

Protocol

Which strategies are effective for reducing the risk of infective complications in men undergoing prostate biopsy?

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Introduction

This systematic review of strategies for reducing the risk of infective complications in men undergoing prostate biopsy is being undertaken under the auspices of the European Association of Urology (EAU). The review will encompass two aspects of the evidence base. First, we will review the evidence solely from randomised controlled trials (RCTs) by updating the 2011 Cochrane review by Zani et al. [1] Then, we will incorporate the evidence from non-randomised studies in order to capture the evidence base for specific risk factors, the impact of technical issues, route of biopsy and image-guidance. A main aim of the review is to inform the EAU guidelines for Urological Infections (and Prostate Cancer) and a more complete picture of the evidence base is desirable. In this protocol we have clarified when there are differing methods for those parts of the review that relate to the Cochrane update only (which we refer to as ‘the Cochrane review’) and where they pertain to the inclusion also of non-randomised studies (which we refer to as ‘the EAU review’).

Description of the condition

Prostate cancer is the second most common cancer in men. In 2012, an estimated 1.1 million men world-wide were diagnosed with prostate cancer with an estimated 307,000 deaths [2]. Diagnosis of prostate cancer is based on the histological evidence of malignancy in prostate biopsies or other metastatic tissue. Indications for prostate biopsy include suspicion of prostate cancer by digital rectal examination, elevation of prostate-specific antigen, and repeat biopsy in case of active surveillance [3, 4]. Although prostate cancer mortality has decreased in most Western countries during the last years, the value of prostate cancer screening is still very controversial [5, 6]. According to recent estimates, approximately 1 million biopsies are performed annually in the United States, and a similar number of TRUS biopsies are performed in the European Union. [7]

Transrectal ultrasound-guided prostate biopsy is the current gold standard for prostate cancer diagnosis worldwide [8-10]. Since the biopsy route has to cross the rectal milieu, antibiotic prophylaxis is commonly used to prevent infective complications [8, 9]. While febrile urinary tract infections, prostatitis, and urosepsis were only rarely reported in the past [11], there is growing evidence of frequent infective complications following prostate biopsy [7, 8, 12, 13].

The 30-day hospital readmission rate after biopsy significantly increased from 1.0% in 1996 to 4.1% in 2005 in one large population based study from Canada reporting on 75,190 men [12]. A possible reason for this increase is the growing incidence of fluoroquinolone resistant bacteria in the faecal reservoir of men undergoing biopsy leading to lack of efficacy of fluoroquinolone-based prophylaxis regimens [14-16]. Of note, infective complications are not randomly distributed, but clustered commonly to designated subgroups of patients harboring specific risk factors (e.g. diabetes, recent antibiotics, indwelling catheter, immunosuppression etc.) [17].

This issue of increasing rate of infection is not only of medical, but also of economic relevance, since infective complications are associated with expenses. In a cost-effectiveness analysis one study showed that an augmented antibiotic regimen resulted in significant cost-saving [18]. Comparable results were reported using rectal swab guidance in antibiotic prophylaxis [19].

Given the need to reduce infective complications in men undergoing prostate biopsy, various strategies including antibiotics, rectal preparations and technical issues will be comprehensively evaluated in this systematic review.

Description of the intervention

Prostate biopsy is a standardized intervention and is generally considered to be a safe procedure when using antibiotic prophylaxis. Several studies demonstrated lower infection rates in patients receiving antibiotic prophylaxis compared to those receiving no treatment/placebo when undergoing prostate biopsy [20-25] leading to the almost universal use of antibiotic prophylaxis for this procedure [8]. However, the optimal antibiotic prophylaxis is unclear with large variability in agent, dose, route, frequency of administration, and duration of treatment. Several studies have used antibiotic prophylaxis dose escalation to combat rising infective complications in recent years without much success [26-30].

An alternative to escalation and combination of antibiotics is to implement the use of rectal swabs and subsequent bacterial culture to guide antibiotic prophylaxis [16, 31-33]. Interestingly, several cohort studies identified patient specific risk factors (e.g. indwelling

urinary catheter, previous biopsy, previous fluoroquinolone therapy, diabetes, age etc.) for developing infectious complications following prostate biopsy [14, 34-38]. Thus, the question arises, if antibiotic prophylaxis should follow different regimes depending on a risk classification of patients [26].

