies compared the number of injections applied for PPNB and assessed post-biopsy infections (supplementary appendix 3). MA showed five infections among 459 men randomized to standard number of injections and four among 468 men randomized to extended PPNB. The difference was not statistically significant (RR 1.30, 95 CI: 0.35 to 4.76; participants=478; studies=3; I^2=0%; low certainty; supplementary figure 4).

Two studies reported hospitalization with two patients being hospitalized among 147 men randomized to standard PPNB and two men among 153 randomized to extended PPNB. The difference was not statistically significant (RR 1.05, 95 CI: 0.15 to 7.32; participants=300; studies=2; I^2=0%; low certainty; supplementary figure 5).

Intervention 5: Impact of disposable needle guides

Two RCTs evaluated the use of disposable needle guides compared to reusable guides in a total of 253 patients (supplementary appendix 3).

There were nine events among 113 men randomized to disposable needle guides and 22 events among 140 men randomized to reusable needle guides. The difference was not statistically significant (RR 0.51, 95% CI: 0.24 to 1.06; participants=253; studies=2; I^2=0%; very low certainty; supplementary figure 6).

Both studies evaluated the impact on hospitalization. While four events occurred in 113 men randomized to the disposable needle guide group, nine events were recorded in 140 men of the reusable needle guide group. The difference was not statistically significant (RR 0.55, 95% CI: 0.17 to 1.74; participants=253; studies=2; I^2=0%; very low certainty; supplementary figure 7).

Intervention 6: Impact of needle type

Only two studies investigated the impact of a coaxial needle versus a non-coaxial needle and reported on infectious complications (supplementary appendix 3). Data analysis revealed no infections in 171 men in the coaxial needle arm, while one case occurred among 171 men in the group randomized to the non-coaxial biopsy needles. MA was not possible, because of zero events in one study. Hospitalization was reported in only one of the two studies and did not occur in any among the 240 patients.

Intervention 7: Impact of needle diameter

The impact of needle diameter was investigated in two studies (supplementary appendix 3). Data analysis revealed no infections in 133 men randomized to the smaller needle diameter, while one case occurred among 163 men in the group randomized to the larger needle diameter. MA was not possible, because of zero events in one study. Hospitalization was not reported as an endpoint in any study.

Intervention 8: Impact of rectal preparation with enema

Four RCTs evaluated rectal preparation with enema (supplementary appendix 3). Among 336 men randomized to enema 30 events were recorded, while among 335 men in control group 31

events were reported. The difference was not statistically significant (RR 0.96, 95% CI: 0.60 to 1.53; participants=671; studies=4; I^2=0%; low certainty; figure 6).

Only two studies with each 231 patients per group reported on hospitalization with nine events in the enema and eight events in the control group. This comparison was not statistically significant (RR 1.13, 95% CI: 0.44 to 2.86; participants=462; studies=2; I^2=0%; low certainty; supplementary figure 8).

Intervention 9: Impact of rectal preparation with chlorhexidine

Two studies investigated the influence of rectal preparation with chlorhexidine (supplementary appendix 3). Although both studies report infectious complications separately for the intervention and control groups, the primary outcome cannot be meta-analyzed due to a possible double case count in one of the studies.

Intervention 10: Impact of rectal preparation with povidone-iodine

Nine studies evaluated the use of rectal preparation with povidone-iodine (supplementary appendix 3) in a total of 1936 patients. MA showed 61 infections among 930 men in the povidone-iodine group and 131 among 1006 in the control group. The difference was statistically significant (RR 0.50, 95% CI: 0.38 to 0.65; participants=1686; studies=8; I^2=27%; low certainty; figure 7).

Four studies reported on hospitalization with a total of 12 men hospitalized among 285 men randomized to povidone iodine preparation and 37 men among 335 randomized to the control group. The difference was statistically significant (RR 0.38, 95% CI: 0.21 to 0.69; participants=620; studies=4; I^2=0%; low certainty; figure 8).

Different unique interventions

Seven RCTs with unique technical interventions (e.g. needle disinfection, needle size, perineal cleansing) were identified. Of those, only one study investigating the timepoint of rectal preparation with povidone-iodine showed significantly reduced infectious complications when applied before vs. after biopsy (table 1).

Discussion

To our knowledge this meta-analysis is the first to assess all the different technical aspects of prostate biopsy that can possibly reduce the risk of infectious complications. Therefore, it complements our comprehensive previous meta-analysis on antibiotic prophylaxis of prostate biopsy.[10] In the current analysis we have reported a total of 90 RCTs exploring non-antibiotic prophylactic strategies including the risk of peri-prostatic nerve block, prostate biopsy route, number of cores, rectal preparation, and type of needle used. Among the different strategies assessed in our analysis, transperineal prostate biopsy route and rectal preparation with povidone-iodine were found as the best interventions (low certainty of evidence) to reduce both post-biopsy infections and hospitalization.

This meta-analysis is the most comprehensive and recent one evaluating specifically infectious complications in the head-to-head comparison between transperineal and transrectal route. The two approaches have been highly debated in recent years with the introduction of MRI targeted biopsy and diagnostic accuracy.[16-20] In addition, there is increasing evidence that MRI diagnostics can be used to avoid unnecessary prostate biopsies - and thus the corresponding complications.[21,22] Until now, the different MRI targeted biopsy methods have not proved a real significant difference in terms of PCa detection.[23,24] The most recent studies were designed to assess the PCa detection rates between the two techniques and the potential risk for adverse events was only a secondary criterion.[25,26] Hence, study size of the aforementioned studies was not calculated to reveal differences in post-biopsy infection, but to investigate diagnostic accuracy. Thus, two older meta-analyses evaluating also infections complications in dependence of the biopsy route did not report a significant difference.[12,27] On the other hand, a recent meta-analysis suggested a benefit of transperineal biopsy, which significantly protected patients from postoperative fever (RR 0.26, 95% CI: 0.14 to 0.28).[28] However, all three of these meta-analyses are limited because they combined estimates from RCTs with those from case-control studies and double counted one study published in duplicate which has a very low number of post-biopsy infections in both groups.[29,30]

In the largest systematic review on infectious complications following prostate biopsy (165 studies including 162,577 patients) the standardized prevalence of sepsis was 0.8% in transrectal and 0.1% in transperineal biopsy and the standardized prevalence of hospitalization was 1.1% vs. 0.9%, respectively.[31] These data are not surprising, as they reinforce the classical principle for a surgical procedure to choose the lowest possible contamination category in order

to reduce the rate of infectious complications.[32] Our meta-analysis based on 7 RCTs confirmed this important aspect and showed a significantly lower infection rate using the transperineal route (RR 0.55, 95% CI: 0.33 to 0.92). Despite the potential logistic challenges attached to the widespread introduction of the local anesthetic transperineal technique, our findings support the "TREXIT 2020" approach to abandon transrectal prostate biopsy.[17]

Another important aspect is the number of biopsy cores taken. Over the years, the number has increased with the aim of improving diagnostic accuracy. Since one passes repeatedly through the rectal mucosa by an increased number of biopsy cylinders, one would expect a higher infection rate. Various cohort studies addressed this important point and were mainly able to show that the number of biopsy cylinders obtained is independent of postoperative infections.[33-35] Our meta-analysis including 11 RCTs shows that the number of cores is not associated with the risk of infection. This confirms the current guidelines which recommend standard biopsies in addition to targeted biopsies.[2,3]

In this context, the question of local anesthesia in the sense of a periprostatic nerve block arises. Various meta-analyses could impressively show that the periprostatic nerve block significantly contributes to perioperative pain control compared to an anesthetic gel applied intrarectally/control.[36-39] However, this requires further passages of a needle through the rectum and the injection of an anesthetic might be associated with the risk of distribution of possible pathogens. Previous meta-analyses on this topic reported sporadically on post-biopsy infections, but never primarily investigated the impact of periprostatic nerve block on infection.[38,39] Our analysis including 41 RCTs could show, that there is no increased risk of infection using periprostatic nerve block. In addition, the number of injections used for the periprostatic nerve block has no impact on the rate of post-biopsy infections. This is absolutely consistent with the number of biopsy cores taken as discussed above, which had no influence on the infection rate.

Since the passage of the needle leads through the contaminated rectal mucosa, there are several studies that have investigated different parameters of the needle. The diameter, shape, disinfection and the nature of the needle guide were each investigated in one or two studies, but no significant advantage in preventing post-biopsy infection was ever detected.[40-45]

Rectal preparation is a heterogenous practice when transrectal biopsies are planned with some urologists using enema, chlorhexidine, povidone-iodine applications, full bowel preparation, or no preparation at all. Here, we found that enema had no impact on postoperative infectious complications. However, rectal preparation with povidone-iodine prior to prostate biopsy significantly reduced the risk of infection (RR 0.50, 95% CI: 0.38-0.65), and hospitalization

(RR 0.38, 95% CI: 0.21-0.69). This is fully in line with a previous meta-analysis.[11] The advantages of rectal povidone-iodine preparation are its simple implementation to daily practice without largely increasing the cost of the procedure.[46] Despite the clear recommendation in guidelines,[2] the value still needs to be spread among urologists.[47]

The major strengths of this SR are that, i) it is the most comprehensive analysis on non-antibiotic prophylaxis strategies to prevent infectious complications after prostate biopsy, ii) we included only RCTs without any language and publication date restriction, iii) it includes studies also with patients being at higher risk for post-biopsy infection, and iv) it reports with post-biopsy infections and hospitalization due to infection the two most important adverse events after prostate biopsy.

Our study has some limitations which should be acknowledged: i) all infections were summed, since in many included studies a distinction between severe infections (e.g. sepsis) and mild infections (urinary tract infection) is not reported in detail, ii) many RCTs were not designed for the evaluation of postoperative complications particularly regarding peri-prostatic nerve block, which might underestimate infections and leads to a possible bias, iii) our analysis has been done without taking the individual antibiotic prophylaxis regimes used in each study into account, since I^2 was low or very low in all interventions, and iv) since it was the evaluation of non-antibiotic measures, the geographical origin of the included RCTs was not considered.

Conclusions

In this systematic review and meta-analysis we evaluated all published non-antibiotic prophylaxis regimens to reduce infectious complications following prostate biopsy. We show with low certainty of evidence, that both transperineal biopsy and rectal preparation with povidone iodine in transrectal biopsy significantly reduce the risk of infection. Whereas many concerns are rising to reduce antibiotic resistance and side effects, these non-antibiotic procedures should be favored in daily practice.

Funding

None

Acknowledgments

The authors would like to thank Emma Smith from the EAU Guidelines Office for her assistance with the systematic review.

References

1. Siegel RL, Miller, KD, Jemal, A: Cancer statistics, 2020. CA Cancer J Clin 2020; **70:** 7.
2. Guidelines E. Arnhem, The Netherlands: EAU Guidelines Office, 2019
3. Liss MA, Ehdaie, B, Loeb, S et al: An Update of the American Urological Association White Paper on the Prevention and Treatment of the More Common Complications Related to Prostate Biopsy. Journal of Urology 2017; **198:** 329.
4. Loeb S, Vellekoop, A, Ahmed, HU et al: Systematic review of complications of prostate biopsy. European Urology 2013; **64:** 876.
5. Roberts MJ, Bennett, HY, Harris, PN et al: Prostate Biopsy-related Infection: A Systematic Review of Risk Factors, Prevention Strategies, and Management Approaches. Urology 2017; **104:** 11.
6. Johansen TEB, Zahl, PH, Baco, E et al: Antibiotic resistance, hospitalizations, and mortality related to prostate biopsy: first report from the Norwegian Patient Registry. World J Urol 2020; **38:** 17.
7. Borghesi M, Ahmed, H, Nam, R et al: Complications After Systematic, Random, and Image-guided Prostate Biopsy [figure presented]. European Urology 2017; **71:** 353.
8. Yang L, Tang, Z, Gao, L et al: The augmented prophylactic antibiotic could be more efficacious in patients undergoing transrectal prostate biopsy: a systematic review and meta-analysis. International Urology and Nephrology 2016; **48:** 1197.
9. Scott S, Harris, PN, Williamson, DA et al: The effectiveness of targeted relative to empiric prophylaxis on infectious complications after transrectal ultrasound-guided prostate biopsy: a meta-analysis. World journal of urology 2018; **36:** 1007.
10. Pilatz A, Dimitropoulos, K, Veeratterapillay, R et al: Antibiotic Prophylaxis for the Prevention of Infectious Complications following Prostate Biopsy: A Systematic Review and Meta-Analysis. J Urol 2020; 101097JU0000000000000814.
11. Pu C, Bai, Y, Yuan, H et al: Reducing the risk of infection for transrectal prostate biopsy with povidone-iodine: A systematic review and meta-analysis. International Urology and Nephrology 2014; **46:** 1691.
12. Xue J, Qin, Z, Cai, H et al: Comparison between transrectal and transperineal prostate biopsy for detection of prostate cancer: A meta-analysis and trial sequential analysis. Oncotarget 2017; **8:** 23322.
13. Moher D, Liberati, A, Tetzlaff, J et al: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; **6:** e1000097.
14. Knoll T, Omar, MI, Maclennan, S et al: Key Steps in Conducting Systematic Reviews for Underpinning Clinical Practice Guidelines: Methodology of the European Association of Urology. Eur Urol 2018; **73:** 290.
15. Higgins JP, Altman, DG, Gotzsche, PC et al: The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Bmj 2011; **343:** d5928.
16. Wegelin O, Exterkate, L, van der Leest, M et al: The FUTURE Trial: A Multicenter Randomised Controlled Trial on Target Biopsy Techniques Based on Magnetic Resonance Imaging in the Diagnosis of Prostate Cancer in Patients with Prior Negative Biopsies. European Urology 2019; **75:** 582.
17. Grummet J, Gorin, MA, Popert, R et al: "TREXIT 2020": why the time to abandon transrectal prostate biopsy starts now. Prostate Cancer Prostatic Dis 2020; **23:** 62.
18. Kasivisvanathan V, Rannikko, AS, Borghi, M et al: MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. N Engl J Med 2018; **378:** 1767.
19. Rouviere O, Puech, P, Renard-Penna, R et al: Use of prostate systematic and targeted biopsy on the basis of multiparametric MRI in biopsy-naive patients (MRI-FIRST): a prospective, multicentre, paired diagnostic study. Lancet Oncol 2019; **20:** 100.
20. van der Leest M, Cornel, E, Israel, B et al: Head-to-head Comparison of Transrectal Ultrasound-guided Prostate Biopsy Versus Multiparametric Prostate Resonance Imaging with Subsequent Magnetic Resonance-guided Biopsy in Biopsy-naive Men with Elevated Prostate-specific Antigen: A Large Prospective Multicenter Clinical Study. Eur Urol 2019; **75:** 570.
21. Donato P, Morton, A, Yaxley, J et al: Improved detection and reduced biopsies: the effect of a multiparametric magnetic resonance imaging-based triage prostate cancer pathway in a public teaching hospital. World J Urol 2020; **38:** 371.

22. Venderink W, van Luijtelaar, A, van der Leest, M et al: Multiparametric magnetic resonance imaging and follow-up to avoid prostate biopsy in 4259 men. BJU Int 2019; **124:** 775.
23. Jambor I, Kahkonen, E, Taimen, P et al: Prebiopsy multiparametric 3T prostate MRI in patients with elevated PSA, normal digital rectal examination, and no previous biopsy. J Magn Reson Imaging 2015; **41:** 1394.
24. Mendhiratta N, Rosenkrantz, AB, Meng, X et al: Magnetic Resonance Imaging-Ultrasound Fusion Targeted Prostate Biopsy in a Consecutive Cohort of Men with No Previous Biopsy: Reduction of Over Detection through Improved Risk Stratification. J Urol 2015; **194:** 1601.
25. Zhu K, Qin, Z, Xue, J et al: Comparison of prostate cancer detection rates between magnetic resonance imaging-targeted biopsy and transrectal ultrasound-guided biopsy according to Prostate Imaging Reporting and Data System in patients with PSA >/=4 ng/mL: a systematic review and meta-analysis. Transl Androl Urol 2019; **8:** 741.
26. Drost FH, Osses, D, Nieboer, D et al: Prostate Magnetic Resonance Imaging, with or Without Magnetic Resonance Imaging-targeted Biopsy, and Systematic Biopsy for Detecting Prostate Cancer: A Cochrane Systematic Review and Meta-analysis. Eur Urol 2020; **77:** 78.
27. Shen PF, Zhu, YC, Wei, WR et al: The results of transperineal versus transrectal prostate biopsy: a systematic review and meta-analysis. Asian J Androl 2012; **14:** 310.
28. Xiang J, Yan, H, Li, J et al: Transperineal versus transrectal prostate biopsy in the diagnosis of prostate cancer: a systematic review and meta-analysis. World J Surg Oncol 2019; **17:** 31.
29. Hara R, Jo, Y, Fujii, T et al: Optimal approach for prostate cancer detection as initial biopsy: prospective randomized study comparing transperineal versus transrectal systematic 12-core biopsy. Urology 2008; **71:** 191.
30. Takenaka A, Hara, R, Ishimura, T et al: A prospective randomized comparison of diagnostic efficacy between transperineal and transrectal 12-core prostate biopsy. Prostate Cancer Prostatic Dis 2008; **11:** 134.
31. Bennett HY, Roberts, MJ, Doi, SA et al: The global burden of major infectious complications following prostate biopsy. Epidemiol Infect 2016; **144:** 1784.
32. Grabe M: Antibiotic prophylaxis in urological surgery, a European viewpoint. International Journal of Antimicrobial Agents 2011; **38:** 58.
33. Wagenlehner FME, Van Oostrum, E, Tenke, P et al: Infective complications after prostate biopsy: Outcome of the Global Prevalence Study of Infections in Urology (GPIU) 2010 and 2011, A prospective multinational multicentre prostate biopsy study. European Urology 2013; **63:** 521.
34. Seo YE, Ryu, H, Oh, JJ et al: Clinical importance of antibiotic regimen in transrectal ultrasound-guided prostate biopsy: A single center analysis of nine thousand four hundred eighty-seven cases. Surgical Infections 2018; **19:** 704.
35. Simsir A, Kismali, E, Mammadov, R et al: Is it possible to predict sepsis, the most serious complication in prostate biopsy? Urologia Internationalis 2010; **84:** 395.
36. Kim DK, Lee, JY, Jung, JH et al: What is the most effective local anesthesia for transrectal ultrasonography-guided biopsy of the prostate? A systematic review and network meta-analysis of 47 randomized clinical trials. Sci Rep 2019; **9:** 4901.
37. Garcia-Perdomo HA, Mejia, NG, Fernandez, L et al: Effectiveness of periprostatic block to prevent pain in transrectal prostate biopsy: A systematic review and a network meta-analysis. Central European Journal of Urology 2019; **72:** 121.
38. Tiong HY, Liew, LCH, Samuel, M et al: A meta-analysis of local anesthesia for transrectal ultrasound-guided biopsy of the prostate. Prostate Cancer and Prostatic Diseases 2007; **10:** 127.
39. Yang Y, Liu, Z, Wei, Q et al: The Efficiency and Safety of Intrarectal Topical Anesthesia for Transrectal Ultrasound-Guided Prostate Biopsy: A Systematic Review and Meta-Analysis. Urologia Internationalis 2017; **99:** 373.
40. Gurbuz C, Canat, L, Atis, G et al: Reducing infectious complications after transrectal prostate needle biopsy using a disposable needle guide: is it possible? In: International braz j urol : official journal of the Brazilian Society of Urology, vol. 37, pp. 79, 2011
41. Tuncel A, Aslan, Y, Sezgin, T et al: Does disposable needle guide minimize infectious complications after transrectal prostate needle biopsy? In: Urology, vol. 71, pp. 1024, 2008
42. Babaei Jandaghi A, Habibzadeh, H, Falahatkar, S et al: Transperineal Prostate Core Needle Biopsy: A Comparison of Coaxial Versus Noncoaxial Method in a Randomised Trial. CardioVascular and Interventional Radiology 2016; **39:** 1736.
43. Novella G, Ficarra, V, Galfano, A et al: Pain assessment after original transperineal prostate biopsy using a coaxial needle. Urology 2003; **62:** 689.

44. Inal GH, Oztekin, VC, Ugurlu, O et al: Sixteen gauge needles improve specimen quality but not cancer detection rate in transrectal ultrasound-guided 10-core prostate biopsies. Prostate Cancer and Prostatic Diseases 2008; **11:** 270.
45. Koc G, Un, S, Filiz, DN et al: Does washing the biopsy needle with povidone-iodine have an effect on infection rates after transrectal prostate needle biopsy? Urologia Internationalis 2010; **85:** 147.
46. Raman JD, Lehman, KK, Dewan, K et al: Povidone Iodine Rectal Preparation at Time of Prostate Needle Biopsy is a Simple and Reproducible Means to Reduce Risk of Procedural Infection. J Vis Exp 2015;
47. Wagenlehner FM, van Oostrum, E, Tenke, P et al: Infective complications after prostate biopsy: outcome of the Global Prevalence Study of Infections in Urology (GPIU) 2010 and 2011, a prospective multinational multicentre prostate biopsy study. Eur Urol 2013; **63:** 521.