Since, the use of antibiotics is inevitably followed by an increase in bacterial resistance [16, 39], non-antibiotic antimicrobial strategies could be beneficial. In this context, rectal cleansing preparations seem promising to reduce infections [40]. Nevertheless, different protocols have been published, and thus the ideal regimen and overall advantage has yet to be determined.

Finally, technical issues might have an important impact on the rate of infection. Several parameters including needle size, number of cores, route of biopsy, or use of local injected anaesthetics have to be evaluated with respect to infective complications [41-44].

Summarizing, this review aims investigating all possible antibiotic, non-antibiotic, and technical issues in patients with and without specific risk factors to reduce infective complications following prostate biopsy.

How the intervention might work

Prostate biopsy is mainly performed as transrectal needle biopsy. Since the needle has to cross the rectal space before reaching the prostate, a spread of microorganisms from the faecal flora into the prostate might occur. Here, antimicrobial prophylaxis is intended to provide bactericidal concentrations of the antibiotic in the target tissue at the time of contamination [45]. However, the efficacy of the prophylactic antibiotic largely depends on the bacterial spectrum at the surgical site, the antibiotic susceptibility of the pathogens, and the pharmacokinetic properties of the agent [46]. Particularly fluoroquinolones have been shown to exhibit high concentrations in prostate secretions and prostate tissue [47-50].

Several randomized controlled trials compared the use of antimicrobial agents with placebo/no treatment and reported a lower incidence of infectious related complications following prostate biopsy [20-25]. However, the optimal regime still has to be elucidated, since there is a between study heterogeneity concerning type, duration, and combination of

one or more antimicrobials. Given the increase in antibiotic resistance among bacteria causing UTI [51], an escalation of antibiotic prophylaxis might be necessary to reduce infective complications [26, 27].

An alternative to fixed empiric antibiotic regimes being routinely applied in all patients is to use a culture guided antibiotic prophylaxis. A recent meta-analysis of cohort studies shows that infective complications after prostate biopsy range from 3.3% to 0.3% by using a culture driven approach compared with the standard empiric therapy [16].

While the majority of patients do not suffer post-biopsy infective complications, another approach is to identify those patients being at higher risk for infections [14, 34-37]. Those patients identified at high risk might receive an extended antimicrobial regimen compared with those at low risk who are taking the standard prophylaxis [26].

In addition, non-antibiotic co-interventions in the form of rectal preparations/disinfections lowering the rectal microflora during the prostate biopsy [52] might be useful in reducing infections after prostate biopsy [53].

Finally, technical issues might have an important impact on infective complications. Here, an increased number of cores as well as larger needle size might be associated with an increased risk of infection [41, 42]. In addition, the biopsy route has to be considered, since the perineal approach specifically offers the possibility of circumventing the rectal flora with equal cancer detection rates [54]. Although the periprostatic nerve block is often applied to reduce pain during biopsy, the injection of local anaesthetic substances might result in the spread of bacteria from the rectal milieu into periprostatic tissue and thus, increased infective complications [43, 44].

Why it is important to do this review

Although there is a Cochrane review of antibiotic prophylaxis in prostate biopsy published in 2011 [1], an update is necessary due to the increase in antimicrobial resistance and thus infective complications following prostate biopsy [8, 12]. In addition, the Cochrane review excluded studies where patients had specific risk factors (e.g. bacteriuria before surgery,

indwelling catheters etc.) rendering them more susceptible for infective complications. Since such high-risk patients are frequently biopsied in the routine clinical setting, there is a need to assess possible antimicrobial strategies in this subgroup of patients [26]. A further interesting approach is the use of targeted antibiotic therapy being based on rectal swabs compared with sole empiric regimes [16].

Another important aspect is that the previous Cochrane review did not assess non-antibiotic interventions. In this context, one meta-analysis investigated rectal preparations with povidone-iodine regimens [53]. However, the impact of technical issues including number of cores, local anaesthesia as well as the route of biopsy (ie. transrectal, transperineal) or image-guidance (ie. ultrasound, magnetic resonance imaging) has not been systematically investigated in terms of infectious complications [41, 54-58]

Aims and objectives

The aim is to perform a systematic review of antimicrobial prophylaxis for prostate biopsy

The objectives of this review are:

1. To determine the most effective antimicrobial strategy for reducing the risk of infective complications due to prostate biopsies.
2. To determine whether specific strategies give most benefit for patient sub-groups identified as being at greater risk for infective complications.

Methods

Trial Eligibility Criteria

Types of studies

For the Cochrane review and EAU review:

We will include all randomized, controlled trials (RCT) or quasi randomised control trials irrespective of language of publication and publication status. Cluster RCTs will be excluded

because clustering (e.g. by hospital) may be related to antibiotic resistance patterns. Cross-over designs are not applicable.

For the EAU review:

We will include all randomized, controlled trials (RCT) or quasi randomised control trials. We will also include non-randomised comparative studies in case randomized controlled trials are lacking for specific parameters. Single arm cohort studies will be excluded **unless** they report on bacterial resistance.

Types of participants

Inclusion criteria

Men who undergo prostate biopsies using any strategy or approach (e.g. transrectal or transperineal). This includes men with suspicion of prostate cancer, or those already diagnosed with prostate cancer (e.g. active surveillance, local recurrence, salvage treatment) and those at higher risk of infective complications.

Exclusion criteria

Men who do not have prostate biopsies (mixed populations are excluded).

Subgroups of interest are:

- Previous biopsy in previous 12 months vs no previous biopsy: Exposure to previous biopsy may increase likelihood of sepsis from faecal reservoir of fluoroquinolone resistant organisms. At a conservative estimate this could take up to 12 months to revert to previous resistance status.
- Antibiotics in previous 6 months vs no antibiotics in previous 6 months: There is known induction of particularly fluoroquinolone resistance by use of other antibiotics such as trimethoprim and cephalosporins, 6 months is taken as a reasonable washout period for commensal bacteria to revert to previous patterns of resistance.
- Asymptomatic bacteriuria vs symptomatic bacteriuria (CDC definitions): Contamination of urine by potential uropathogens at the time of biopsy may increase risk of infectious complication and compromise effectiveness of antimicrobial strategies (includes men practicing clean intermittent catheterisation)

- Indwelling catheter vs no indwelling catheter: People with indwelling bladder catheter are likely to have bacteriuria and to have received antibiotics in the last 6 months
- Urethral instrumentation in previous 6 months vs no urethral instrumentation in previous 6 months: Urethral instrumentation is a risk factor for prostatic inflammation and bacteriuria as signaled by a rise in PSA giving higher risk of infective complications after prostate biopsy
- Previous local treatment for prostate cancer vs no previous treatment: Men having biopsies for possible recurrent or persistent disease following local therapy such as radiation or partial ablation will have existing necrosis and inflammatory change in the remaining prostate which could plausibly affect the rate of infectious complications

Types of interventions

The experimental intervention can be grouped into the following:

A) Antibiotics

- 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
- Dose of antibiotic (standard vs non-standard, as defined by 2015 EAU Guidelines)
- Timing (for single doses: ≤ 1 hour vs > 1 hour)
- Duration (single vs multiple within 24 hours vs multiple within > 24 hours)
- Route of antimicrobial administration (oral vs rectal vs intramuscular/intravenous)

B) Co-interventions

- Rectal preparation vs placebo or no treatment
- Use of rectal swab vs no rectal swab to guide prophylaxis
- Treatment of asymptomatic bacteriuria (ABU) vs no treatment prior to biopsy
- Use of rectal cleaning or preparation, including enema, disinfectant or antiseptic solution, or washing, prior to biopsy vs no use.

C) Technical aspects

- Number of cores

- Needle size
- Needle dwell time
- Transrectal vs perineal
- Fusion vs no fusion
- Local injected anaesthetic vs no local anaesthetic

The control intervention is placebo or no treatment or another active treatment. All combinations of antibiotics, co-interventions, and technical aspects are allowed.