Tables

Table 1 - Showing unique RCTs

Legends

Figure 1 – Preferred Reporting Items for Systematic Reviews and Meta-analyses flow chart.

Figure 2 – Risk of bias assessment. (A) Risk of bias summary according to the judgment of the review authors on each risk of bias item for each study included. (B) Risk of bias graph according to the judgment of the review authors for each risk of bias item presented as a percentage across all the studies included.

Figure 3 – Comparison of transperineal to transrectal biopsy on infections complications following prostate biopsy. CI = confidence interval; df = degrees of freedom.

Figure 4 – Comparison of standard to extended biopsy cores on infections complications following prostate biopsy. CI = confidence interval; df = degrees of freedom. Note: Emilozzi 2004 reports transperineal biopsy, while all other studies performed transrectal biopsy.

Figure 5 - Effect of periprostatic nerve block on infections complications following prostate biopsy. CI = confidence interval; df = degrees of freedom.

Figure 6 – Effect of rectal preparation with enema on infections complications following prostate biopsy. CI = confidence interval; df = degrees of freedom.

Figure 7 – Effect of rectal preparation with povidone-iodine on infections complications following prostate biopsy. CI = confidence interval; df = degrees of freedom.

Figure 8 – Effect of rectal preparation with povidone-iodine on hospitalization following prostate biopsy. CI = confidence interval; df = degrees of freedom.

Key of Definitions for Abbreviations (only include abbreviations used 3 times or more in manuscript)

Abbreviations and Acronyms

CI = confidence interval

GRADE = Grading of Recommendations, Assessment, Development and Evaluations

MA = meta-analysis

MRI = Magnetic resonance imaging

PB = prostate biopsy

PCa = prostate cancer

PPNB = periprostatic nerve block

RCT = randomized controlled trials

RoB = risk of bias

RR = risk ratio

SR = systematic review

UTI = urinary tract infection

Table 1: Unique RCTs

Study and Year	Intervention	Outcome
Bingqian 2009	PPNB plus intraprostatic injection vs. control	Infectious complications not significantly different
Bolat 2016	Transperineal prostatic nerve block vs. transrectal periprostatic nerve block	Infectious complications not significantly different[#]
Costa 2019	Rectal preparation with povidone-iodine plus formalin needle disinfection vs. control	Lower complications in intervention group, but not statistically significant
De Nunzio 2015	Enema vs. full bowel preparation	Infectious complications not significantly different*
Koc 2010	Needle washing with povidone-iodine vs. control	Lower complications in intervention group, but not statistically significant
Taher 2014	Perineal cleansing vs. no perineal cleansing in transrectal prostate biopsy	Lower complications in intervention group, but not statistically significant
Yu 2015	Timepoint of rectal preparation with povidone-iodine (before vs. after vs. before plus after)	Significantly reduced infectious complications in groups with rectal preparation before biopsy

[#] raw data provided from authors; febrile UTI: 3 vs. 2

* raw data provided from authors; urosepsis 1 vs. 1; hospitalization 1 vs. 1

Figure 1_R1

Click here to access/download;Figure (upload each figure separately, indicate number in Description box);Figure 1_R1.jpg

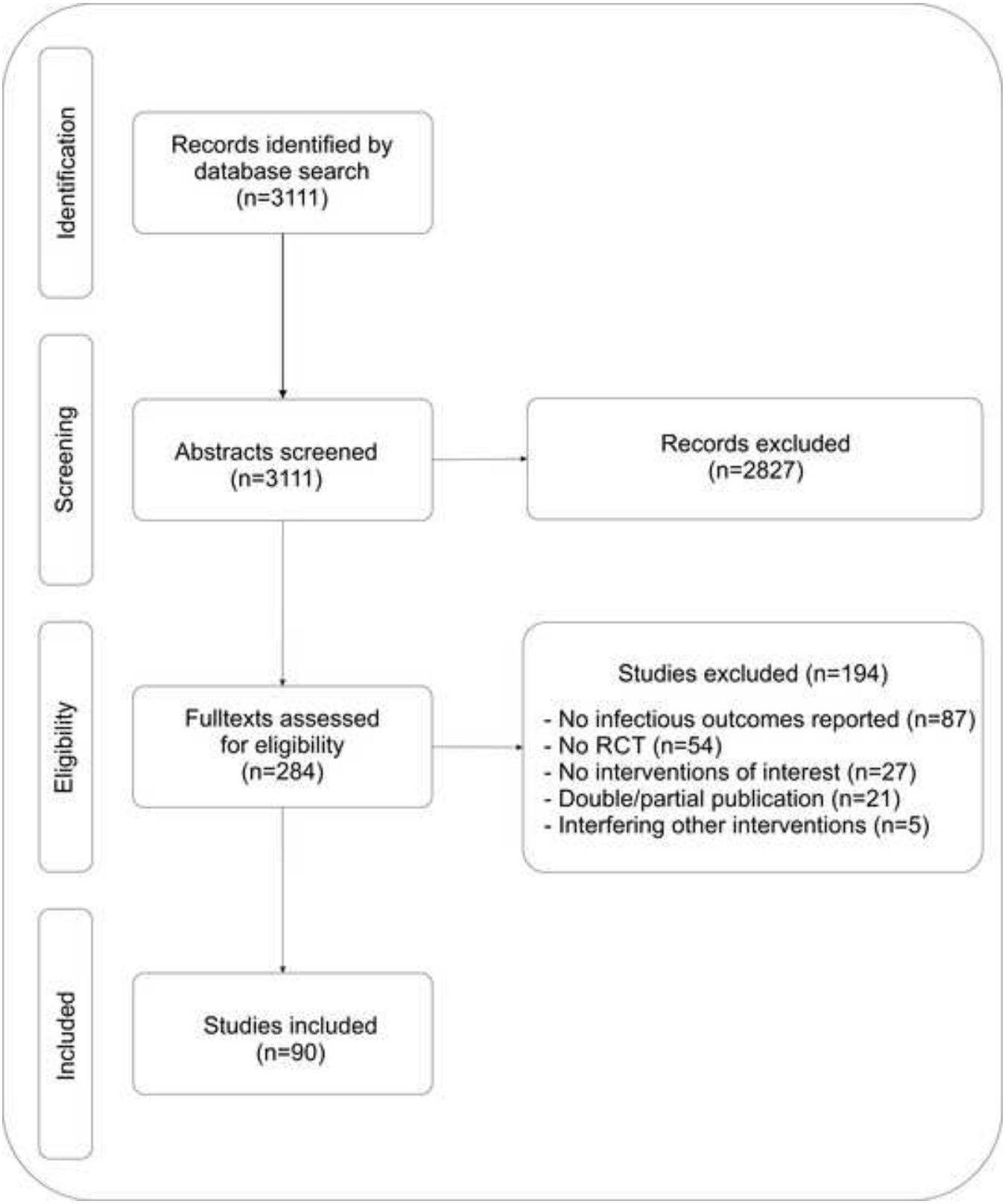
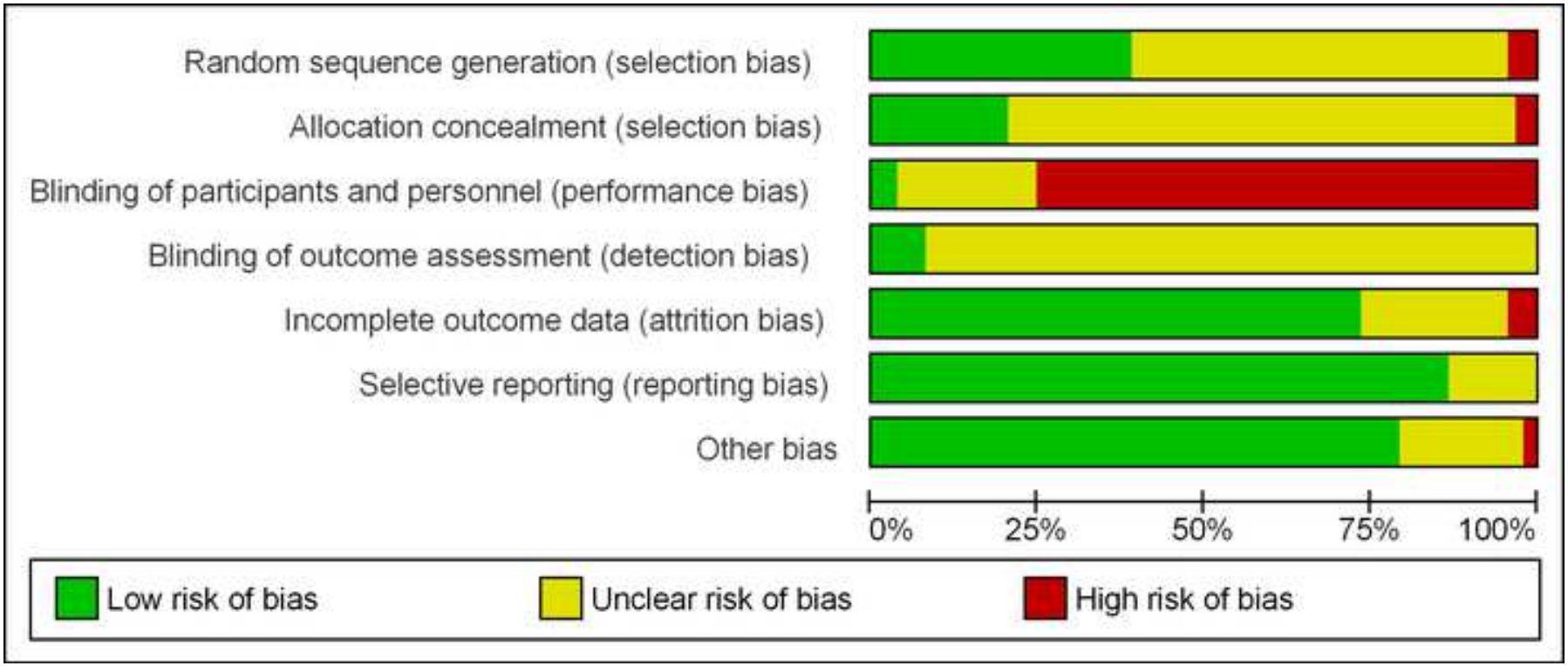


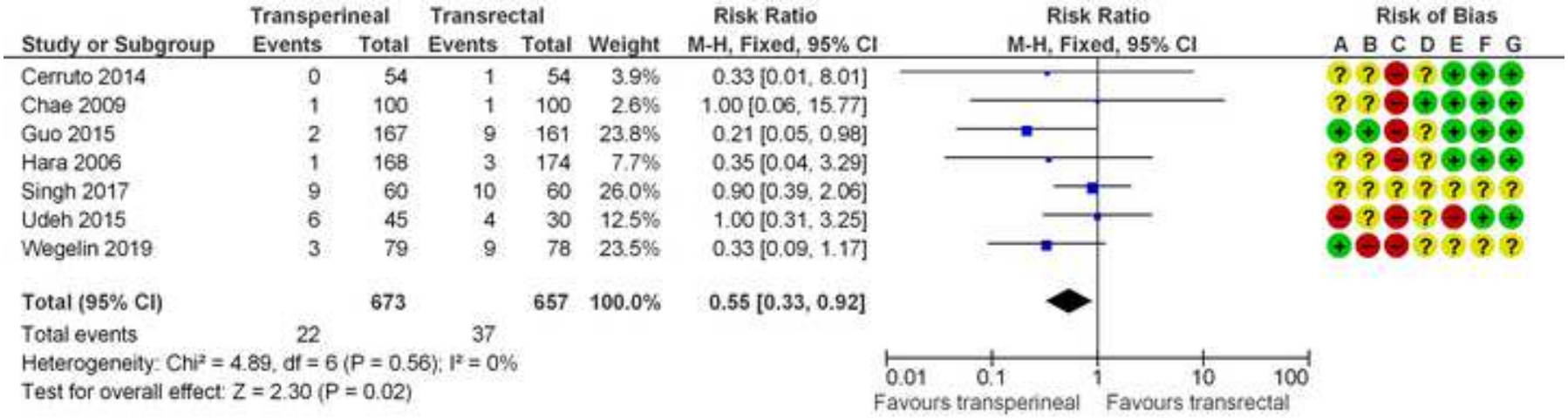
Figure 2a_R1

Click here to access/download;Figure (upload each figure separately, indicate number in Description box);Figure

Figure 2b_R1

Click here to access/download;Figure (upload each figure separately, indicate number in Description box);Figure 2b_R1.jpg



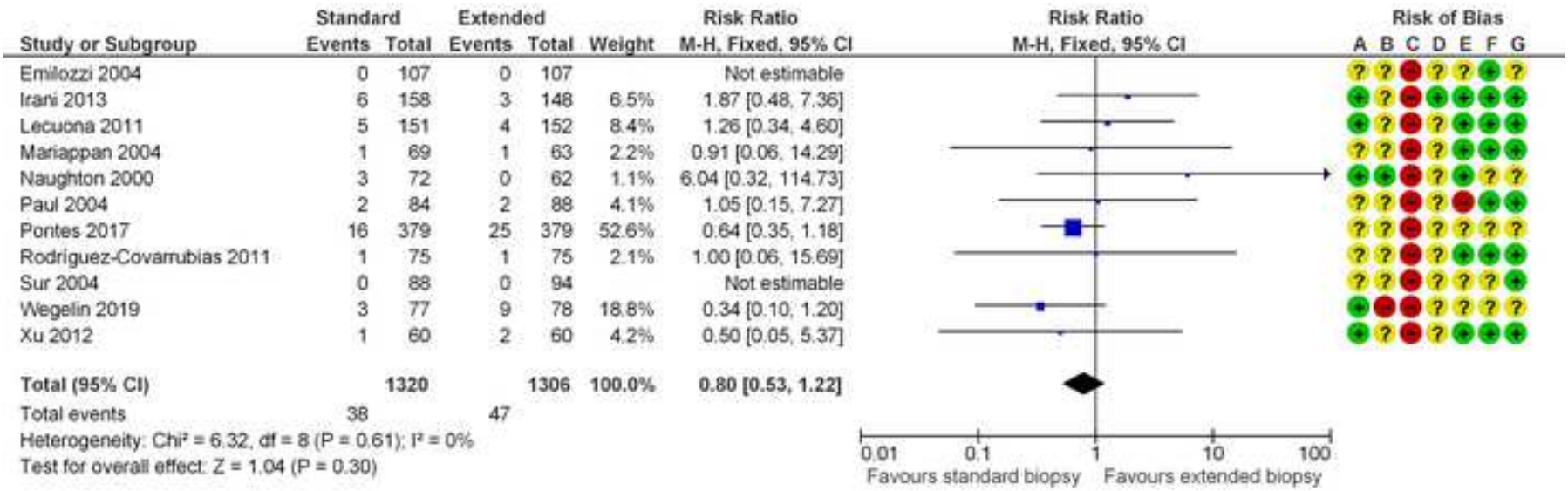


Risk of bias legend

(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Figure 4_R1

Click here to access/download;Figure (upload each figure separately, indicate number in Description box);Figure 4_R1.jpg

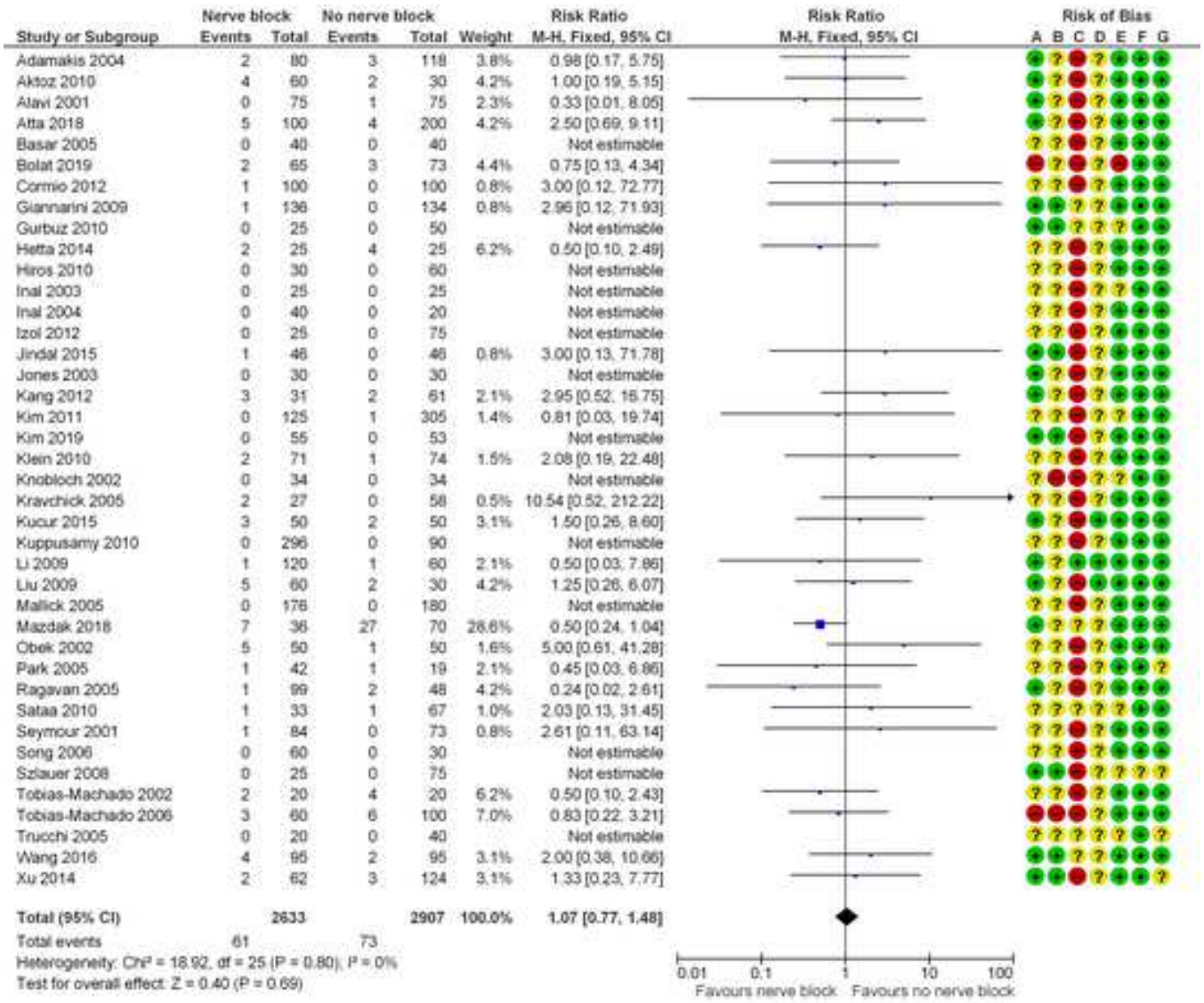


Risk of bias legend

(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Figure 5_R1

Click here to access/download;Figure (upload each figure separately, indicate number in Description box);Figure 5_R1.jpg

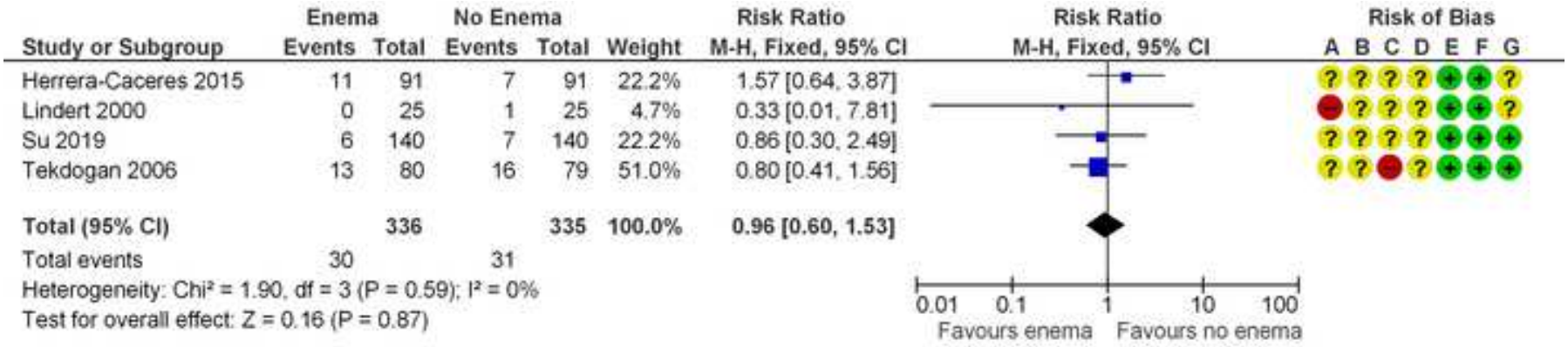


Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 6_R1

Click here to access/download;Figure (upload each figure separately, indicate number in Description box);Figure 6_R1.jpg

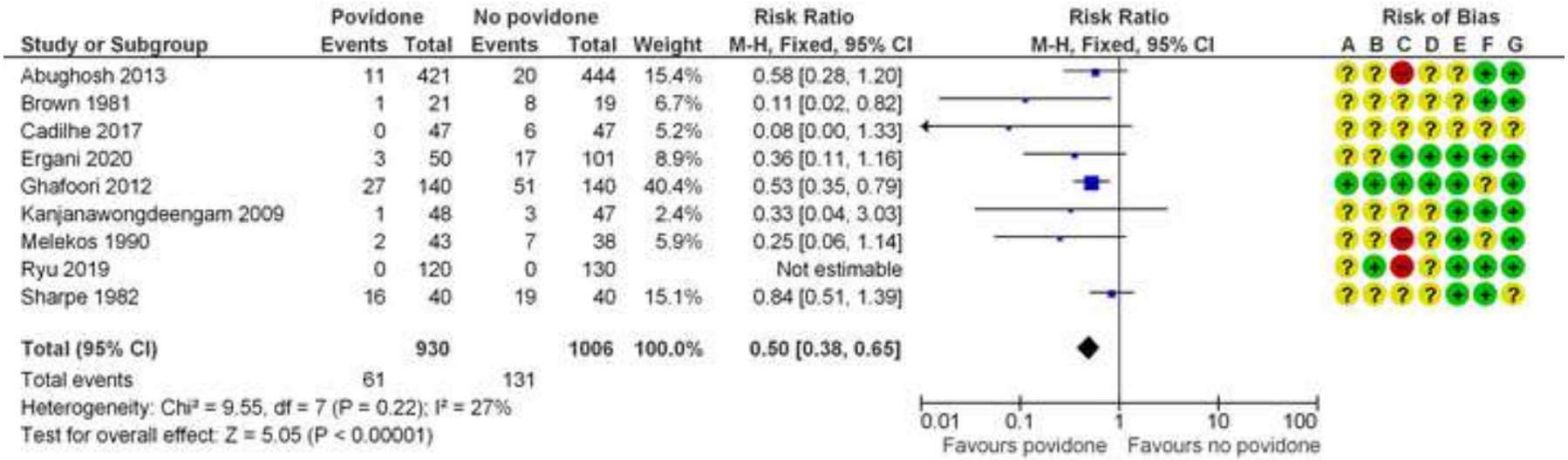


Risk of bias legend

(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Figure 7_R1

Click here to access/download;Figure (upload each figure separately, indicate number in Description box);Figure 7_R1.jpg

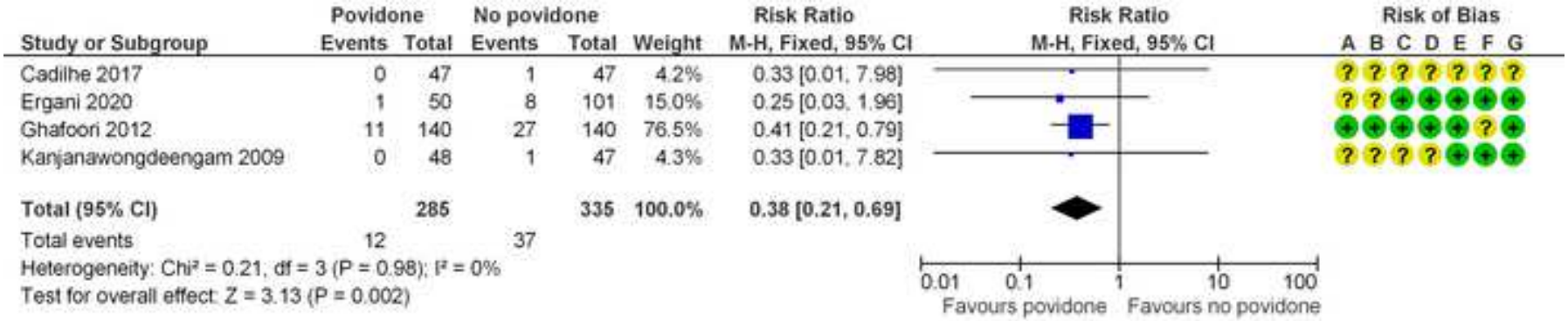


Risk of bias legend

(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Figure 8_R1

Click here to access/download;Figure (upload each figure separately, indicate number in Description box);Figure 8_R1.jpg



Risk of bias legend

(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Supplementary appendix 1: PICO elements - Post prostate biopsy infection

PICO elements	Characteristics
Question	Which strategies are effective for reducing the risk of infectious complications for men undergoing prostate biopsy?
Objectives	• To determine the effective strategies for reducing infectious complications of prostate biopsy • To determine whether specific strategies give most benefit for patient sub-groups identified as being at greater risk for infective complications by using sensitivity analysis on relevant subgroups

Population	• Men who undergo prostate biopsies using any strategy or approach; includes men with suspicion of prostate cancer, or those already diagnosed with prostate cancer (e.g. active surveillance) or those who undergo biopsy to confirm local recurrence to consider salvage treatment.
	• Exclusion criteria: Men who do not have prostate biopsies (i.e. for inclusion, all studies must include only men who have had biopsies, and mixed populations are excluded).
	• Subgroups of interest:
	(1) Proportion of men with factors conferring higher risk of infective complications:
	  • Patient age (< 75 years vs ≥75 years)
	  • Immunosuppressive drugs or co-morbidity (yes/no)
	  • Valvular heart disease (y/n)
	  • CNS disorder (y/n)
	  • Previous biopsy (y/n)
	  • Antibiotics in previous 6 months (y/n)
	  • Hospitalization in previous 6 months (y/n)
	  • Urethral instrumentation in previous 6 months (y/n)
	  • Asymptomatic bacteriuria (y/n)
	  • History of prostatitis (y/n)
	  • Indwelling or intermittent urinary catheter (y/n)
	  • Recent travel areas with high prevalence of multi-resistant E. coli high risk area (y/n)
	  • PSA (< 10/≥ 10)
	  • Prostate volume (< 40 ml/≥ 40 ml)
	  • Prostate cancer in histology (y/n)
	  • Others defined by trialists

Interventions/ Exposure	Experimental interventions (including variations and co-interventions) (1) Antibiotics: (a) Types: fluoroquinolones vs gentamicin vs metronidazole vs carbapenem vs trimethoprim/sulphamethoxazole vs Co-amoxiclav vs combinations of any two or more vs any other antibiotic judged relevant by

	reviewer; (b) Dose of antibiotic (standard vs non-standard, as defined by present EAU Guidelines); (c) Timing (for single doses: ≤1 hour vs >1 hour); (d) Duration (single vs multiple within 24 hours vs multiple within >24 hours); (e) Route of antimicrobial administration (Oral vs Rectal vs Intramuscular/Intravenous); **(2) Co-interventions: (a) Use of rectal swab versus no rectal swab to guide prophylaxis; (b) treatment of asymptomatic bacteriuria (ABU) vs no treatment prior to biopsy; (c) Use of rectal cleansing or preparation, including enema, disinfectant or antiseptic solution, or washing, prior to biopsy vs no use.** **(3) Technical aspects: (a) number of cores, (b) needle size, (c) needle dwell time, (d) transrectal vs perineal, (d) fusion vs no fusion, (e) local injected anaesthetic vs no local anaesthetic** **(4) Any other intervention judged relevant by reviewer** ***Control interventions: Placebo or no treatment; standard or alternative prophylaxis as defined by trialist**
Comparisons	• **Experimental vs Control** • **Experimental vs Experimental** • **Experimental only not included (but single-arm case series reporting on bacterial resistance will be included, and those reporting on other outcomes will be retained for discussion if relevant)**
Outcomes	**Primary outcomes** • **Symptomatic infectious complication** **Secondary outcomes** • **Asymptomatic bacteriuria** • **Hospitalization due to infective complications** • **Mortality** • **Adverse effects of antimicrobial strategy** • **Change in bacterial resistance (before, after biopsy**
	Study types main question • **RCTs** • **Non-randomised comparative studies for those interventions, where RCTs are not available** **Study types sub-question on patients risk factor analysis** • **RCTs for Cochrane review** • **Non-randomised comparative studies** • **Single-arm studies for anti-microbial resistance** **Restriction of date of publication** • **No restriction** **Language restrictions**

	• **No language restriction** **Key words** **Both medical subject heading (MeSH) and free text terms as well as variations of root word will be searched.** **Key terms related to "prostate" or "prostate neoplasms" will be combined using the set operator AND key terms related to "biopsy or biopsies" AND key terms related to "anti-infective agents or disinfectants or technical modifications" AND key terms related to "prophylaxis or prevention".** **Databases** **Embase (OvidSP)** **Medline (OvidSP)** **Cochrane databases (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and Cochrane Health Technology Assessment)** **clinicaltrials.gov** **WHO international Clinical Trials Registry Platform (ICTRP)**

Confounders (confounders will be used for risk of bias assessment only and will not affect decisions on whether to include or exclude studies)	**Factors that may directly affect efficacy of interventions and should be balanced between groups**
	• **Patient age (< 75 years vs ≥75 years)**
	• **Presence of multi-resistant E. coli**
	  • **In urine**
	  • **In faeces**
	• **Asymptomatic bacteriuria (y/n)**
	• **Indwelling or intermittent urinary catheter (y/n)**

Supplementary appendix 2:

Search Strategy Search Strategy (Medline and Embase via OvidSP, from inception to May 27, 2020)

1. exp prostate/
2. exp Prostatic Neoplasms/ or exp prostate tumor/
3. (prostatic or prostate).ti,ab,kw.
4. or/1-3
5. exp biopsy/
6. (biopsy or biopsies or biopsied).ti,ab,kw.
7. or/5-6
8. 4 and 7
9. exp antiinfective agent/
10. exp Anti-Infective Agents/
11. exp quinolone derivative/ or exp Quinolones/
12. exp metronidazole/
13. exp gentamicin/ or exp Gentamicins/
14. exp carbapenem/ or exp Carbapenems/
15. exp trimethoprim/
16. exp sulfamethoxazole/
17. exp amoxicillin plus clavulanic acid/
18. exp piperacillin/
19. exp cotrimoxazole/
20. exp netilmicin/
21. exp cefuroxime/
22. exp norfloxacin/
23. exp ciprofloxacin/
24. exp ofloxacin/
25. exp tinidazole/
26. exp ceftriaxone/
27. exp Disinfection/ or exp Disinfectants/ or exp disinfectant agent/
28. (antibiotic* or antibacterial or anti bacterial or antiseptic* antimicrobial* or anti infect* or antiinfect* or disinfectant* or disinfection).tw.
29. (fluoroquinolone* or quinolone* or gentamicin* or metronidazole or falgyl).tw.
30. (carbapenem or trimethoprim or sulphamethoxazole or Co-amoxiclav).tw.
31. (clavulanic acid or sulfonamide* or aminoglycoside* or cephalosporin* or piperacillin or cefuroxime or norfloxacin).tw.
32. (ciprofloxacin or ofloxacin or tinidazole or cephtriaxon or ceftriaxone or netilmicin or netromycine).tw.
33. (cotrimoxazole or co-trimoxazole or sulfamethoxazole or (beta lactamase adj2 (inhibitors* or antagonist*))).tw.
34. exp sulfonamide/ or exp Sulfonamides/

35. exp aminoglycoside/ or exp Aminoglycosides/
36. exp cephalosporin/ or exp Cephalosporins/
37. exp beta lactamase inhibitor/ or exp beta-Lactamase Inhibitors/
38. (povidone iodine or betadine or iodophor or povidone).tw.
39. exp povidone iodine/ or exp povidone/ or exp iodophor/ or exp Iodophors/
40. or/9-39
41. exp prophylaxis/
42. exp Antibiotic Prophylaxis/ or exp Pre-Exposure Prophylaxis/
43. exp prevention/
44. (prophyla* or prevent* or reduced or reduction or reducing).tw.
45. (pre-biopsy or prebiopsy or pre-biopsies or prebiopsies).ti,ab.
46. (pre-operativ* or pre-intervention* or pre-procedure* or preoperativ* or preintervention or preprocedure*).tw.
47. (before or prior).tw.
48. or/41-47
49. 8 and 40 and 48
50. ((rectal or rectum) adj3 (swab or cleaning or washing or preparation* or sterilization)).tw.
51. exp enema/ or enema.tw.
52. ((transrectal or trans-rectal) and (transperineal or perineal)).tw.
53. (fusion adj3 (guided or guidance or guide or guiding)).tw.
54. exp local anesthetic agent/ or exp Anesthetics, Local/ or ((local or topical) adj2 (anaesthetic* or anesthetic*)).tw.
55. (needle adj3 (size or dwell time)).tw.
56. (dipstick urinalysis or midstream specimen).tw.
57. (technical modification* or technical alternation*).tw.
58. (number adj2 cores).tw.
59. or/50-58
60. 8 and 48 and 59
61. Biopsy, Needle/mt
62. ((compared adj5 protocol) or protocols).tw.
63. or/61-62
64. 8 and 63
65. 49 or 60 or 64
66. (randomized controlled trial or controlled clinical trial).pt.
67. random*.mp.
68. placebo.ab.
69. trial.ab.
70. groups.ab.
71. Placebo*.mp.
72. double-blind*.mp. or blind*.tw.
73. clinical trial:.mp.
74. or/66-73
75. 65 and 74

76. note/ or editorial/ or letter/ or Comment/ or news/
77. case report/ or case reports/ or case report.ti.
78. (exp animals/ or exp animal/ or exp nonhuman/ or exp animal experiment/ or animal model/ or animal tissue/ or non human/ or (rat or rats or mice or mouse or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti.) not (humans/ or human/ or human experiment/ or (human* or men or women or patients or subjects).tw.)
79. or/76-78
80. 75 not 79
81. remove duplicates from 80

Note: The search strategy included both antibiotic and non-antibiotic prophylaxis. For the present publication only studies with non-antibiotic interventions were used.

Supplementary appendix 3: References of included RCTs

All included RCTs

1. Adamakis I, Mitropoulos, D, Haritopoulos, K et al: Pain during transrectal ultrasonography guided prostate biopsy: a randomized prospective trial comparing periprostatic infiltration with lidocaine with the intrarectal instillation of lidocaine-prilocain cream. World journal of urology 2004; **22:** 281.
2. Aktoz T, Kaplan, M, Turan, U et al: 'Multimodal' approach to management of prostate biopsy pain and effects on sexual function: Efficacy of levobupivacaine adjuvant to diclofenac sodium - A prospective randomized trial. Andrologia 2010; **42:** 35.
3. Alavi AS, Soloway, MS, Vaidya, A et al: Local anesthesia for ultrasound guided prostate biopsy: a prospective randomized trial comparing 2 methods. In: Journal of urology, vol. 166, pp. 1343, 2001
4. Atta H, Mostafa, M, Shalaby, M: Which is better for pain reduction during transrectal ultrasound-guided biopsy of the prostate: Intravenous diazepam, local periprostatic nerve block, or combination? controlled randomized study. Saudi Journal of Anaesthesia 2018; **12:** 16.
5. Basar MM, Ozcan, S, Akpinar, S et al: Local anesthesia in transrectal ultrasound-guided prostate biopsy: EMLA cream as a new alternative technique. Scandinavian Journal of Urology and Nephrology 2005; **39:** 130.
6. Bolat MS, Cinar, O, Asci, R et al: A novel method for pain control: infiltration free local anesthesia technique (INFLATE) for transrectal prostatic biopsy using transcutaneous electrical nerve stimulation (TENS). Int Urol Nephrol 2019; **51:** 2119.
7. Cormio L, Pagliarulo, V, Lorusso, F et al: Combined perianal-intrarectal (PI) lidocaine-prilocaine (LP) cream and lidocaine-ketorolac gel provide better pain relief than combined PI LP cream and periprostatic nerve block during transrectal prostate biopsy. In: BJU international, vol. 109, pp. 1776, 2012
8. Giannarini G, Autorino, R, Valent, F et al: Combination of Perianal-Intrarectal Lidocaine-Prilocaine Cream and Periprostatic Nerve Block for Pain Control During Transrectal Ultrasound Guided Prostate Biopsy: A Randomized, Controlled Trial. Journal of Urology 2009; **181:** 585.
9. Gurbuz C, Canat, L, Bayram, G et al: Visual pain score during transrectal ultrasound-guided prostate biopsy using no anaesthesia or three different types of local anaesthetic application. Scandinavian Journal of Urology and Nephrology 2010; **44:** 212.
10. Hetta WM, Niazi, G, Elfawy, D: Local anesthesia by periprostatic block in transrectal ultrasound guided prostatic biopsy. Egyptian Journal of Radiology and Nuclear Medicine 2014; **45:** 137.
11. Hiros M, Selimovic, M, Spahovic, H et al: Transrectal ultrasound-guided prostate biopsy, periprostatic local anesthesia and pain tolerance. Bosnian Journal of Basic Medical Sciences 2010; **10:** 68.
12. Inal G, Yazici, S, Adsan, O et al: Periprostatic nerve blockade before transrectal ultrasound-guided prostate biopsy: the Ankara Numune experience. Urologia Internationalis 2003; **71:** 165.
13. Inal G, Yazici, S, Kosan, M et al: Comparison of 2 ml and 6 ml of periprostatic 1% lidocaine injections before transrectal ultrasound guided prostate biopsy. Turk Uroloji Dergisi 2004; **30:** 173.
14. Izol V, Soyupak, B, Seydaoglu, G et al: Three different techniques for administering analgesia during transrectal ultrasound-guided prostate biopsy: A comparative study. International Braz J Urol 2012; **38:** 122.
15. Jindal T, Mukherjee, S, Sinha, RK et al: Transrectal ultrasonography (TRUS)-guided pelvic plexus block to reduce pain during prostate biopsy: A randomised controlled trial. BJU International 2015; **115:** 892.
16. Jones JS, Ulchaker, JC, Nelson, D et al: Periprostatic local anesthesia eliminates pain of office-based transrectal prostate biopsy. Prostate cancer and prostatic diseases 2003; **6:** 53.
17. Kang KS, Yeo, JK, Park, MG et al: Efficacy of periprostatic anesthesia according to lidocaine dose during transrectal ultrasound-guided biopsy of the prostate. Korean Journal of Urology 2012; **53:** 750.
18. Kim S, Yoon, BI, Kim, SJ et al: Effect of oral administration of acetaminophen and topical application of emla on pain during transrectal ultrasound- guided prostate biopsy. Korean Journal of Urology 2011; **52:** 452.
19. Kim SJ, Lee, J, An, DH et al: A randomized controlled comparison between periprostatic nerve block and pelvic plexus block at the base and apex of 14-core prostate biopsies. World J Urol 2019; **37:** 2663.
20. Klein T, Palisaar, RJ, Holz, A et al: The impact of prostate biopsy and periprostatic nerve block on erectile and voiding function: a prospective study. In: Journal of urology, vol. 184, pp. 1447, 2010

21. Knobloch R, Weber, J, Varga, Z et al: Bilateral fine-needle administered local anaesthetic nerve block for pain control during TRUS-guided multi-core prostate biopsy: a prospective randomised trial. In: European urology, vol. 41, pp. 508, 2002
22. Kravchick S, Peled, R, Ben-Dor, D et al: Comparison of different local anesthesia techniques during TRUS-guided biopsies: A prospective pilot study. Urology 2005; **65:** 109.
23. Kucur M, Goktas, S, Kaynar, M et al: Selective Low-Dose Spinal Anesthesia for Transrectal Prostate Biopsy: A Prospective and Randomized Study. Journal of endourology / Endourological Society 2015; **29:** 1412.
24. Kuppusamy S, Faizal, N, Quek, KF et al: The efficacy of periprostatic local anaesthetic infiltration in transrectal ultrasound biopsy of prostate: A prospective randomised control study. World Journal of Urology 2010; **28:** 673.
25. Li X, Qiu, M: Lidocaine Hydrochloride Injection preventing pain in patients who underwent transrectal ultrasound-guided prostate biopsy: A single center, prospective, randomized single-blind, placebo-controlled clinical trial. Chinese Journal of Andrology 2009; **23:** 25.
26. Liu BQ, Wang, ZY, Wei, JX et al: [Comparison of three different methods of anesthesia during transrectal ultrasound guided prostate biopsy: a prospective, double-blind, randomized trial.]. Zhonghua Wai Ke Za Zhi 2009; **47:** 1651.
27. Mallick S, Braud, F, Fofana, M et al: Which anaesthesia should be recommended for prostate biopsy? West Indian Medical Journal 2005; **54:** 135.
28. Mazdak H, Abtahi, AM, Momeni, F et al: A comparison of pain control and complications using three different ways of anesthesia in patients undergoing transrectal ultrasound-guided prostate biopsy. Journal of Research in Medical Sciences 2018; **23:** 17.
29. Medina Marquez C, Cadena Gonzalez, Y, Guerra Garzon, A et al: Comparison of the use of local anaesthetic versus lidocaine injection under ultrasound guide for the pain control in patients undergoing prostate biopsy. Actas urologicas espanolas 2006; **30:** 987.
30. Obek C, Onal, B, Ozkan, B et al: Is periprostatic local anesthesia for transrectal ultrasound guided prostate biopsy associated with increased infectious or hemorrhagic complications? A prospective randomized trial. Journal of Urology 2002; **168:** 558.
31. Park SM, Hong, SJ, Roh, SH: The effects of combination of intrarectal lidocaine-gel with periprostatic lidocaine injection on the pain relief in repeated transrectal prostate biopsy. [Korean]. In: Korean journal of urology, vol. 46, pp. 1051, 2005
32. Ragavan N, Philip, J, Balasubramanian, SP et al: A randomized, controlled trial comparing lidocaine periprostatic nerve block, diclofenac suppository and both for transrectal ultrasound guided biopsy of prostate. J Urol 2005; **174:** 510.
33. Sataa S, Ramzi, M, Mohamed, C et al: [Local anesthesia in transrectal ultrasound-guided prostate biopsy: apical periprostatic nerve block versus endorectal lidocaine gel. A randomized controlled trial of 100 patients]. In: La Tunisie médicale, vol. 88, pp. 217, 2010
34. Seymour H, Perry, MJ, Lee-Elliot, C et al: Pain after transrectal ultrasonography-guided prostate biopsy: the advantages of periprostatic local anaesthesia. BJU Int 2001; **88:** 540.
35. Song SH, Kim, JK, Song, K et al: Effectiveness of local anaesthesia techniques in patients undergoing transrectal ultrasound-guided prostate biopsy: A prospective randomized study. International Journal of Urology 2006; **13:** 707.
36. Szlauer R, Gotschl, R, Gnad, A et al: Comparison of lidocaine suppositories and periprostatic nerve block during transrectal prostate biopsy. Urologia Internationalis 2008; **80:** 253.
37. Tobias Machado M, Aragao, AJ, Rodrigues, AO et al: Periprostatic local anesthesia in transrectal ultrasound-guided prostate biopsy: Is it possible to improve pain tolerance? International Braz J Urol 2002; **28:** 323.
38. Tobias-Machado M, Verotti, MJ, Aragao, AJ et al: Prospective randomized controlled trial comparing three different ways of anesthesia in transrectal ultrasound-guided prostate biopsy. International Braz J Urol 2006; **32:** 172.
39. Trucchi A, Nunzio, C, Mariani, S et al: Local anesthesia reduces pain associated with transrectal prostatic biopsy. A prospective randomized study. In: Urologia internationalis, vol. 74, pp. 209, 2005
40. Wang N, Fu, Y, Ma, H et al: Advantages of caudal block over intrarectal local anesthesia plus periprostatic nerve block for transrectal ultrasound guided prostate biopsy. Pakistan Journal of Medical Sciences 2016; **32:** July.
41. Xu N, Xue, XY, Li, XD et al: Meperidine relieves pain during transrectal ultrasound-guided prostate biopsy. Saudi Medical Journal 2014; **35:** 454.