Types of outcomes measures

The primary harm outcome is

- Symptomatic infectious complication
- Adverse effects of antimicrobial strategy

The secondary outcomes are

- Asymptomatic bacteriuria
- Hospitalization due to infective complications
- Mortality
- Adverse effects of antimicrobial strategy
- Change in bacterial resistance (before, after biopsy)

Literature Search

The Medline, Embase, LILACS and Cochrane controlled trials databases and clinicaltrial.gov will be searched for all relevant publications. PubMed will be searched, alongside an update search near the end of the project to ensure that recent publications are captured. We will search opengrey.eu and oclc.org for grey literature. We will try to identify other potentially-eligible trials or ancillary publications by searching the reference lists of retrieved included trials, reviews, meta-analyses and health technology assessment reports. We will also contact study authors of included trials to identify any further studies that we may have missed. There will be no date or language restrictions. The full search strategy is provided in Appendix 1.

Data collection and analysis

Selection of studies

Following de-duplication, two review authors will independently screen the titles and abstracts of identified records for eligibility. The full-text of all potentially eligible records will be retrieved and screened independently by two review authors using a standardised form, linking together multiple records of the same study in the process. Any disagreements will be resolved by discussion or by consulting a third review author. The study selection process will be described using a PRISMA flow diagram [59].

Data extraction and management for Cochrane and EAU review

Two review authors will independently extract study characteristic and outcome data. Any disagreements will be resolved by discussion or by consulting a third review author. We will use a standardised data extraction form which will be piloted. In case of any incompletely reported data, study authors will be contacted.

Data to be extracted and included in the 'characteristics of included studies' table are:

- Study citation,
- Study design.
- Study dates (if dates are not available then this will be reported as such).
- Study settings and country.
- Participant inclusion and exclusion criteria.
- Participant details, baseline demographics.
- The number of participants by study and by study arm.
- Details of relevant experimental and comparator interventions such as dose, route, frequency, and duration.
- Definitions of relevant outcomes, and method and timing of outcome measurement as well as any relevant subgroups.
- Study funding sources.
- Declarations of interest by primary investigators.
- (For EAU review) If not by randomization, then how intervention comparator groups were formed
- (For EAU review) whether there was an *a priori* protocol or analysis plan

- Number who received intended treatment and analysed
- Losses and exclusions of participants, with reasons.

We will extract relevant outcome data as needed for calculation of summary statistics and measures of variance. For dichotomous outcomes, we will attempt to obtain numbers of events and totals for population of a 2 x 2 table, as well as summary statistics with corresponding measures of variance. For continuous outcomes, we will attempt to obtain means and standard deviations or data necessary to calculate this information. For time-to-event outcomes, we will attempt to obtain hazard ratios (HRs) with corresponding measures of variance or data necessary to calculate this information.

Assessment of risk of bias in included studies

For Cochrane review and EAU review:

The 'risk of bias' of each included study will be assessed by two review authors working independently. Any disagreements will be resolved by discussion or by consulting a third review author. Risk of bias RCTs will be assessed by using the recommended tool in the *Cochrane Handbook for Systematic Reviews of Interventions* [60]. This includes the assessment of: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other sources of bias.

For performance bias (blinding of participants and personnel) and detection bias (blinding of outcome assessment), we will evaluate the risk of bias separately for each outcome, and we will clarify which outcomes were measured subjectively or objectively and consider this too when reporting our findings in the 'Risk of bias' tables.

We will also assess attrition bias (incomplete outcome data) on an outcome-specific basis, and will group outcomes with like judgements when reporting our findings in the 'Risk of bias' tables.

We will further summarize the risk of bias across domains for each outcome in each included study, as well as across studies and domains for each outcome.

Additional for EAU review:

Risk of bias in non-randomised comparative studies will be assessed using all the seven domains above, and an extra item to assess the risk of findings being explained by confounding. This is a pragmatic approach informed by methodological literature pertaining to assessing risk of bias in non-randomized studies [61, 62]. A list of the five most important potential confounders for infective complications following prostate biopsy was developed *a priori* with clinical content experts (EAU Urological Infections guideline panel). The potential confounding factors are:

- Previous biopsy
- Antibiotics in previous 6 months
- Asymptomatic bacteriuria
- Indwelling catheter
- Urethral instrumentation in previous 6 months

For each study, an algorithmic approach will be used to assess risk of confounding bias. The following will be considered in sequence:

1. Was the prognostic confounder considered (yes/no)? If ‘no’, the study is at ‘high’ risk of bias for this confounder. If ‘yes’ go to question 2.
2. Was the confounder balanced between the intervention(s) and control group (s) (yes/no)? If ‘yes’, the study is a ‘low’ risk of bias. If ‘no’, go to questions 3.
3. Was the confounder was controlled for in the analysis, for example by statistical adjustment such as univariate or multivariate analysis or propensity score matching? If ‘yes’ the study is at low risk bias. If ‘no’ the study is at high risk of bias.