42. Akan H, Yildiz, O, Dalva, I et al: Comparison of two periprostatic nerve blockade techniques for transrectal ultrasound-guided prostate biopsy: bilateral basal injection and single apical injection. In: Urology, vol. 73, pp. 23, 2009
43. Cevik I, Dillioglugil, O, Zisman, A et al: Combined "periprostatic and periapical" local anesthesia is not superior to "periprostatic" anesthesia alone in reducing pain during Tru-Cut prostate biopsy. In: Urology, vol. 68, pp. 1215, 2006
44. Ould Ismail T, Janane, A, Dakkak, Y et al: The contribution of periapical nerve block in transrectal ultrasound-guided prostate biopsy: Results from a prospective randomized trial. In: African Journal of Urology, vol. 18, pp. 78, 2012
45. Ozden E, Yaman, O, Gogus, C et al: The optimum doses of and injection locations for periprostatic nerve blockade for transrectal ultrasound guided biopsy of the prostate: a prospective, randomized, placebo controlled study. J Urol 2003; **170:** 2319.
46. Toi A, Yang, R, Moshonov, H et al: Does the addition of apical injection of local anesthesia to basal injection diminish pain related to transrectal ultrasound guided prostate biopsy? Journal of Urology 2012; **Conference:** 2012 Annual Meeting of the American Urological Association.
47. Xu N, Xue, XY, Li, XD et al: Diagnostic value of transrectal ultrasound-guided saturation prostate biopsy after initial negative result. Chinese Journal of Interventional Imaging and Therapy 2012; **9:** 648.
48. Sur RL, Borboroglu, PG, Roberts, JL et al: A prospective randomized comparison of extensive prostate biopsy to standard biopsy with assessment of diagnostic yield, biopsy pain and morbidity. Prostate Cancer and Prostatic Diseases 2004; **7:** 126.
49. Rodríguez-Covarrubias F, González-Ramírez, A, Aguilar-Davidov, B et al: Extended sampling at first biopsy improves cancer detection rate: results of a prospective, randomized trial comparing 12 versus 18-core prostate biopsy. In: Journal of urology, vol. 185, pp. 2132, 2011
50. Pontes J, Melo, PAS, Rodrigues, RN et al: A prospective randomized controlled trial to compare the outcomes of 12 versus 20 core ultrasound guided transrectal prostate biopsy. Journal of Urology 2017; **197:** e484.
51. Paul R, Scholer, S, Van Randenborgh, H et al: Morbidity of prostatic biopsy for different biopsy strategies: Is there a relation to core number and sampling region? European Urology 2004; **45:** 450.
52. Naughton CK, Ornstein, DK, Smith, DS et al: Pain and morbidity of transrectal ultrasound guided prostate biopsy: a prospective randomized trial of 6 versus 12 cores. In: Journal of urology, vol. 163, pp. 168, 2000
53. Mariappan P, Chong, WL, Sundram, M et al: Increasing prostate biopsy cores based on volume vs the sextant biopsy: A prospective randomized controlled clinical study on cancer detection rates and morbidity. BJU International 2004; **94:** 307.
54. Lecuona A, Heyns, CF: A prospective, randomized trial comparing the Vienna nomogram to an eight-core prostate biopsy protocol. BJU International 2011; **108:** 204.
55. Irani J, Blanchet, P, Salomon, L et al: Is an extended 20-core prostate biopsy protocol more efficient than the standard 12-core? A randomized multicenter trial. In: Journal of urology, vol. 190, pp. 77, 2013
56. Emiliozzi P, Scarpone, P, DePaula, F et al: The incidence of prostate cancer in men with prostate specific antigen greater than 4.0 ng/ml: a randomized study of 6 versus 12 core transperineal prostate biopsy. J Urol 2004; **171:** 197.
57. Udeh EI, Amu, OC, Nnabugwu, II et al: Transperineal versus transrectal prostate biopsy: our findings in a tertiary health institution. Nigerian journal of clinical practice 2015; **18:** 110.
58. Singh S, Dorairajan, LN, Manikandan, R et al: Comparison of infective complications in transperineal versus transrectal ultrasound guided prostatic biopsy in patients suspected to have prostate cancer. Indian Journal of Urology 2017; **33:**
59. Hara R, Jo, Y, Fujii, T et al: Prostatic biopsy at Kawasaki Medical School: A prospective study of the results of transperineal biopsy over the past 13 years and the results of systematic 12-site biopsy using the transperineal and transrectal methods. Nishinihon Journal of Urology 2006; **68:** 403.
60. Guo LH, Wu, R, Xu, HX et al: Comparison between Ultrasound Guided Transperineal and Transrectal Prostate Biopsy: A Prospective, Randomized, and Controlled Trial. Scientific reports 2015; **5:** 16089.
61. Chae Y, Kim, Y-J, Kim, T et al: The Comparison between Transperineal and Transrectal Ultrasound-Guided Prostate Needle Biopsy. Korean J Urol 2009; **50:** 119.
62. Cerruto MA, Vianello, F, D'Elia, C et al: Transrectal versus transperineal 14-core prostate biopsy in detection of prostate cancer: a comparative evaluation at the same institution. Archivio italiano di urologia, andrologia : organo ufficiale [di] Societa italiana di ecografia urologica e nefrologica / Associazione ricerche in urologia 2014; **86:** 284.

63. Yu L, Ma, L, Yu, H: Impact of insertion timing of iodophor cotton ball on the control of infection complications after transrectal ultrasound guided prostate biopsy. National Medical Journal of China 2014; **94:** 609.
64. Taher Y, Akdogan, B, Ozen, H et al: Prospective randomized controlled study to assess the effect of perineal region cleansing with povidone iodine before transrectal needle biopsy of the prostate on infectious complications. In: Urology, vol. 84, p. S306, 2014
65. Salomon G, Prues, S, Saul, J et al: Antimicrobial Lubricant Did Not Reduce Infection Rate in Transrectal Biopsy Patients in a Large Randomized Trial Due to Low Complication Rates. Eur Urol Focus 2019; **5:** 992.
66. Koc G, Un, S, Filiz, DN et al: Does washing the biopsy needle with povidone-iodine have an effect on infection rates after transrectal prostate needle biopsy? Urologia Internationalis 2010; **85:** 147.
67. Inal GH, Oztekin, VC, Ugurlu, O et al: Sixteen gauge needles improve specimen quality but not cancer detection rate in transrectal ultrasound-guided 10-core prostate biopsies. Prostate Cancer and Prostatic Diseases 2008; **11:** 270.
68. De Nunzio C, Lombardo, R, Presicce, F et al: Transrectal-ultrasound prostatic biopsy preparation: Rectal enema vs. mechanical bowel preparation. Central European Journal of Urology 2015; **68:** 223.
69. Costa F, Pontes, J, Albertini, A et al: A randomized controlled trial to investigate the infectious outcomes of intrarectal povidone-iodine cleansing plus formalin disinfection of needle tip during transrectal ultrasound guided prostate biopsy. Journal of Urology 2019; **201:** e271.
70. Bolat D, Degirmenci, T, Gunlusoy, B et al: A Novel Pain Alternative for Patients with Anorectal Pathologies: The Comparison of Transperineal Prostatic Blockage Technique with Periprostatic Nerve Blockage and Rectal Gel Technique in Initial Transrectal Ultrasound-Guided Prostate Biopsy - A Prospective, Randomized Trial. Urologia Internationalis 2016; **97:** 416.
71. Bingqian L, Peihuan, L, Yudong, W et al: Intraprostatic Local Anesthesia With Periprostatic Nerve Block for Transrectal Ultrasound Guided Prostate Biopsy. Journal of Urology 2009; **182:** 479.
72. Sharpe JR, Sadlowski, RW, Finney, RP et al: Urinary tract infection after transrectal needle biopsy of the prostate. J Urol 1982; **127:** 255.
73. Ryu H, Song, SH, Lee, SE et al: A prospective randomized trial of povidone-iodine suppository before transrectal ultrasonography-guided prostate biopsy. Medicine 2019; **98:** e14854.
74. Lindert KA, Kabalin, JN, Terris, MK: Bacteremia and bacteriuria after transrectal ultrasound guided prostate biopsy. Journal of Urology 2000; **164:** 76.
75. Kanjanawongdeengam P, Viseshsindh, W, Santanirand, P et al: Reduction in bacteremia rates after rectum sterilization before transrectal, ultrasound-guided prostate biopsy: a randomized controlled trial. In: Chotmaihet thangphaet [Journal of the Medical Association of Thailand], vol. 92, pp. 1621, 2009
76. Herrera-Caceres JO, Del Moral, S, Villeda-Sandoval, C et al: Utility of enemas before transrectal prostate biopsies: Preliminary report. Journal of Urology 2015; **Conference:** 2015 Annual Meeting of the American Urological Association.
77. Ghafoori M, Shakiba, M, Seifmanesh, H et al: Decrease in infection rate following use of povidone-iodine during transrectal ultrasound guided biopsy of the prostate: a double blind randomized clinical trial. Iranian Journal of Radiology 2012; **9:** 67.
78. Cadilhe J: Transrectal prostate biopsy after prophylatic preparation of the rectum with povidone-iodine-a prospective randomized trial. Journal of Urology 2017; **197:** e143.
79. Abughosh Z, Margolick, J, Goldenberg, SL et al: A prospective randomized trial of povidone-iodine prophylactic cleansing of the rectum before transrectal ultrasound guided prostate biopsy. In: Journal of urology, vol. 189, pp. 1326, 2013
80. Novella G, Ficarra, V, Galfano, A et al: Pain assessment after original transperineal prostate biopsy using a coaxial needle. Urology 2003; **62:** 689.
81. Babaei Jandaghi A, Habibzadeh, H, Falahatkar, S et al: Transperineal Prostate Core Needle Biopsy: A Comparison of Coaxial Versus Noncoaxial Method in a Randomised Trial. CardioVascular and Interventional Radiology 2016; **39:** 1736.
82. Tuncel A, Aslan, Y, Sezgin, T et al: Does disposable needle guide minimize infectious complications after transrectal prostate needle biopsy? In: Urology, vol. 71, pp. 1024, 2008
83. Gurbuz C, Canat, L, Atis, G et al: Reducing infectious complications after transrectal prostate needle biopsy using a disposable needle guide: is it possible? In: International braz j urol : official journal of the Brazilian Society of Urology, vol. 37, pp. 79, 2011
84. Wegelin O, Exterkate, L, van der Leest, M et al: Complications and Adverse Events of Three Magnetic Resonance Imaging-based Target Biopsy Techniques in the Diagnosis of Prostate Cancer Among Men with

Prior Negative Biopsies: Results from the FUTURE Trial, a Multicentre Randomised Controlled Trial. Eur Urol Oncol 2019; **2:** 617.
85. Tekdogan U, Tuncel, A, Eroglu, M et al: The efficiency of prophylactic antibiotic treatment in patients without risk factor who underwent transrectal. Turk Uroloji Dergisi 2006; **32:** 261.
86. Su R, Wang, KY, Zhang, D et al: Comparison of levofloxacin-based prophylaxis regimens for transrectal prostate biopsy: a prospective randomized single-center study. Eur J Clin Microbiol Infect Dis 2019; **38:** 967.
87. Melekos MD: Efficacy of prophylactic antimicrobial regimens in preventing infectious complications after transrectal biopsy of the prostate. International Urology and Nephrology 1990; **22:** 257.
88. Brown RW, Warner, JJ, Turner, BI et al: Bacteremia and bacteriuria after transrectal prostatic biopsy. Urology 1981; **18:** 145.
89. Ergani B, Cetin, T, Yalcin, MY et al: Effect of rectal mucosa cleansing on acute prostatitis during prostate biopsy: A randomized prospective study. Turk J Urol 2020; **46:** 159.
90. Bas E: Can smaller needle size in prostate biopsy reduce complications without affecting cancer detection rates? Bulletin of Urooncology 2019; **18:** 381.

Intervention 1: Impact of biopsy route

1. Cerruto MA, Vianello, F, D'Elia, C et al: Transrectal versus transperineal 14-core prostate biopsy in detection of prostate cancer: a comparative evaluation at the same institution. Archivio italiano di urologia, andrologia : organo ufficiale [di] Societa italiana di ecografia urologica e nefrologica / Associazione ricerche in urologia 2014; **86:** 284.
2. Chae Y, Kim, Y-J, Kim, T et al: The Comparison between Transperineal and Transrectal Ultrasound-Guided Prostate Needle Biopsy. Korean J Urol 2009; **50:** 119.
3. Guo LH, Wu, R, Xu, HX et al: Comparison between Ultrasound Guided Transperineal and Transrectal Prostate Biopsy: A Prospective, Randomized, and Controlled Trial. Scientific reports 2015; **5:** 16089.
4. Hara R, Jo, Y, Fujii, T et al: Prostatic biopsy at Kawasaki Medical School: A prospective study of the results of transperineal biopsy over the past 13 years and the results of systematic 12-site biopsy using the transperineal and transrectal methods. Nishinihon Journal of Urology 2006; **68:** 403.
5. Singh S, Dorairajan, LN, Manikandan, R et al: Comparison of infective complications in transperineal versus transrectal ultrasound guided prostatic biopsy in patients suspected to have prostate cancer. Indian Journal of Urology 2017; **33:**
6. Udeh EI, Amu, OC, Nnabugwu, II et al: Transperineal versus transrectal prostate biopsy: our findings in a tertiary health institution. Nigerian journal of clinical practice 2015; **18:** 110.
7. Wegelin O, Exterkate, L, van der Leest, M et al: Complications and Adverse Events of Three Magnetic Resonance Imaging-based Target Biopsy Techniques in the Diagnosis of Prostate Cancer Among Men with Prior Negative Biopsies: Results from the FUTURE Trial, a Multicentre Randomised Controlled Trial. Eur Urol Oncol 2019; **2:** 617.

Intervention 2: Impact of number of biopsy cores

1. Emiliozzi P, Scarpone, P, DePaula, F et al: The incidence of prostate cancer in men with prostate specific antigen greater than 4.0 ng/ml: a randomized study of 6 versus 12 core transperineal prostate biopsy. J Urol 2004; **171:** 197.
2. Irani J, Blanchet, P, Salomon, L et al: Is an extended 20-core prostate biopsy protocol more efficient than the standard 12-core? A randomized multicenter trial. In: Journal of urology, vol. 190, pp. 77, 2013
3. Lecuona A, Heyns, CF: A prospective, randomized trial comparing the Vienna nomogram to an eight-core prostate biopsy protocol. BJU International 2011; **108:** 204.
4. Mariappan P, Chong, WL, Sundram, M et al: Increasing prostate biopsy cores based on volume vs the sextant biopsy: A prospective randomized controlled clinical study on cancer detection rates and morbidity. BJU International 2004; **94:** 307.
5. Naughton CK, Ornstein, DK, Smith, DS et al: Pain and morbidity of transrectal ultrasound guided prostate biopsy: a prospective randomized trial of 6 versus 12 cores. In: Journal of urology, vol. 163, pp. 168, 2000
6. Paul R, Scholer, S, Van Randenborgh, H et al: Morbidity of prostatic biopsy for different biopsy strategies: Is there a relation to core number and sampling region? European Urology 2004; **45:** 450.

7. Pontes J, Melo, PAS, Rodrigues, RN et al: A prospective randomized controlled trial to compare the outcomes of 12 versus 20 core ultrasound guided transrectal prostate biopsy. Journal of Urology 2017; **197:** e484.
8. Rodríguez-Covarrubias F, González-Ramírez, A, Aguilar-Davidov, B et al: Extended sampling at first biopsy improves cancer detection rate: results of a prospective, randomized trial comparing 12 versus 18-core prostate biopsy. In: Journal of urology, vol. 185, pp. 2132, 2011
9. Sur RL, Borboroglu, PG, Roberts, JL et al: A prospective randomized comparison of extensive prostate biopsy to standard biopsy with assessment of diagnostic yield, biopsy pain and morbidity. Prostate Cancer and Prostatic Diseases 2004; **7:** 126.
10. Wegelin O, Exterkate, L, van der Leest, M et al: Complications and Adverse Events of Three Magnetic Resonance Imaging-based Target Biopsy Techniques in the Diagnosis of Prostate Cancer Among Men with Prior Negative Biopsies: Results from the FUTURE Trial, a Multicentre Randomised Controlled Trial. Eur Urol Oncol 2019; **2:** 617.
11. Xu N, Xue, XY, Li, XD et al: Diagnostic value of transrectal ultrasound-guided saturation prostate biopsy after initial negative result. Chinese Journal of Interventional Imaging and Therapy 2012; **9:** 648.

Intervention 3: Impact of periprostatic nerve block

1. Adamakis I, Mitropoulos, D, Haritopoulos, K et al: Pain during transrectal ultrasonography guided prostate biopsy: a randomized prospective trial comparing periprostatic infiltration with lidocaine with the intrarectal instillation of lidocaine-prilocain cream. World journal of urology 2004; **22:** 281.
2. Aktoz T, Kaplan, M, Turan, U et al: 'Multimodal' approach to management of prostate biopsy pain and effects on sexual function: Efficacy of levobupivacaine adjuvant to diclofenac sodium - A prospective randomized trial. Andrologia 2010; **42:** 35.
3. Alavi AS, Soloway, MS, Vaidya, A et al: Local anesthesia for ultrasound guided prostate biopsy: a prospective randomized trial comparing 2 methods. In: Journal of urology, vol. 166, pp. 1343, 2001
4. Atta H, Mostafa, M, Shalaby, M: Which is better for pain reduction during transrectal ultrasound-guided biopsy of the prostate: Intravenous diazepam, local periprostatic nerve block, or combination? controlled randomized study. Saudi Journal of Anaesthesia 2018; **12:** 16.
5. Basar MM, Ozcan, S, Akpinar, S et al: Local anesthesia in transrectal ultrasound-guided prostate biopsy: EMLA cream as a new alternative technique. Scandinavian Journal of Urology and Nephrology 2005; **39:** 130.
6. Bolat MS, Cinar, O, Asci, R et al: A novel method for pain control: infiltration free local anesthesia technique (INFLATE) for transrectal prostatic biopsy using transcutaneous electrical nerve stimulation (TENS). International Urology and Nephrology 2019;
7. Cormio L, Pagliarulo, V, Lorusso, F et al: Combined perianal-intrarectal (PI) lidocaine-prilocaine (LP) cream and lidocaine-ketorolac gel provide better pain relief than combined PI LP cream and periprostatic nerve block during transrectal prostate biopsy. In: BJU international, vol. 109, pp. 1776, 2012
8. Giannarini G, Autorino, R, Valent, F et al: Combination of Perianal-Intrarectal Lidocaine-Prilocaine Cream and Periprostatic Nerve Block for Pain Control During Transrectal Ultrasound Guided Prostate Biopsy: A Randomized, Controlled Trial. Journal of Urology 2009; **181:** 585.
9. Gurbuz C, Canat, L, Bayram, G et al: Visual pain score during transrectal ultrasound-guided prostate biopsy using no anaesthesia or three different types of local anaesthetic application. Scandinavian Journal of Urology and Nephrology 2010; **44:** 212.
10. Hetta WM, Niazi, G, Elfawy, D: Local anesthesia by periprostatic block in transrectal ultrasound guided prostatic biopsy. Egyptian Journal of Radiology and Nuclear Medicine 2014; **45:** 137.
11. Hiros M, Selimovic, M, Spahovic, H et al: Transrectal ultrasound-guided prostate biopsy, periprostatic local anesthesia and pain tolerance. Bosnian Journal of Basic Medical Sciences 2010; **10:** 68.
12. Inal G, Yazici, S, Adsan, O et al: Periprostatic nerve blockade before transrectal ultrasound-guided prostate biopsy: the Ankara Numune experience. Urologia Internationalis 2003; **71:** 165.
13. Inal G, Yazici, S, Kosan, M et al: Comparison of 2 ml and 6 ml of periprostatic 1% lidocaine injections before transrectal ultrasound guided prostate biopsy. Turk Uroloji Dergisi 2004; **30:** 173.
14. Izol V, Soyupak, B, Seydaoglu, G et al: Three different techniques for administering analgesia during transrectal ultrasound-guided prostate biopsy: A comparative study. International Braz J Urol 2012; **38:** 122.

15. Jindal T, Mukherjee, S, Sinha, RK et al: Transrectal ultrasonography (TRUS)-guided pelvic plexus block to reduce pain during prostate biopsy: A randomised controlled trial. BJU International 2015; **115:** 892.
16. Jones JS, Ulchaker, JC, Nelson, D et al: Periprostatic local anesthesia eliminates pain of office-based transrectal prostate biopsy. Prostate cancer and prostatic diseases 2003; **6:** 53.
17. Kang KS, Yeo, JK, Park, MG et al: Efficacy of periprostatic anesthesia according to lidocaine dose during transrectal ultrasound-guided biopsy of the prostate. Korean Journal of Urology 2012; **53:** 750.
18. Kim S, Yoon, BI, Kim, SJ et al: Effect of oral administration of acetaminophen and topical application of emla on pain during transrectal ultrasound- guided prostate biopsy. Korean Journal of Urology 2011; **52:** 452.
19. Kim SJ, Lee, J, An, DH et al: A randomized controlled comparison between periprostatic nerve block and pelvic plexus block at the base and apex of 14-core prostate biopsies. World journal of urology 2019;
20. Klein T, Palisaar, RJ, Holz, A et al: The impact of prostate biopsy and periprostatic nerve block on erectile and voiding function: a prospective study. In: Journal of urology, vol. 184, pp. 1447, 2010
21. Knobloch R, Weber, J, Varga, Z et al: Bilateral fine-needle administered local anaesthetic nerve block for pain control during TRUS-guided multi-core prostate biopsy: a prospective randomised trial. In: European urology, vol. 41, pp. 508, 2002
22. Kravchick S, Peled, R, Ben-Dor, D et al: Comparison of different local anesthesia techniques during TRUS-guided biopsies: A prospective pilot study. Urology 2005; **65:** 109.
23. Kucur M, Goktas, S, Kaynar, M et al: Selective Low-Dose Spinal Anesthesia for Transrectal Prostate Biopsy: A Prospective and Randomized Study. Journal of endourology / Endourological Society 2015; **29:** 1412.
24. Kuppusamy S, Faizal, N, Quek, KF et al: The efficacy of periprostatic local anaesthetic infiltration in transrectal ultrasound biopsy of prostate: A prospective randomised control study. World Journal of Urology 2010; **28:** 673.
25. Li X, Qiu, M: Lidocaine Hydrochloride Injection preventing pain in patients who underwent transrectal ultrasound-guided prostate biopsy: A single center, prospective, randomized single-blind, placebo-controlled clinical trial. Chinese Journal of Andrology 2009; **23:** 25.
26. Liu BQ, Wang, ZY, Wei, JX et al: [Comparison of three different methods of anesthesia during transrectal ultrasound guided prostate biopsy: a prospective, double-blind, randomized trial.]. Zhonghua Wai Ke Za Zhi 2009; **47:** 1651.
27. Mallick S, Braud, F, Fofana, M et al: Which anaesthesia should be recommended for prostate biopsy? West Indian Medical Journal 2005; **54:** 135.
28. Mazdak H, Abtahi, AM, Momeni, F et al: A comparison of pain control and complications using three different ways of anesthesia in patients undergoing transrectal ultrasound-guided prostate biopsy. Journal of Research in Medical Sciences 2018; **23:** 17.
29. Medina Marquez C, Cadena Gonzalez, Y, Guerra Garzon, A et al: Comparison of the use of local anaesthetic versus lidocaine injection under ultrasound guide for the pain control in patients undergoing prostate biopsy. Actas urologicas espanolas 2006; **30:** 987.
30. Obek C, Onal, B, Ozkan, B et al: Is periprostatic local anesthesia for transrectal ultrasound guided prostate biopsy associated with increased infectious or hemorrhagic complications? A prospective randomized trial. Journal of Urology 2002; **168:** 558.
31. Park SM, Hong, SJ, Roh, SH: The effects of combination of intrarectal lidocaine-gel with periprostatic lidocaine injection on the pain relief in repeated transrectal prostate biopsy. [Korean]. In: Korean journal of urology, vol. 46, pp. 1051, 2005
32. Ragavan N, Philip, J, Balasubramanian, SP et al: A randomized, controlled trial comparing lidocaine periprostatic nerve block, diclofenac suppository and both for transrectal ultrasound guided biopsy of prostate. J Urol 2005; **174:** 510.
33. Sataa S, Ramzi, M, Mohamed, C et al: [Local anesthesia in transrectal ultrasound-guided prostate biopsy: apical periprostatic nerve block versus endorectal lidocaine gel. A randomized controlled trial of 100 patients]. In: La Tunisie médicale, vol. 88, pp. 217, 2010
34. Seymour H, Perry, MJ, Lee-Elliot, C et al: Pain after transrectal ultrasonography-guided prostate biopsy: the advantages of periprostatic local anaesthesia. BJU Int 2001; **88:** 540.
35. Song SH, Kim, JK, Song, K et al: Effectiveness of local anaesthesia techniques in patients undergoing transrectal ultrasound-guided prostate biopsy: A prospective randomized study. International Journal of Urology 2006; **13:** 707.
36. Szlauer R, Gotschl, R, Gnad, A et al: Comparison of lidocaine suppositories and periprostatic nerve block during transrectal prostate biopsy. Urologia Internationalis 2008; **80:** 253.

37. Tobias Machado M, Aragao, AJ, Rodrigues, AO et al: Periprostatic local anesthesia in transrectal ultrasound-guided prostate biopsy: Is it possible to improve pain tolerance? International Braz J Urol 2002; **28:** 323.
38. Tobias-Machado M, Verotti, MJ, Aragao, AJ et al: Prospective randomized controlled trial comparing three different ways of anesthesia in transrectal ultrasound-guided prostate biopsy. International Braz J Urol 2006; **32:** 172.
39. Trucchi A, Nunzio, C, Mariani, S et al: Local anesthesia reduces pain associated with transrectal prostatic biopsy. A prospective randomized study. In: Urologia internationalis, vol. 74, pp. 209, 2005
40. Wang N, Fu, Y, Ma, H et al: Advantages of caudal block over intrarectal local anesthesia plus periprostatic nerve block for transrectal ultrasound guided prostate biopsy. Pakistan Journal of Medical Sciences 2016; **32:** July.
41. Xu N, Xue, XY, Li, XD et al: Meperidine relieves pain during transrectal ultrasound-guided prostate biopsy. Saudi Medical Journal 2014; **35:** 454.

Intervention 4: Impact of number of injections for periprostatic nerve block

1. Akan H, Yildiz, O, Dalva, I et al: Comparison of two periprostatic nerve blockade techniques for transrectal ultrasound-guided prostate biopsy: bilateral basal injection and single apical injection. In: Urology, vol. 73, pp. 23, 2009
2. Cevik I, Dillioglugil, O, Zisman, A et al: Combined "periprostatic and periapical" local anesthesia is not superior to "periprostatic" anesthesia alone in reducing pain during Tru-Cut prostate biopsy. In: Urology, vol. 68, pp. 1215, 2006
3. Kuppusamy S, Faizal, N, Quek, KF et al: The efficacy of periprostatic local anaesthetic infiltration in transrectal ultrasound biopsy of prostate: A prospective randomised control study. World Journal of Urology 2010; **28:** 673.
4. Ould Ismail T, Janane, A, Dakkak, Y et al: The contribution of periapical nerve block in transrectal ultrasound-guided prostate biopsy: Results from a prospective randomized trial. In: African Journal of Urology, vol. 18, pp. 78, 2012
5. Ozden E, Yaman, O, Gogus, C et al: The optimum doses of and injection locations for periprostatic nerve blockade for transrectal ultrasound guided biopsy of the prostate: a prospective, randomized, placebo controlled study. J Urol 2003; **170:** 2319.
6. Toi A, Yang, R, Moshonov, H et al: Does the addition of apical injection of local anesthesia to basal injection diminish pain related to transrectal ultrasound guided prostate biopsy? Journal of Urology 2012; **Conference:** 2012 Annual Meeting of the American Urological Association.

Intervention 5: Impact of disposable needle guides

1. Gurbuz C, Canat, L, Atis, G et al: Reducing infectious complications after transrectal prostate needle biopsy using a disposable needle guide: is it possible? In: International braz j urol : official journal of the Brazilian Society of Urology, vol. 37, pp. 79, 2011
2. Tuncel A, Aslan, Y, Sezgin, T et al: Does disposable needle guide minimize infectious complications after transrectal prostate needle biopsy? In: Urology, vol. 71, pp. 1024, 2008

Intervention 6: Impact of needle type

1. Babaei Jandaghi A, Habibzadeh, H, Falahatkar, S et al: Transperineal Prostate Core Needle Biopsy: A Comparison of Coaxial Versus Noncoaxial Method in a Randomised Trial. CardioVascular and Interventional Radiology 2016; **39:** 1736.
2. Novella G, Ficarra, V, Galfano, A et al: Pain assessment after original transperineal prostate biopsy using a coaxial needle. Urology 2003; **62:** 689.

Intervention 7: Impact of needle diameter

1. Bas E: Can smaller needle size in prostate biopsy reduce complications without affecting cancer detection rates? Bulletin of Urooncology 2019; **18:** 381.

2. Inal GH, Oztekin, VC, Ugurlu, O et al: Sixteen gauge needles improve specimen quality but not cancer detection rate in transrectal ultrasound-guided 10-core prostate biopsies. Prostate Cancer and Prostatic Diseases 2008; **11:** 270.

Intervention 8: Impact of rectal preparation with enema

1. Herrera-Caceres JO, Del Moral, S, Villeda-Sandoval, C et al: Utility of enemas before transrectal prostate biopsies: Preliminary report. Journal of Urology 2015; **Conference:** 2015 Annual Meeting of the American Urological Association.
2. Lindert KA, Kabalin, JN, Terris, MK: Bacteremia and bacteriuria after transrectal ultrasound guided prostate biopsy. Journal of Urology 2000; **164:** 76.
3. Su R, Wang, KY, Zhang, D et al: Comparison of levofloxacin-based prophylaxis regimens for transrectal prostate biopsy: a prospective randomized single-center study. European Journal of Clinical Microbiology and Infectious Diseases 2019;
4. Tekdogan U, Tuncel, A, Eroglu, M et al: The efficiency of prophylactic antibiotic treatment in patients without risk factor who underwent transrectal. Turk Uroloji Dergisi 2006; **32:** 261.

Intervention 9: Impact of rectal preparation with chlorhexidine

1. Ergani B, Cetin, T, Yalcin, MY et al: Effect of rectal mucosa cleansing on acute prostatitis during prostate biopsy: A randomized prospective study. Turk J Urol 2020; **46:** 159.
2. Salomon G, Prues, S, Saul, J et al: Antimicrobial Lubricant Did Not Reduce Infection Rate in Transrectal Biopsy Patients in a Large Randomized Trial Due to Low Complication Rates. Eur Urol Focus 2019; **5:** 992.

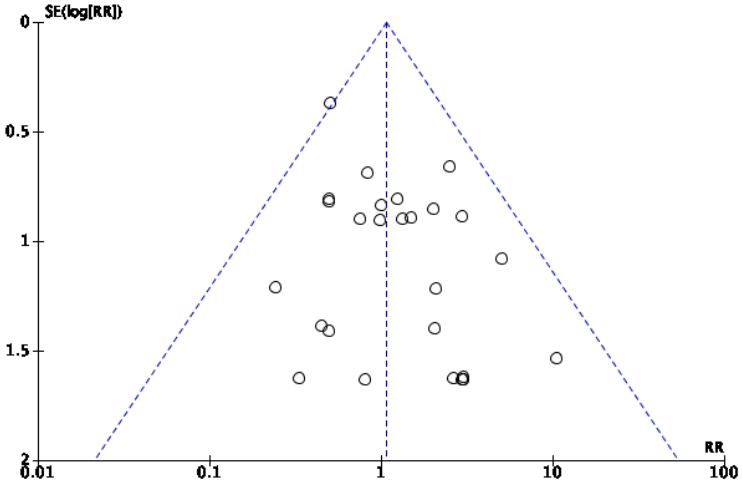
Intervention 10: Impact of rectal preparation with povidone-iodine

1. Abughosh Z, Margolick, J, Goldenberg, SL et al: A prospective randomized trial of povidone-iodine prophylactic cleansing of the rectum before transrectal ultrasound guided prostate biopsy. In: Journal of urology, vol. 189, pp. 1326, 2013
2. Brown RW, Warner, JJ, Turner, BI et al: Bacteremia and bacteriuria after transrectal prostatic biopsy. Urology 1981; **18:** 145.
3. Cadilhe J: Transrectal prostate biopsy after prophylatic preparation of the rectum with povidone-iodine-a prospective randomized trial. Journal of Urology 2017; **197:** e143.
4. Ergani B, Cetin, T, Yalcin, MY et al: Effect of rectal mucosa cleansing on acute prostatitis during prostate biopsy: A randomized prospective study. Turk J Urol 2020; **46:** 159.
5. Ghafoori M, Shakiba, M, Seifmanesh, H et al: Decrease in infection rate following use of povidone-iodine during transrectal ultrasound guided biopsy of the prostate: a double blind randomized clinical trial. Iranian Journal of Radiology 2012; **9:** 67.
6. Kanjanawongdeengam P, Viseshsindh, W, Santanirand, P et al: Reduction in bacteremia rates after rectum sterilization before transrectal, ultrasound-guided prostate biopsy: a randomized controlled trial. In: Chotmaihet thangphaet [Journal of the Medical Association of Thailand], vol. 92, pp. 1621, 2009
7. Melekos MD: Efficacy of prophylactic antimicrobial regimens in preventing infectious complications after transrectal biopsy of the prostate. International Urology and Nephrology 1990; **22:** 257.
8. Ryu H, Song, SH, Lee, SE et al: A prospective randomized trial of povidone-iodine suppository before transrectal ultrasonography-guided prostate biopsy. Medicine 2019; **98:** e14854.
9. Sharpe JR, Sadlowski, RW, Finney, RP et al: Urinary tract infection after transrectal needle biopsy of the prostate. J Urol 1982; **127:** 255.

Different unique interventions

1. Bingqian L, Peihuan, L, Yudong, W et al: Intraprostatic Local Anesthesia With Periprostatic Nerve Block for Transrectal Ultrasound Guided Prostate Biopsy. Journal of Urology 2009; **182:** 479.
2. Bolat D, Degirmenci, T, Gunlusoy, B et al: A Novel Pain Alternative for Patients with Anorectal Pathologies: The Comparison of Transperineal Prostatic Blockage Technique with Periprostatic Nerve Blockage and Rectal Gel Technique in Initial Transrectal Ultrasound-Guided Prostate Biopsy - A Prospective, Randomized Trial. Urologia Internationalis 2016; **97:** 416.
3. Costa F, Pontes, J, Albertini, A et al: A randomized controlled trial to investigate the infectious outcomes of intrarectal povidone-iodine cleansing plus formalin disinfection of needle tip during transrectal ultrasound guided prostate biopsy. Journal of Urology 2019; **201:** e271.
4. De Nunzio C, Lombardo, R, Presicce, F et al: Transrectal-ultrasound prostatic biopsy preparation: Rectal enema vs. mechanical bowel preparation. Central European Journal of Urology 2015; **68:** 223.
5. Koc G, Un, S, Filiz, DN et al: Does washing the biopsy needle with povidone-iodine have an effect on infection rates after transrectal prostate needle biopsy? Urologia Internationalis 2010; **85:** 147.
6. Taher Y, Akdogan, B, Ozen, H et al: Prospective randomized controlled study to assess the effect of perineal region cleansing with povidone iodine before transrectal needle biopsy of the prostate on infectious complications. In: Urology, vol. 84, p. S306, 2014
7. Yu L, Ma, L, Yu, H: Impact of insertion timing of iodophor cotton ball on the control of infection complications after transrectal ultrasound guided prostate biopsy. National Medical Journal of China 2014; **94:** 609.

Supplementary appendix 2:



Funnel plot of comparison: Intervention 3 - periprostatic nerve block vs. no periprostatic nerve block, outcome: Pooled infectious complications. Publication bias was not suspected as there is symmetrical scatter of the studies in the funnel plot.

Supplementary appendix 5: GRADE for the ten different interventions

Intervention 1

Summary of findings:

Transperineal compared to transrectal prostate biopsy for prevention of infectious complications following prostate biopsy

Patient or population: Prevention of infectious complications following prostate biopsy

Setting: Patients undergoing prostate biopsy

Intervention: Transperineal prostate biopsy

Comparison: Transrectal prostate biopsy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with transrectal prostate biopsy	Risk with Transperineal				
Pooled infectious complications	56 per 1,000	**31 per 1,000** (19 to 52)	**RR 0.55** (0.33 to 0.92)	1330 (7 RCTs)	⨁⨁◯◯ LOW [a]	Transperineal biopsy likely results in a reduction in pooled infectious complications.
Hospitalization	18 per 1,000	**7 per 1,000** (2 to 28)	**RR 0.38** (0.09 to 1.61)	685 (3 RCTs)	⨁◯◯◯ VERY LOW [a,b]	Transperineal biopsy probably results in little to no difference in hospitalization.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Risk of bias for random sequence generation, blinding, allocation concealment high/unclear in a number of included RCTs

b. 95% CI includes no effect and wide CI (0.09-1.61)

Intervention 2

Summary of findings:

Standard compared to extended number of biopsy cores for prevention of infectious complications following prostate biopsy

Patient or population: Prevention of infectious complications following prostate biopsy

Setting: Patients undergoing prostate biopsy

Intervention: Standard number of biopsy cores

Comparison: Extended number of biopsy cores

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with extended number of biopsy cores	**Risk with Standard**				
Pooled infectious complications	43 per 1,000	**34 per 1,000** (23 to 52)	**RR 0.80** (0.53 to 1.22)	2230 (9 RCTs)	⨁⨁◯◯ LOW [a,b]	The evidence suggests that using a standard compared to extended number of biopsy cores results in little to no difference in pooled infectious complications.
Hospitalization	10 per 1,000	**3 per 1,000** (0 to 21)	**RR 0.34** (0.05 to 2.13)	826 (5 RCTs)	⨁◯◯◯ VERY LOW [a,c]	A Standard (compared to extended) number of biopsy cores probably results in little to no difference in hospitalization.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Bias for allocation concealment, blinding of participants and outcome assessment mostly high/unclear

b. 95% CI includes no effect

c. Wide CI (0.05-2.13) and 95% CI included no effect

Intervention 3

Summary of findings:

Periprostatic nerve block compared to no periprostatic nerve block for prevention of infectious complications following prostate biopsy

Patient or population: Prevention of infectious complications following prostate biopsy

Setting: Patients undergoing prostate biopsy

Intervention: Periprostatic nerve block

Comparison: No periprostatic nerve block

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no periprostatic nerve block	**Risk with Periprostatic nerve block**				
Pooled infectious complications	25 per 1,000	**27 per 1,000** (19 to 37)	**RR 1.07** (0.77 to 1.48)	5540 (40 RCTs)	⨁◯◯◯ VERY LOW [a,b]	Periprostatic nerve block may result in little to no difference in pooled infectious complications.
Hospitalization	12 per 1,000	**14 per 1,000** (7 to 26)	**RR 1.13** (0.59 to 2.16)	2199 (14 RCTs)	⨁◯◯◯ VERY LOW [a,b]	The evidence suggests that periprostatic nerve block results in little to no difference in hospitalization.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Risk of bias for allocation concealment, blinding and random sequence generation unclear/high across most studies

b. 95% CI included no effect

Intervention 4

Summary of findings:

Standard compared to extended number of injections for periprostatic nerve block for prevention of infectious complications following prostate biopsy

Patient or population: Prevention of infectious complications following prostate biopsy

Setting: Patients undergoing prostate biopsy

Intervention: Standard number of injections for periprostatic nerve block

Comparison: Extended number of injections for periprostatic nerve block

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with extended number of injections for periprostatic nerve block	**Risk with Standard**				
Pooled infectious complications	9 per 1,000	**11 per 1,000** (3 to 41)	**RR 1.30** (0.35 to 4.76)	927 (6 RCTs)	⨁⨁◯◯ LOW [a,b]	Standard number of injections (compared to extended) may result in little to no difference in pooled infectious complications.
Hospitalization	13 per 1,000	**14 per 1,000** (2 to 96)	**RR 1.05** (0.15 to 7.32)	300 (2 RCTs)	⨁⨁◯◯ LOW [a,b]	Standard number of injections (compared to extended) may result in little to no difference in hospitalization

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. High and unclear risk of bias for blinding of participant, allocation concealment, outcomes

b. Wide CI and 95% CI overlaps no effect

Intervention 5

Summary of findings:

Disposable needle guide compared to reusable needle guide for prevention of infectious complications following prostate biopsy

Patient or population: Prevention of infectious complications following prostate biopsy

Setting: Patients undergoing prostate biopsy

Intervention: Disposable needle guide

Comparison: Reusable needle guide

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with reusable needle guide	**Risk with Disposable needle guide**				
Pooled infectious complications	157 per 1,000	**80 per 1,000** (38 to 167)	**RR 0.51** (0.24 to 1.06)	253 (2 RCTs)	⨁◯◯◯ VERY LOW [a,b]	Disposable needle guide may result in little to no difference in pooled infectious complications.
Hospitalization	64 per 1,000	**35 per 1,000** (11 to 112)	**RR 0.55** (0.17 to 1.74)	253 (2 RCTs)	⨁◯◯◯ VERY LOW [a,b]	The evidence suggests that disposable needle guide results in little to no difference in hospitalization.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Bias for random sequence generation, blinding of participants, blinding of outcome assessment high or unclear in one of 2 studies

b. 95% CI overlaps no effect

Intervention 6

No GRADE analysis performed, because no meta-analysis possible.

Intervention 7

No GRADE analysis performed, because no meta-analysis possible.

Intervention 8

Summary of findings:

Enema compared to no enema for prevention of infectious complications following prostate biopsy

Patient or population: Prevention of infectious complications following prostate biopsy

Setting: Patients undergoing prostate biopsy

Intervention: Rectal preparation with enema

Comparison: Rectal preparation without enema

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no enema	Risk with Enema				
Pooled infectious complications	93 per 1,000	**89 per 1,000** (56 to 142)	**RR 0.96** (0.60 to 1.53)	671 (4 RCTs)	⨁⨁◯◯ LOW a,b	Enema may result in little to no difference in pooled infectious complications.
Hospitalization	35 per 1,000	**39 per 1,000** (15 to 99)	**RR 1.13** (0.44 to 2.86)	462 (2 RCTs)	⨁⨁◯◯ LOW a,b	The evidence suggests that enema results in little to no difference in hospitalization.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. Bias for Blinding of participants, Blinding of outcome assessment, Allocation concealment and random sequence generation was mostly high or unclear in included RCTs

b. 95% CI overlaps no effect

Intervention 9

No GRADE analysis performed, because no meta-analysis possible.

Intervention 10

Summary of findings:

Povidone-iodine rectal preparation compared to no povidone-iodine rectal preparation for prevention of infectious complications following prostate biopsy

Patient or population: Prevention of infectious complications following prostate biopsy

Setting: Patients undergoing prostate biopsy

Intervention: Rectal preparation with povidone-iodine

Comparison: Rectal preparation without povidone-iodine

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no povidone-iodine rectal preparation	Risk with Povidone-iodine rectal preparation				
Pooled infectious complications	150 per 1,000	**75 per 1,000** (57 to 99)	**RR 0.50** (0.38 to 0.65)	1686 (8 RCTs)	⨁⨁◯◯ LOW [a]	Povidone-iodine rectal preparation likely results in a reduction in pooled infectious complications.
Hospitalization	110 per 1,000	**42 per 1,000** (26 to 93)	**RR 0.38** (0.21 to 0.69)	620 (4 RCTs)	⨁⨁◯◯ LOW [a,b]	Povidone-iodine rectal preparation probably reduces hospitalization.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

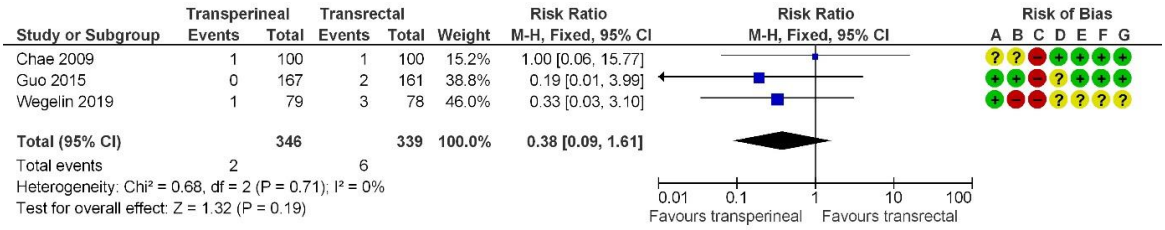
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

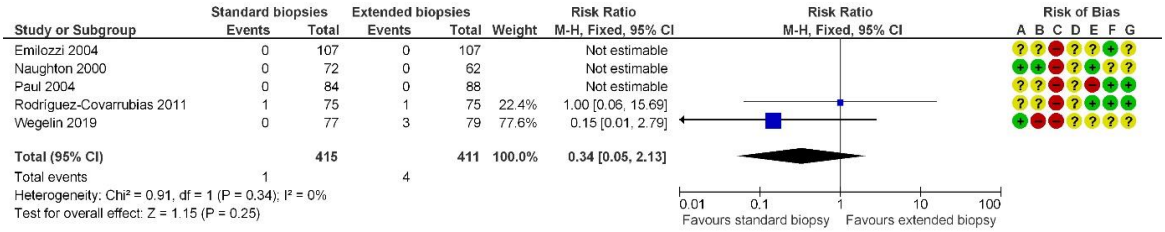
a. High and unclear risk of bias for blinding of participant, allocation concealment, outcomes

Supplementary Figures



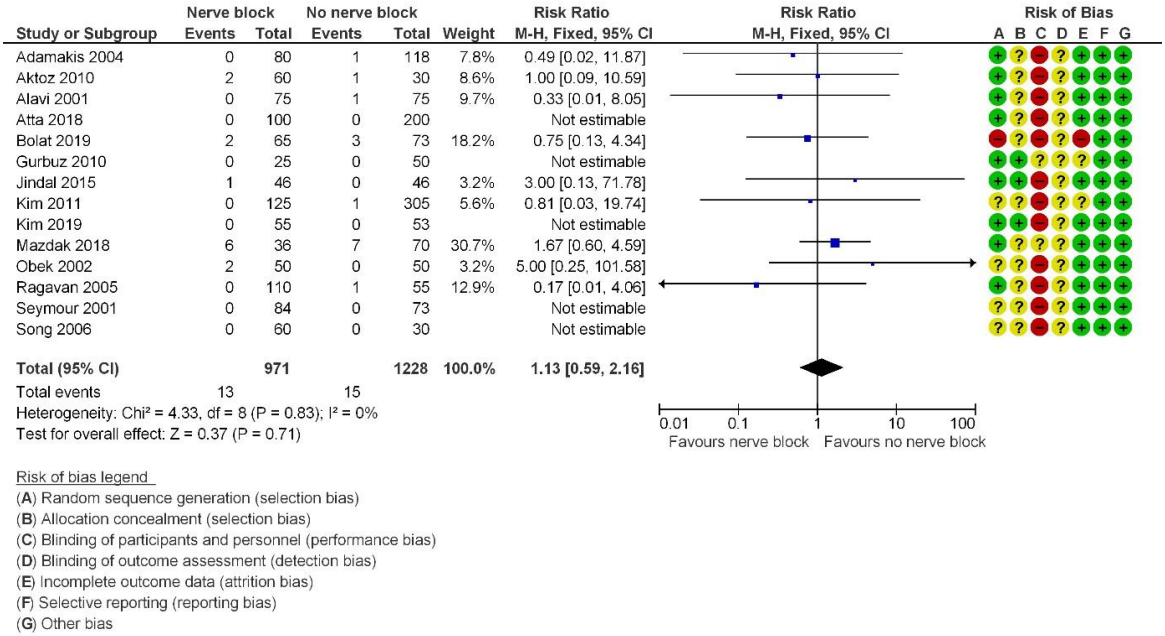
Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Supplementary Figure 1 – Comparison of transperineal to transrectal biopsy on hospitalization following prostate biopsy. CI = confidence interval; df = degrees of freedom.

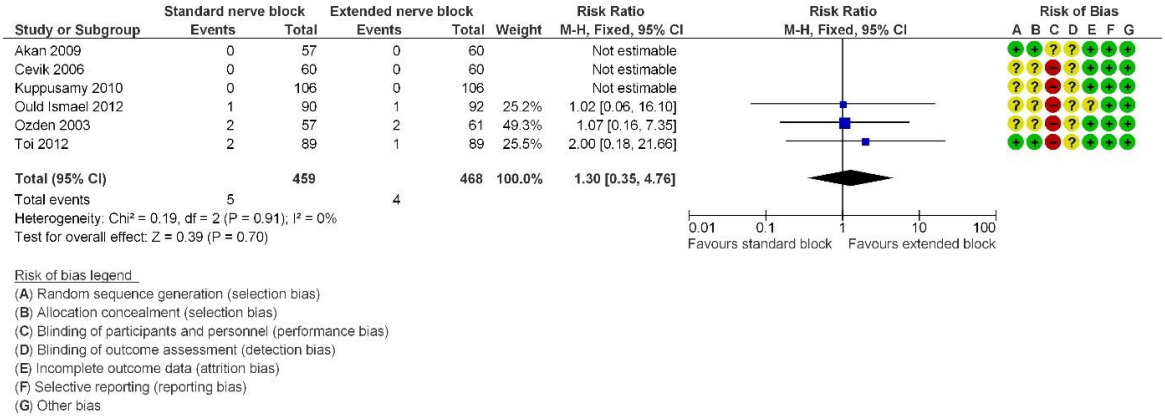


Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

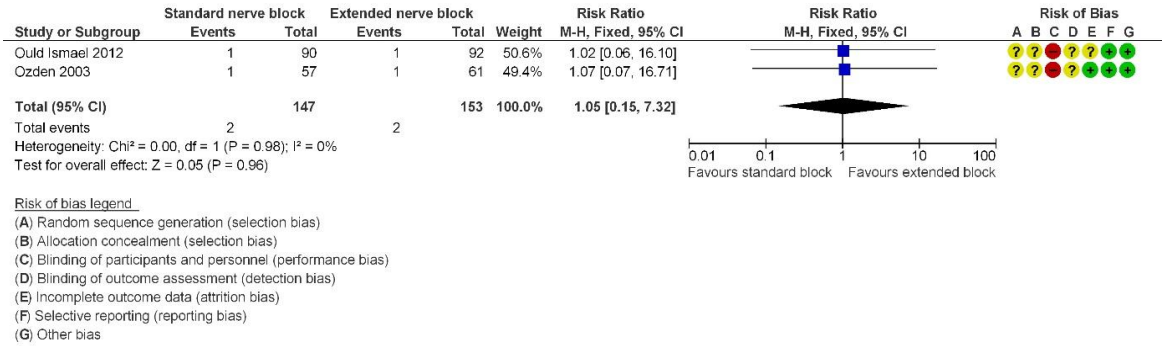
Supplementary Figure 2 – Comparison of standard to extended biopsy cores on hospitalization following prostate biopsy. CI = confidence interval; df = degrees of freedom.



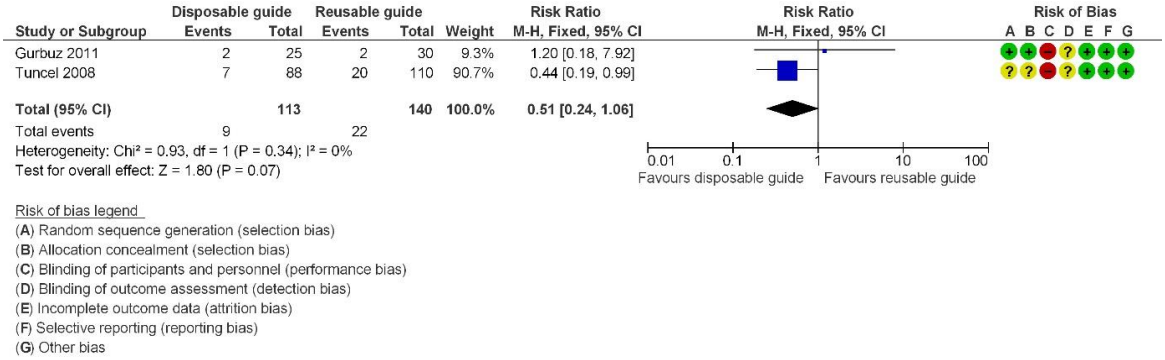
Supplementary Figure 3 – Effect of periprostatic nerve block on hospitalization following prostate biopsy. CI = confidence interval; df = degrees of freedom.



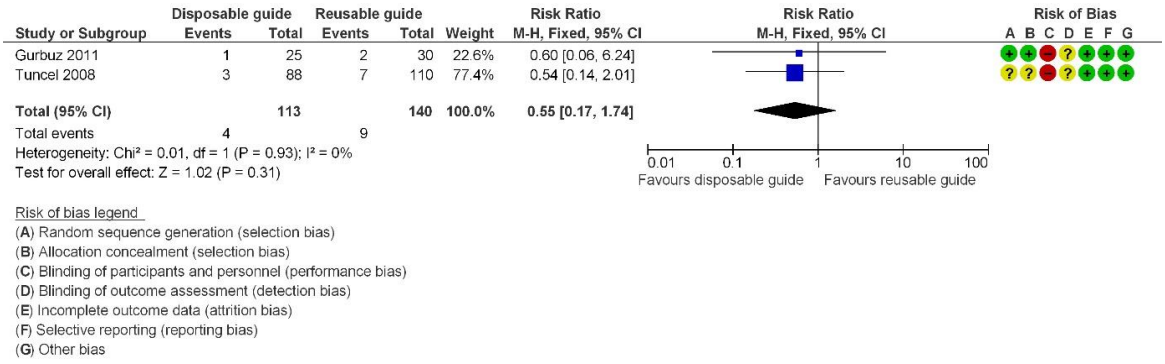
Supplementary Figure 4 – Impact of number of injections for periprostatic nerve block on infections complications following prostate biopsy. CI = confidence interval; df = degrees of freedom.



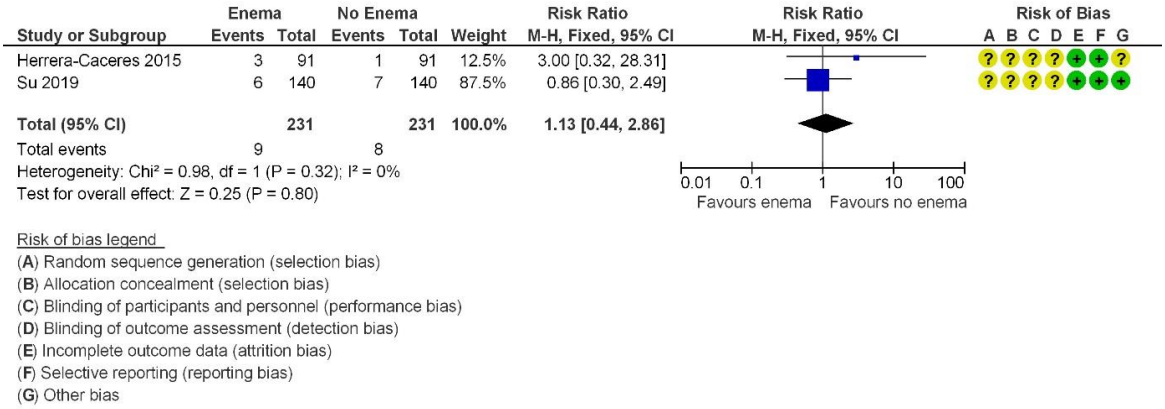
Supplementary Figure 5 – Impact of number of injections for periprostatic nerve block on hospitalization following prostate biopsy. CI = confidence interval; df = degrees of freedom.



Supplementary Figure 6 – Impact of disposable needle guides on infections complications following prostate biopsy. CI = confidence interval; df = degrees of freedom.



Supplementary Figure 7 – Impact of disposable needle guides on hospitalization following prostate biopsy. CI = confidence interval; df = degrees of freedom.



Supplementary Figure 8 – Effect of rectal preparation with enema on hospitalization following prostate biopsy. CI = confidence interval; df = degrees of freedom.

Supplementary table 1 - Synopsis of included studies and detail of reported infectious outcomes

Author, year	Fever	Symptomatic UTI	Sepsis	Pooled infectious complications	Bacteriaemia	Bacteriuria	Hospitalization	Mortality
Abughosh, 2013	X	X	X	X				
Adamakis, 2004		X	X	X			X	
Akan, 2009	X			X				
Aktoz, 2010	X		X	X			X	
Alavi, 2001		X[a]		X			X	
Atta, 2018				X[b]			X	
Babaei Jandaghi, 2016	X			X			X	
Bas, 2019				X				
Basar, 2005	X			X				
Bingqian, 2009	X			X			X	
Bolat, 2016	X[c]			X			X	
Bolat, 2019	X			X			X	
Brown, 1981	X				X	X		
Cadilhe, 2017				X				
Cerruto, 2014	X			X				
Cevik, 2006	X		X	X				
Chae, 2009		X	X	X			X	
Cormio, 2012	X			X				
Costa, 2019	X		X	X		X		
De Nunzio, 2015			X[d]				X[d]	
Emiliozzi, 2004	X			X			X	
Ergani, 2020		X[a]	X	X			X	
Ghafoori, 2012		X	X	X			X	X
Giannarini, 2009			X	X				
Guo, 2015	X		X	X			X	
Gurbuz, 2010			X	X			X	
Gurbuz, 2011	X	X		X	X	X	X	
Hara, 2006	X		X					X
Herrera-Caceres, 2015	X	X		X		X	X	
Hetta, 2014	X	X[a]		X				
Hiros, 2010	X			X				
Inal, 2003			X	X				

Inal, 2004			X	X				
Inal, 2008	X			X				
Irani, 2013	X	X[a]		X				
Izol, 2012				X[e]				
Jindal, 2015	X		X	X			X	
Jones, 2003				X[f]				
Kang, 2012				X[f]				
Kanjanawongdeengam, 2009	X	X	X	X	X		X	
Kim, 2011		X[a]		X			X	
Kim, 2019	X		X	X				
Klein, 2010		X[a]		X				
Knobloch, 2002		X[a]		X				
Koc, 2010	X	X		X		X	X	
Kravchick, 2005		X[c]		X				
Kucur, 2015		X[a]		X				
Kuppusamy, 2010			X	X				
Lecuona, 2011	X			X				
Li, 2009	X		X	X				
Lindert, 2000	X			X	X	X		
Liu, 2009	X			X				
Mallick, 2005	X			X				
Mariappan, 2004	X			X				
Mazdak, 2018	X		X	X			X	
Medina Marquez, 2006					X			
Melekos, 1990	X			X	X	X		
Naughton, 2000	X			X			X	
Novella, 2003	X	X		X				
Obek, 2002	X			X		X	X	
Ould Ismail, 2012		X[a]		X			X	
Ozden, 2003	X			X			X	
Park, 2005	X	X		X				
Paul, 2004	X			X			X	
Pontes, 2017		X[a]		X				
Ragavan, 2005	X			X			X	
Rodríguez-Covarrubias, 2011	X			X			X	
Ryu, 2019	X			X				
Salomon, 2019	X	X					X	
Sataa, 2010		X[a]		X				
Seymour, 2001	X			X			X	
Sharpe, 1982	X			X		X		
Singh, 2017	X			X		X		
Song, 2006		X		X			X	
Su, 2019		X		X			X	
Sur, 2004		X[a]	X	X				

Szlauer, 2008		X[a]		X				
Taher, 2014				X[f]				
Tekdogan, 2006	X	X		X		X		
Tobias Machado, 2002	X	X[a]		X				
Tobias-Machado, 2006		X		X				
Toi, 2012			X	X				
Trucchi, 2005		X[a]	X	X				
Tuncel, 2008	X	X		X	X	X	X	
Udeh, 2015	X			X				
Wang, 2016	X			X				
Wegelin, 2019	X	X		X			X	
Xu, 2012	X			X				
Xu, 2014	X			X				
Yu, 2014		X		X				
Total, n (%)	55 (63%)	33 (38%)	23 (26%)	84 (95%)	7 (8%)	12 (14%)	34 (39%)	2 (2%)

[a]prostatitis
[b]minor and major infectious complications
[c]febrile UTI
[d]additional information provided by authors
[e]no complications
[f]infections

Supplementary table 2 - Characteristics of excluded studies

Study	Reason for exclusion
Abboud, 2015	No RCT, but non-randomized trial
Abughosh, 2011	Partial publication (abstract only), fulltext included (Abughosh 2013)
Abughosh, 2012	Partial publication (abstract only), fulltext included (Abughosh 2013)
Abughosh, 2012	Partial publication (abstract only), fulltext included (Abughosh 2013)
Addla, 2003	Periprostatic injection in all groups
Akay, 2006	Inadequate randomization by order of the arrival
Akdeniz, 2018	Periprostatic injection in all groups
Akdere, 2013	No infective outcome reported
Akpinar, 2009	Periprostatic injection in all groups
Alabi, 2018	Inadequate randomization by alternation[a]
Alam, 2017	No infective outcome reported
Alberts, 2017	No infective outcome reported
Alireza, 2012	No infective outcome reported
Allen, 2017	No RCT, but non-randomized trial
Ananth, 2000	No RCT, but study comment
Anastasi, 2016	No infective outcome reported
Anup, 2013	Periprostatic injection in all groups
Arguelles Salido, 2008	No detailed raw data on infective complications available[a]
Arsov, 2015	No infective outcome reported
Arsov, 2015	Interfering second intervention (antibiotics)
Arsov, 2016	Interfering second intervention (antibiotics)
Ashley, 2007	No infective outcome reported
Avci, 2012	No infective outcome reported
Baco E, 2016	No infective outcome reported
Barbosa, 2010	No clear evidence for RCT, no feedback from authors recieved
Barry Delongchamps, 2013	No RCT, but uncontrolled trial
Berger, 2003	Periprostatic injection in all groups
Bidnur, 2016	No RCT, but study comment
Black, 2011	No clear raw data on infectious complications
Boehm, 2017	Partial publication (abstract only), fulltext included (Salomon 2018)
Bozlu, 2004	Periprostatic injection in all groups
Buckley, 2006	Inadequate randomization by alternation of week
Cam, 2008	Periprostatic injection in all groups
Cantiello, 2012	Periprostatic injection in all groups
Cengiz, 2013	No infective outcome reported
Cermak, 2009	No infective outcome reported
Cermak, 2010	No RCT, but retrospective data analysis of a uncontrolled trial
Cerruto, 2010	Partial publication (abstract only), fulltext included (Cerruto 2014)
Chen, 2018	No RCT, but retrospective data analysis of a controlled trial
Chen, 2018	No RCT, but retrospective data analysis of a controlled trial
Cheng, 2018	No infective outcome reported
Chi, 2011	No RCT, but non-randomized controlled trial
Ching, 2009	No RCT, but non-randomized observational study
Cicione, 2012	No infective outcome reported

Cicione, 2013	No infective outcome reported
Conde Redondo, 2006	No clear raw data on infectious complications, no feedback from authors recieved
Cormio, 2010	No clear raw data on infectious complications
Cormio, 2011	No infective outcome reported
Damiano, 2004	No clear raw data on infectious complications, no feedback from authors recieved
de la Rosette, 2009	No infective outcome reported
De Nunzio, 2011	Inadequate randomization by alternation[a]
Del Campo, 2016	No RCT, but observational study
D'Elia, 2019	Inadequate randomization by date of birth
D'Eramo, 2012	Periprostatic injection in all groups
Ding, 2018	No infective outcome reported
Durmus, 2013	No RCT, but retrospective data analysis of a controlled trial
Emiliozzi, 2003	No RCT, but prospective observational study
Gavazzi, 2009	No RCT, but non-randomized controlled trial
Ghafoori, 2015	No clear raw data on infectious complications, no feedback from authors recieved
Ghani, 2004	No RCT, but prospective non-randomized trial
Giannarini, 2009	No infective outcome reported
Giannarini, 2009	No infective outcome reported
Griwan, 2012	No clear raw data on infectious complications
Guo, 2017	No RCT, but retrospective data analysis
Haga, 2012	No intervention of interest
Haggarth, 2002	Periprostatic injection in all groups
Hamid, 2019	No intervention of interest
Hara, 2008	Partial publication, Fulltext included (Hara 2006)
Herranz Amo, 2010	No infective outcome reported
Ho, 2010	No clear raw data on infectious complications, no feedback from authors recieved
Horinaga, 2006	No infective outcome reported
Huang, 2006	No RCT, but retrospective data analysis
Inal, 2004	No infective outcome reported
Irani, 2013	Partial publication (abstract only), fulltext included (Irani 2013)
Ismail, 2015	No infective outcome reported
Jambor, 2019	No RCT, but prospective non-randomized trial
Kandirali, 2009	No intervention of interest
Karman, 2009	No infective outcome reported
Kato, 2011	No RCT, but non-randomized controlled trial
Kaufmann, 2018	No RCT, but non-randomized controlled trial
Kaver, 2002	No infective outcome reported
Kim, 2004	No infective outcome reported
Kim, 2010	No infective outcome reported
Klein, 2009	No RCT, but prospective non-randomized trial
Koprulu, 2012	No RCT, but non-randomized retrospective and prospective trial
Kumar, 2012	No infective outcome reported
Kumar, 2013	Periprostatic injection in all groups
Kuppusamy, 2009	No infective outcome reported
Lee, 2007	Periprostatic injection in all groups
Lee, 2017	Partial publication (abstract only), Fulltext included (Ryu 2019)
Lee, 2020	Inadequate randomization by alternation of month

Leibovici, 2002	Periprostatic injection in all groups
Leitao, 2011	No infective outcome reported
Li, 2014	No clear evidence for RCT
Li, 2017	No infective outcome reported
Lim, 2016	No infective outcome reported
Lipczynski, 2012	No intervention of interest
Lorusso, 2010	No infective outcome reported
Lujan Marco, 2009	Inadequate randomization by alternation of day
Lunacek A, 2014	No infective outcome reported
Lunacek, 2013	No infective outcome reported
Lunacek, 2014	No infective outcome reported
Lynn, 2002	No infective outcome reported
Mallick, 2004	Partial publication, fulltext included (Mallick 2005)
Mallick, 2004	Partial publication in French, fulltext included (Mallick 2005)
Mamoulakis, 2009	Partial publication (abstract only), fulltext excluded (de la Rosette 2009)
Mamoulakis, 2009	Partial publication (abstract only), fulltext excluded (de la Rosette 2009)
Manikandan, 2003	No infective outcome reported
Matlaga, 2003	No infective outcome reported
McCormack, 2012	Inadequate randomization by patients chart number (even/odd)[a]
McGee, 2015	No RCT, but retrospective data analysis
Mitterberger M, 2007	No infective outcome reported
Mitterberger, 2007	No RCT, but all patients recieved both techniques
Montoliu Garcia A, 2010	No clear raw data on infectious complications, no feedback from authors recieved
Montoliu Garcia, 2009	Inadequate randomization by number of medical history (even/odd)
Moreira, 2016	No RCT, but retrospective analysis of a RCT
Moudouni, 2011	Partial publication (abstract only), fulltext is Moudouni 2014
Moudouni, 2014	No clear raw data on infectious complications, no feedback from authors recieved
Nambirajan, 2004	Periprostatic injection in all groups
Nash, 1996	No infective outcome reported
Nasu, 2009	No infective outcome reported
Naughton, 2001	No infective outcome reported
Nava, 1993	No RCT, but non-randomized controlled trial
Nguyen, 2007	No infective outcome reported
Noh, 2010	Periprostatic injection in all groups
Nour, 2009	No clear raw data on infectious complications
Nouri, 2010	No infective outcome reported
Novac, 2013	No infective outcome reported
Obek, 2004	Interfering second intervention (antibiotics)
Obi, 2011	No infective outcome reported
Obi, 2015	No infective outcome reported
Ortegren, 2019	No RCT, but retrospective data analysis of infections
Ozcan, 2017	No clear evidence for RCT, no feedback from authors recieved
Ozok, 2010	Periprostatic injection in all groups
Ozveri H, 2003	No clear evidence for RCT, no feedback from authors recieved
Paffen, 2015	No clear evidence for RCT
Park, 2009	No RCT, but non-randomized controlled trial
Park, 2010	No clear raw data, no feedback from authors recieved

Pathak, 2015	No infective outcome reported
Pathak, 2017	No infective outcome reported
Paul, 2005	Partial publication, complete study published under Paul 2004
Pepe, 2017	No RCT, all patients recieved both interventions
Porpiglia, 2016	Interfering second intervention (antibiotics)
Qu, 2016	No RCT, but non-randomized controlled trial
Raber, 2008	Interfering second intervention (antibiotics)
Raber, 2011	No infective outcome reported
Rabets, 2004	No infective outcome reported
Raman, 2015	No RCT, but non-randomized prospective trial
Raman, 2015	No RCT, but description of rectal preparation with povidone-iodine
Robins, 2017	No infective outcome reported
Robins, 2018	No RCT, but non-randomized controlled trial
Rochester, 2009	No infective outcome reported
Rodriguez, 2002	No infective outcome reported
Rodriguez, 2003	No infective outcome reported
Rohit, 2019	No infective outcome reported
Saha, 2014	No infective outcome reported
Sahin, 2015	No infective outcome reported
Salido, 2008	No clear raw data on infectious complications
Salomon, 2017	Partial publication (abstract only), fulltext included (Salomon 2018)
Salomon, 2018	Double publication, fulltext included (Salomon 2018)
Saredi, 2009	No clear raw data on infectious complications, no feedback from authors recieved
Saredi, 2010	No clear raw data on infectious complications, no feedback from authors recieved
Sarmiento, 2018	No clear evidence for RCT
Schostak, 2002	No infective outcome reported
Sekiner, 2011	Periprostatic injection in all groups
Sen, 2015	Periprostatic injection in all groups
Siddiqui, 2006	No RCT, but non-randomized controlled trial
Singh, 2011	No infective outcome reported
Singh, 2012	Periprostatic injection in all groups
Song, 2004	Double publication in Korean, English publication included (Song 2006)
Sridhar, 2020	No clear raw data on infectious complications
Stamatiou, 2007	No clear evidence for RCT
Stirling, 2002	No infective outcome reported
Stirling, 2002	No infective outcome reported
Stravodimos, 2007	No infective outcome reported
Taher, 2015	Double publication (abstract only), Taher 2014 (abstract only) included
Takenaka, 2008	Partial publication, Fulltext included (Hara 2006)
Tas, 2005	Double publication (Inal 2008)
Taverna, 2011	No infective outcome reported
Turgut At, 2006	No infective outcome reported
Turgut, 2006	No infective outcome reported
Valero Sarmiento, 2018	No clear evidence for RCT
van der Leest, 2019	No intervention of interest
Walker, 2002	Periprostatic injection in all groups
Walsh, 2004	No infective outcome reported

Wang, 2019	No clear evidence for RCT
Wegelin, 2019	Double publication, fulltext included (Wegelin 2019)
Woolsey S, 2002	Periprostatic injection in all groups
Wu, 2001	No infective outcome reported
Yang, 2009	No infective outcome reported
Yildirim, 2015	No RCT, but retrospective data analysis of a non-randomized controlled trial
Yun, 2007	Periprostatic injection in all groups
Yurdakul, 2009	No infective outcome reported
Zare, 2012	No clear evidence for RCT

[a]information provided by authors

Supplementary table 3: Characteristics of included studies

Author, year	Country	Publication language	Study period	Intervention category	Detailed Intervention	Follow-Up
Abughosh, 2013	Canada	English	2009-2011	Povidone-iodine	Group 1) 421 patients received povidone-iodine gauze cleansing intrarectally 2 min before biopsy Group 2) 444 patients received no rectal preparation with povidone-iodine	7 days
Adamakis, 2004	Greece	English	not reported	Nerve block	Group 1) 40 patients received 10 ml ultrasound gel intrarectally 10 min before biopsy Group 2) 78 patients received 10 ml EMLA intrarectally 10 min before biopsy Group 3) 80 patients received periprostatic nerve block 10 ml 2% lidocaine with 5	14 days
Akan, 2009	Turkey	English	2004-2007	Extended nerve block	Group 1) 60 patients received periprostatic nerve block with 2 injections of 5 mL 1% lidocaine basal 5 min before biopsy Group 2) 57 patients received periprostatic nerve block with 5 mL of 1% lidocaine at the apex 5 min before biopsy	not reported
Aktoz, 2010	Turkey	English	2008	Nerve block	Group 1) 30 patients received 50 mg diclofenac sodium suppository 30 min before biopsy Group 2) 30 patients received 3.3 ml of 0.75% levobupivacaine as bilateral periprostatic nerve block directly before biopsy Group 3) 30 patients received 50 mg diclofenac 30 min before biopsy plus 3.3 ml of 0.75% levobupivacaine injection as bilateral periprostatic nerve block directly before biopsy	14 days
Alavi, 2001	US	English	1999 - 2000	Nerve block	Group 1) 75 patients received a periprostatic nerve block with 10 ml 1% lidocaine bilaterally at the prostate base 3 min before biopsy Group 2) 75 patients received 10 ml 2% lidocaine gel intrarectally 10 min before biopsy	14 days
Atta, 2018	Egypt	English	2013 - 2014	Nerve block	Group 1) 100 patients received i.v. sedation with diazepam 5 mg 3-5 min before biopsy Group 2) 100 patients underwent bilateral periprostatic nerve block with 10 ml 1% lidocaine 2-3 min before biopsy Group 3) 100 patients received i.v. sedation with diazepam 5 mg and bilateral periprostatic nerve block with 10 ml 1% lidocaine 3-5 min before biopsy.	7 days
Babaei Jandaghi, 2016	Iran	English	2014 - 2015	Needle type	Group 1) 125 patients transperineal biopsy with a coaxial Tru-Cut needle (18/17-gauge) Group 2) 125 patients transperineal biopsy with a non-coaxial 18-gauge needle	7 days
Bas, 2019	Turkey	English	not reported	Needle diameter	Group 1) 60 patients underwent prostate biopsy with 18 G needle Group 2) 32 patients underwent prostate biopsy with 20 G needle	not reported
Basar, 2005	Turkey	English	not reported	Nerve block	Group 1) 20 patients received ultrasound gel intrarectally15 min before biopsy Group 2) 20 patients received 1g EMLA cream intrarectally 15 min before biopsy Group 3) 20 patients underwent periprostatic nerve block with 6 ml 1% prilocaine 15 min before biopsy	not reported

					Group 4) 20 patients underwent periprostatic nerve block with 6 ml 1% lidocaine 15 min before biopsy	
Bingqian, 2009	China	English	2005-2008	Unique	Group 1) 100 patients underwent periprostatic nerve block with 5 ml of 2% lidocaine solution (2.5 ml on each basal side) and intraprostatic injection of 5 ml of 2% lidocaine solution (2.5 ml on each side) Group 2) 100 patients underwent periprostatic nerve block with 5 ml of 2% lidocaine solution (2.5 ml on each basal side) and intraprostatic injection of 5 ml of 0.9% NaCl solution (2.5 ml on each side) Group 3) 100 patients received no anesthesia	7 days
Bolat, 2016	Turkey	English	2015	Unique	Group 1) 198 patients underwent transperineal prostatic block with 10 ml 2% prilocaine Group 2) 178 patients underwent intrarectal 10 ml 2% lidocaine gel followed by TRUS-guided PPNB with 10 ml 2% prilocaine	not reported
Bolat, 2019	Turkey	English	2018-2019	Nerve block	Group 1) 73 patients underwent infiltration free local anesthesia via TENS stimulation Group 2) 65 patients underwent intrarectal 60 mg lidocaine gel followed by TRUS-guided PPNB with 5 ml 2% prilocaine and 5 ml of 0.25 bupivacaine mixture 5 min before biopsy	not reported
Brown, 1981	US	English	1978 - 1979	Povidone-iodine	Group 1) 9 patients rectal preparation with saline enema only Group 2) 10 patients rectal preparation with 50 ml 10% povidone-iodine Group 3) 10 patients 80 mg gentamicin intramuscular 30 min before biopsy Group 4) 11 patients 50 ml 10% povidone-iodine and 80 mg gentamicin	1 week
Cadilhe, 2017	Portugal	English	2014 - 2016	Povidone-iodine	Group 1) 47 patients rectal preparation with 2,5 ml of betadine 100 mg/ml Group 2) 47 patients without rectal preparation	14 days
Cerruto, 2014	Italy	English	not reported	Biopsy route	Group 1) 54 patients received transperineal biopsy with 14 cores under local anesthesia with 2 ml 1% mepivacaine injected at the prostate apex Group 2) 54 patients received transrectal biopsy with 14 cores under periprostatic nerve block using 1% lidocaine injected at the prostate apex and the seminal vesicle-prostatic angles	30 days
Cevik, 2006	Turkey	English	2003 - 2005	Extended nerve block	Group 1) 60 patients underwent periprostatic nerve block with 6 ml of 1% lidocaine solution (3 ml on each basal side) Group 2) 60 patients underwent periprostatic nerve block with 4 ml of 1% lidocaine solution (2 ml on each side basal side) and 2 ml (1 ml on each side) apical	30 days
Chae, 2009	Korea	Korean	2006 - 2007	Biopsy route	Group 1) 100 patients underwent transperineal biopsy Group 2) 100 patients underwent transrectal biopsy	7 days
Cormio, 2012	Italy	English	not reported	Nerve block	Group 1) 100 patients received 5 g 2.5% lidocaine gel and 0.3% ketorolac tromethamine solution gel 1 h before biopsy followed by 5 g 2.5% lidocaine and 2.5% prilocaine cream (EMLA) 20 min before biopsy Group 2) 100 patients received 5 g 2.5% lidocaine and 2.5% prilocaine cream 20 min before biopsy followed by periprostatic nerve block with 10 ml 2% mepivacaine 5 min before biopsy	20 days

Costa, 2019	Brazil	English	not reported	Unique	Group 1) 401 patients underwent rectal cleansing with povidone-iodine plus formalin disinfection of biopsy needle tip Group 2) 401 patients served as control without rectal preparationand without needle disinfection	7 days
De Nunzio, 2015	Italy	English	2012 - 2013	Unique	Group 1) 97 patients received enema night before/on day of biopsy Group 2) 101 patients received bowel preparation with 34.8 g/4L polyethylene glycol-electrolyte solution (PEG) the day before the biopsy.	30 days
Emiliozzi, 2004	Italy	English	2001 - 2002	Biopsy cores	Group 1) 107 patients with 6 cores taken Group 2) 107 patients with 12 cores taken	not reported
Ergani, 2020	Turkey	English	2019	Povidone-iodine Chlorhexidine	Group 1) 101 patients received no rectal preparation with 2% lidocaine gel (control) Group 2) 49 patients received rectal preparation with 4% chlorhexidine mixed with 2% lidocaine gel Group 3) 50 patients received rectal preparation with 10% povidone iodine mixed with 2% lidocaine gel	30 days
Ghafoori, 2012	Iran	English	2009 - 2010	Povidone-iodine	Group 1) 140 patients 50 g of lidocaine 2% gel with 20 ml of povidone-iodine solution before biopsy Group 2) 140 patients 50 g of lidocaine 2% gel only before biopsy	30 days
Giannarini, 2009	Italy	English	2006 - 2007	Nerve block	Group 1) 68 patients received intrarectal 5 g lidocaine-prilocaine cream plus 10 ml 1% lidocaine (5 ml per side) as periprostatic nerve block 5 min before biopsy Group 2) 67 patients received intrarectal 5 g lidocaine-prilocaine cream 30 min before biopsy Group 3) 68 patients received 10 ml 1% lidocaine (5 ml per side) as periprostatic nerve block 5 min before biopsy Group 4) 67 patients received intrarectal lubricant gel 30 min before biopsy	30 days
Guo, 2015	China	English	2012-2014	Biopsy route	Group 1) 173 patients received transperineal biopsy with 8 cores (prostate volume < 50ml) or 12 cores (prostate volume >50 ml) using periprostatic nerve block with 10 ml 2% lidocaine Group 2) 166 patients received transrectal biopsy with 8 cores (prostate volume < 50ml) or 12 cores (prostate volume >50 ml) using periprostatic nerve block with 10 ml 2% lidocaine	7 days
Gurbuz, 2010	Turkey	English	2008 - 2009		Group 1) 25 patients with no local anaesthesia Group 2) 25 patients received 5 ml 1% lidocaine as injection at the 3 o clock and 9 o clock position of the anus Group 3) 25 patients underwent periprostatic nerve block with 10 ml (5 ml per side) 1% lidocaine applied at the prostatic base and in an apical location Group 4) 25 patients received intrarectal 5 ml of lidocaine prilocaine cream (EMLA)	14 days
Gurbuz, 2011	Turkey	English	2009	Needle guide	Group 1) 25 patients transrectal 10 core biopsy with disposable needle guide Group 2) 30 patients transrectal 10 core biopsy with reusable needle guide	14 days
Hara, 2006	Japan	Japanese	2003 - 2005	Biopsy route	Group 1) 168 patients received transperineal biopsy with 12 cores	not reported

					Group 2) 174 patients received transrectal biopsy with 12 cores	
Herrera-Caceres, 2015	Mexico	English	2013 - not reported	Enema	Group 1) 91 patients received two gylcine enemas Group 2) 91 patients received no enemas	10 days
Hetta, 2014	Egypt	English	2012-2013	Nerve block	Group 1) 25 patients received periprostatic nerve block with 5 ml lidocaine injected on each side Group 2) 25 patients received local xylocaine creme	14 days
Hiros, 2010	Bosnia and Herzegovina	English	2008 - 2009	Nerve block	Group 1) 30 patients received 4 periprostatic injections of 2,5 ml of 1% lidocaine as periprostativ nerve block Group 2) 30 patients received diclofenac suppository intrarectal an hour before biopsy Group 3) 30 patients received 20 ml ultrasound gel intrarectally	14-21 days
Inal, 2003	Turkey	English	2001	Nerve block	Group 1) 25 patients received periprostatic nerve block with 3 ml 1% lidocaine per side Group 2) 25 patients received no anaesthesia	not reported
Inal, 2004	Turkey	Turkish	2001	Nerve block	Group 1) 20 patients received no local anesthesia Group 2) 20 patients received periprostatic nerve block with 2 ml 1% lidocaine (1ml per side) 5 min before biopsy Group 3) 20 patients received periprostatic nerve block with 6 ml 1% lidocaine (3 ml per side) 5 min before biopsy	not reported
Inal, 2008	Turkey	English	2004 - 2005	Needle diameter	Group 1) 103 patients received biopsy with an 16 G needle Group 2) 101 patients received biopsy with an 18 G needle	7 days
Irani, 2013	France	English	2009 - 2011	Biopsy cores	Group 1) 158 patients with 12 cores taken Group 2) 148 patients with 20 cores taken	15 days
Izol, 2012	Turkey	English	not reported	Nerve block	Group 1) 25 patients received no analgesia Group 2) 25 patients received periprostatic nerve block with 5 ml 2% lidocaine before biopsy Group 3) 25 patients received local anesthesia with 10 ml 2% lidocaine gel 10 min before biopsy Group 4) 25 patients received i.v. sedation with 2 mg of midazolam and 2µg/kg of fentanyl	21 days
Jindal, 2015	India	English	2012 - 2013	Nerve block	Group 1) 47 patients received Intrarectal local anaesthesia with 10 ml 2% lignocaine jelly and underwent pelvic plexus block with 2.5 ml 2% lignocaine injection on each side Group 2) 46 patients received Intrarectal local anaesthesia with 10 ml 2% lignocaine jelly and periprostatic nerve block with 2,5 ml of 2% lignocaine injection on each side Group 3) 46 patients received only Intrarectal local anaesthesia with 10 ml 2% lignocaine jelly	14 days
Jones, 2003	USA	English	Not reported	Nerve block	Group 1) 30 patients received periprostatic nerve block with 10 ml lidocaine (5 ml on each side) Group 1) 30 patients received no analgesia	not reported

Kang, 2012	South Korea	English	2006-2008	Nerve block	Group 1) 31 patients received 10 ml 2% lidocaine gel Group 2) 30 patients received periprostatic nerve block with 10 ml 1% lidocaine after local application of 10 ml 2% lidocaine gel 5 min before biopsy Group 3) 31 patients received periprostatic nerve block with 20 ml 1% lidocaine after local application of 10 ml 2% lidocaine gel 5 min before biopsy	not reported
Kanjanawongdeengam, 2009	Thailand	English	2008 - 2009	Povidone-iodine	Group 1) 50 patients received enema only Group 2) 50 patients received enema and gauze soaked with l0% povidone-iodine solution for 5-10 min in rectum	7 days
Kim, 2011	South Korea	English	2009 - 2010	Nerve block	Group 1) 125 patients underwent periprostatic nerve block with 1% lidocaine injection Group 2) 158 patients received oral acetaminophen 650 mg Group 3) 147 patients received 5 g EMLA cream intrarectal	3 days
Kim, 2019	South Korea	English	2015 - 2016	Nerve block	Group 1) 55 patients underwent intrarectal local anesthesia with 10 ml of 2% lidocaine gel plus pelvic plexus block with 3 ml of 2% lidocaine injected at the bilateral pelvic plexus Group 2) 55 patients underwent intrarectal local anesthesia with 10 ml of 2% lidocaine gel plus periprostatic nerve block with 3 ml of 2% lidocaine injected at both periprostatic nerves Group 3) 53 patients underwent intrarectal local anesthesia with 10 ml of 2% lidocaine gel	14 days
Klein, 2010	Germany	English	2008 - 2009	Nerve block	Group 1) 74 patients received 2% lidocaine gel 15 min topical before biopsy Group 2) 71 patients underwent periprostatic nerve block with 10 ml 2% prilocaine (5 ml per side) plus 2% lidocaine gel 15 min topical before biopsy	12 weeks
Knobloch, 2002	Germany	English	2000 - 2001	Nerve block	Group 1) 34 patients underwent periprostatic nerve block with 5-10 ml 1% articaine (5 ml per side) 2-3 min before biopsy and received 6 ml 2% topical lidocaine creme Group 2) 34 patients received 6 ml 2% topical lidocaine creme	7 days
Koc, 2010	Turkey	English	2008 - 2009	Unique	Group 1) 84 patients transrectal 12 core biopsy with biopsy needle disinfection with 10% povidone-iodine after each biopsy taken Group 2) 96 patients transrectal 12 core biopsy without needle disinfection	14 days
Kravchick, 2005	Israel	English	Not reported	Nerve block	Group 1) 28 patients received 10 ml of 2% lidocaine gel intrarectal 10 min before biopsy Group 2) 30 patients received 10 ml intrarectal 40% DMSO with 10 ml 2% lidocaine gel intrarectal 10 min before biopsy Group 3) 29 patients received 10 ml perianal injection of 1% lidocaine 2 minutes before the procedure Group 4) 27 patients received periprostatic nerve block with 5 ml 1% lidocaine on each side	10 days
Kucur, 2015	Turkey	English	2012 - 2013	Nerve block	Group 1) 50 patients received 10 ml of 2% lidocaine gel intrarectal and underwent 5 minutes later a prostatic nerve block with 2.5 ml of 2% lidocaine injected each side	30 days

					Group 2) 50 patients received low dose spinal anesthesia by injecting 0.3 ml, 0.5% hyperbaric bupivacaine into the spinal subarachnoid space between L4/L5 vertebra	
Kuppusamy, 2010	Malaysia	English	2006-2008	Nerve block & extended nerve block	Group 1) 90 patients received no analgesia Group 2) 106 patients received periprostatic nerve block with 10 ml 1% lignocaine in one apical injection 10 min before biopsy Group 3) 87 patients received periprostatic nerve block with 5 ml 1% lignocaine injected on both basal sides 10 min before biopsy Group 4) 106 patients received periprostatic nerve block with 4 ml 1% lignocaine injected in the apex region and 3 ml 1% lignocaine injected in both basal sides 10 min before biopsy	not reported
Lecuona, 2011	South Africa	English	2006 - 2009	Biopsy cores	Group 1)152 patients with number of cores taken according to the Vienna nomogram Group 2) 151 patients with 8 cores taken	not reported
Li, 2009	China	Chinese	Not reported	Nerve block	Group 1) 60 patients recieved periprostatic nerve block with 10 ml 2% lidocaine injection (5 ml each side) Group 2) 60 patients received periprostatic nerve block with 10 ml NaCl injection (5 ml each side) Group 3) 60 patients received periprostatic no nerve block (control).	7 days
Lindert, 2000	US	English	Not reported	Enema	Group 1) 25 patients with pre-biopsy enema Group 2) 25 patients without enema	1 day
Liu, 2009	China	Chinese	2006 - 2008	Nerve block	Group 1) 30 patients received no anesthesia Group 2) 30 patients underwent periprostatic nerve block with 5 ml 1% lidocaine injection per side 5 min before biopsy Group 3) 30 patients received intrarectal lidocaine gel and underwent 5 min later a periprostatic nerve block with 5 ml 1% lidocaine injection per side 5 min before biopsy Group 4) 30 patients received 2 ml 1% lidocaine injection on both prostatic lobes and thereafter a periprostatic nerve block with 5 ml 1% lidocaine injection per side 5 min before biopsy	7 days
Mallick, 2005	Guadeloupe	English	2002 - 2003	Nerve block	Group 1) 180 patients received 15 ml 2% lidocaine gel intrarectally 10 min before biopsy Group 2) 176 patients underwent periprostatic nerve block with 10 ml 1% lidocaine infiltration (5 ml per side) 4 min before biopsy	21 days
Mariappan, 2004	Malaysia	English	2001 - 2003	Biopsy cores	Group 1) 69 patients underwent 6 core biopsy Group 2) 63 patients underwent >6 core biopsy (depending on prostate size)	7-14 days
Mazdak, 2018	Iran	English	2015 - 2016	Nerve block	Group 1) 36 patients underwent local anesthesia with intrarectal application of 10 ml lidocaine gel and periprostatic nerve block with 5 ml of 2% lignocaine. Group 2) 35 patients underwent spinal anesthesia with 1.5 ml of 0.5% bupivacaine Group 3) 35 patients received general sedation with 25 µg/kg midazolam, 2µg/kg fentanyl, and 1 mg/kg ketamine.	14 days

Medina Marquez, 2006	Colombia	Spanish	2012 - 2013	Nerve block	Group 1) 22 patients received 10 ml of 2% lidocaine gel intrarectal Group 2) 22 patients received periprostatic nerve block with 5 ml 1% lidocaine	not reported
Melekos, 1990	Greece	English	not reported	Povidone-iodine	Group 1) 18 patients received 50 ml of 5% povidone-iodine enema (PIE) for 10 minutes just before biopsy Group 2) 22 patients received 2 g of ppiperacillin i.v. 2 hours before and 2 hours after biopsy Group 3) 25 patients received 50 ml of 5% povidone-iodine enema (PIE) for 10 minutes just before biopsy and 2 g of piperacillin i.v. 2 hours before and 2 hours after biopsy Group 4) 16 patients received a saline cleansing enema only	1 week
Naughton, 2000	US	English	not reported	Biopsy cores	Group 1) 72 patients with 6 cores taken Group 2) 62 patients with 12 cores taken	28 days
Novella, 2003	Italy	English	2002 - 2003	Needle type	Group 1) 51 patients underwent transperineal biopsy using a coaxial needle as sheeth Group 2) 51 patients underwent transperineal biopsy using the conventional transperineal approach	30 days
Obek, 2002	Turkey	English	2000 - 2001	Nerve block	Group 1) 50 patients underwent periprostatic nerve block with 2.5 ml 2% lidocaine on each side 3 min before biopsy Group 2) 50 patients received no analgesia	14 days
Ould Ismail, 2012	Morocco	English	2007 - 2009	Extended nerve block	Group 1) 90 patients received periprostatic nerve block with 8 ml 1% lidocaine basal injection on each side Group 2) 92 patients received periprostatic nerve block with 8 ml 1% lidocaine basal injection on each side and 2 ml 1% lidocaine apical per side	15 days
Ozden, 2003	Turkey	English	2001 - 2002	Extended nerve block	Group 1) 25 patients underwent unilateral periprostatic nerve block with 5 ml normal saline Group 2) 25 patients underwent periprostatic nerve block with a total of 2.5 ml 1% lidocaine injected on each side of the base Group 3) 25 patients underwent periprostatic nerve block with a total of 2.5 ml 1% lidocaine injected on each side of the base plus each side of the apex Group 4) 25 patients underwent periprostatic nerve block with a total of 5 ml 1% lidocaine injected on each side of the base Group 5) 25 patients underwent periprostatic nerve block with a total of 5 ml 1% lidocaine injected on each side of the base plus each side of the apex Group 6) 25 patients underwent periprostatic nerve block with a total of 10 ml 1% lidocaine injected on each side of the base Group 7) 25 patients underwent periprostatic nerve block with a total of 10 ml 1% lidocaine injected on each side of the base plus each side of the apex	10 days
Park, 2005	South Korea	Korean	2001 - 2005	Nerve block	Group 1) 19 patients underwent periprostatic nerve block with 10 ml of 1% lidocaine on bilateral plus intrarectal application of 20 ml of 2% lidocaine gel 10 minutes before biopsy Group 2) 23 patients underwent periprostatic nerve block with 10 ml of 1% lidocaine on bilateral	not reported

					Group 3) 19 patients received intrarectal application of 20 ml of 2% lidocaine gel 10 minutes before biopsy	
Paul, 2004	Germany	English	2000 - 2001	Biopsy cores	Group 1) 84 patients with 6 cores taken Group 2) 88 patients with 10 cores taken	28 days
Pontes, 2017	Brazil	English	not reported	Biopsy cores	Group 1) 379 patients with 12 cores taken Group 2) 379 patients with 20 cores taken	not reported
Ragavan, 2005	UK	English	2002 - 2003	Nerve block	Group 1) 55 patients underwent periprostatic nerve block with 10 ml 1% lidocaine injection basal at each side some minutes before biopsy Group 2) 55 patients received a 100 mg diclofenac suppository 40 min before biopsy and periprostatic nerve block with 10 ml 1% lidocaine injection basal at each side some minutes before biopsy Group 3) 55 patients received 100 mg diclofenac suppository 40 min before biopsy	not reported
Rodríguez-Covarrubias, 2011	Mexico	English	2009 - 2010	Biopsy cores	Group 1) 75 patients with 12 cores taken Group 2) 75 patients with 18 cores taken	7 days
Ryu, 2019	South Korea	English	2014 - 2016	Povidone-iodine	Group 1) 120 patients received a 200 mg povidone-iodine suppository which was inserted 1 to 2h before biopsy. Group 2) 130 patients received no povidone-iodine suppository	14 days
Salomon, 2019	Germany	English	2013 - 2015	Chlorhexidine	Group 1) 494 patients received an antimicrobial lubricant consisting of lidocaine 2% and chlorhexidine 0.05% with residence time of at least 5 minutes. Group 2) 506 patients received the standard non-antimicrobial lubricant.	21 days
Sataa, 2010	Tunisie	French	2005 - 2006	Nerve block	Group 1) 33 patients received 10 ml 2% lidocaine gel intrarectal Group 2) 33 patients underwent periprostatic nerve block with 10 ml 1% lidocaine injection apical 10 min before biopsy Group 3) 34 patients received 10 ml ultrasound gel intrarectal	not reported
Seymour, 2001	UK	English	1999 - 2000	Nerve block	Group 1) 84 patients underwent periprostatic nerve block with 5 ml 2% lignocaine injection on each side of the apex 2 min before biopsy Group 2) 73 controls received no analgesia	7 days
Sharpe, 1982	US	English	not reported	Povidone-iodine	Group 1) 40 patients cleansing enema night before and 20 ml povidone-iodine solution before biopsy Group 2) 40 patients cleansing enema night before and 20 ml saline solution before biopsy	1 day
Singh, 2017	India	English	not reported	Biopsy route	Group 1) 60 patients received transperineal biopsy with 12 cores Group 2) 60 patients received transrectal biopsy with 12 cores	not reported
Song, 2006	South Korea	English	2004	Nerve block	Group 1) 30 patients received each 20 ml 2% lidocine gel intarectally 10 min before biopsy Group 2) 30 patients underwent periprostatic nerve block with 2.5 ml 2% lidocaine injection basal on each side 10 min before biopsy	14 days

					Group 3) 30 patients underwent periprostatic injection with 2.5 ml normal saline on each side 10 min before biopsy	
Su, 2019	China	English	2015 - 2018	Enema	Group 1) 140 patients received levofloxacin 500 mg p.o. 1 h before biopsy without an enema Group 2) 140 patients received levofloxacin 500 mg p.o. 1 h before biopsy with an enema Group 3) 140 patients received levofloxacin 500 mg p.o. starting 1 h before biopsy for a total of three days with an enema	14 days
Sur, 2004	US	English	2000 - 2001	Biopsy cores	Group 1) 88 patients with 6-12 cores taken Group 2) 94 patients with 24 cores taken	14 days
Szlauer, 2008	Austria	English	not reported	Nerve block	Group 1) 25 patients received a suppository containing 60 mg lidocaine 2 h before biopsy Group 2) 25 patients received a suppository containing 120 mg lidocaine 1 h before biopsy Group 3) 25 patients received a suppository containing 120 mg lidocaine 2 h before biopsy Group 4) 25 patients underwent periprostatic nerve block with 5 ml 2% lidocaine 5 min before biopsy	not reported
Taher, 2014	Turkey	English	2013 - 2014	Unique	Group 1) 60 patients received perineal cleansing with povidone iodine Group 2) 60 patients without perineal cleansing	not reported
Tekdogan, 2006	Turkey	Turkish	not reported	Enema	Group 1) 39 patients received ciprofloxacin 1000 mg p.o. per day starting the evening before biopsy for 4 days Group 2) 40 patients received ciprofloxacin 1000 mg p.o. per day starting the evening before biopsy for 4 days and 250 mg of rifampicin local enema Group 3) 40 patients received only 250 mg of rifampicin local enema Group 4) 40 patients received no prophylaxis	10 days
Tobias Machado, 2002	Brazil	English	not reported	Nerve block	Group 1) 20 patients underwent periprostatic nerve block with 2.5 ml of 1% lidocaine using 4 injections Group 2) 20 patients underwent no periprostatic nerve block	7 days
Tobias-Machado, 2006	Brazil	English	2000 - 2001	Nerve block	Group 1) 20 patients received 20 ml of 2% lidocaine gel intrarectal 10 min before biopsy Group 2) 60 patients underwent periprostatic nerve block with 2.5 ml of 1% lidocaine using 4 injections Group 3) 60 patients received 20 ml lubricant gel and i.v. seation with midazolam 1.5 mg and meperidine 2 mg i.v. 10 minutes before the procedure. Group 4) 20 patients received 15 ml lubricant gel	7 days
Toi, 2012	Canada	English	2011	Extended nerve block	Group 1) 89 patients underwent periprostatic nerve block with 10 ml of 1% lidocaine into the base (5 ml per side) Group 2) 89 patients underwent periprostatic nerve block with 10 ml of 1% lidocaine into the base (3 ml per side) and apex (2 ml per side)	21-35 days
Trucchi, 2005	Italy	English	2003	Nerve block	Group 1) 20 patients received no analgesia Group 2) 20 patients received 10 ml 1% lidocaine gel intrarectal 10 min before biopsy	not reported

					Group 3) 20 patients underwent periprostatic nerve block with 10 ml 1% mepivacaine bilateral 10 min before biopsy	
Tuncel, 2008	Turkey	English	2005 - 2007	Needle guide	Group 1) 110 patients transrectal 10 core biopsy with a reusable biopsy needle guide Group 2) 88 patients transrectal 10 core biopsy with a disposable biopsy needle guide	10 days
Udeh, 2015	Nigeria	English	2011	Biopsy route	Group 1) 45 patients received transperineal biopsy with 8 cores by digital rectal guidance Group 2) 30 patients received transrectal biopsy with 8 cores by digital rectal guidance	30 days
Wang, 2016	China	English	not reported	Nerve block	Group 1) 95 patients received 20 ml 1.2% lidocaine as caudal block 5 min before biopsy Group 2) 95 patients received 10 ml 0.3% oxybuprocaine gel perianal and underwent periprostatic nerve block with 5 ml of a mixture of 1% lidocaine and 0.5% ropivacaine per side	3 days
Wegelin, 2019	Netherlands	English	2014 - 2017	Biopsy cores & Biopsy route	Group 1) 77 patients recieved transrectal in-bore MRI targeted biopsy Group 2) 79 patients recieved transperineal MRI-transrectal ultrasound fusion targeted biopsy Group 3) 78 patients recieved transrectal cognitive TRUS targeted biopsy	30 days
Xu, 2012	China	Chinese	2005 - 2010	Biopsy cores	Group 1) 60 patients underwent 12 cores biopsy Group 2) 60 patients underwent 20 cores biopsy	7 days
Xu, 2014	China	English	2010 - 2012	Nerve block	Group 1) 62 patients underwent periprostatic nerve block with 5 ml of 2% lidocaine on each side 10 min before biopsy Group 2) 62 patients received intramuscular injection with meperidine 1mg/kg 30 min before biopsy Group 3) 62 patients received intra-muscular injection with saline 30 min before biopsy	not reported
Yu, 2014	China	Chinese	2012 - 2013	Unique	Group 1) 66 patients received rectal desinfection with a iodophor cotton ball after prostate biopsy Group 2) 66 patients received rectal desinfection with a iodophor cotton ball before prostate biopsy Group 3) 65 patients received rectal desinfection with a iodophor cotton ball before and after prostate biopsy	2 days