These three factors will be considered in making an overall risk of bias judgement for each confounder.

Risk of bias in non-comparative studies, if included, cannot be assessed with the approach described above, which is designed to assess internal validity of comparative studies. Therefore, concern will be extended to addressing external validity (applicability of results to

different people, places or time) of non-comparative studies by assessing whether study participants were selected consecutively or representative of a wider patient population. Attrition bias, selective outcome reporting and whether an a priori protocol is available (indicating prospective study design) is available, will also be assessed. This too is a pragmatic approach informed by the methodological literature [63, 64].

Measures of treatment effect

We will express dichotomous data as risk ratios (RR) with 95% confidence intervals (CIs) where available. We will express continuous data as mean difference (MD) with 95% confidence intervals (CIs). Where continuous outcomes are measured using different scales, we will express the data as standardised mean differences with 95% CIs. Time to event data will be expressed as hazard ratios (HR) with 95% CIs.

Unit of analysis issues

The primary analysis will be per participant randomised. For studies with more than two intervention groups, only the intervention groups relevant to the review will be selected, or groups will be combined to create a single pair-wise comparison where possible.

Dealing with missing data

We will conduct an intention-to-treat analysis, if data are available; we will otherwise conduct an available case analysis. We will not impute missing data. In case of any incompletely reported data, we will attempt to contact authors.

Assessment of publication bias

The review authors aim to minimise potential publication bias by conducting a comprehensive literature search for eligible studies. If 10 or more studies investigating a particular outcome are included, we will use funnel plots to assess heterogeneity of study effects. Several explanations can be offered for the asymmetry of a funnel plot, including true heterogeneity of effect with respect to trial size, poor methodological design (and hence bias of small trials) and publication bias. We will therefore interpret results carefully.

Data synthesis

For Cochrane review and EAU review:

Meta-analysis will be performed if there is more than one randomised or quasi-randomised controlled trial reporting the same outcome. For studies with multiple publications, only the most up-to-date or complete data for each outcome will be utilized. Quantitative synthesis will not be undertaken for non-randomised studies. Unless there is good evidence for homogeneous effects across studies, we will summarize data using a random-effects model. We will interpret random-effects meta-analyses with due consideration of the whole distribution of effects. In addition, we will perform statistical analyses according to the statistical guidelines contained in the *Cochrane Handbook for Systematic Reviews of Interventions*. [60] For time-to-event data, the log (hazard ratio) and its variance will be combined using the generic inverse variance method. Dichotomous outcomes will be combined using the Mantel-Haenszel risk ratio method. Continuous outcomes will be combined using the inverse variance mean difference method. If studies use different scales to assess the same continuous outcome, the standardized mean difference will be used instead of the mean difference.

Additional for the EAU review

If meta-analyses are inappropriate, we will use the narrative synthesis approach to summarise the results [65].

Assessment of heterogeneity

Heterogeneity between studies will be assessed by visual inspection of plots of the data, the Chi² test for heterogeneity and I² statistics [61]. We will consider substantial heterogeneity present if I² is greater than 50%. Possible reasons for heterogeneity will be explored, such as differences in the population studied, the treatment given, or the way in which the outcomes were assessed.

If there are sufficient data, subgroup analysis will be conducted to explore potential heterogeneity based on the prioritized subgroups.

- 1) Previous biopsy
- 2) Antibiotics in previous 6 months
- 3) Asymptomatic bacteriuria
- 4) Indwelling catheter
- 5) Urethral instrumentation in previous 6 months

Sensitivity analysis

If there are sufficient included studies, we will conduct a sensitivity analysis to assess the robustness of our review results by repeating the analysis only including studies with an overall medium to low risk of bias.

Assessment of reporting biases

The review authors will, aim to minimise potential biases by conducting a comprehensive literature search for eligible studies.

For Cochrane review:

Summary of findings table:

We will present the overall quality of the evidence for each outcome according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which takes into account five criteria not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity such as directness of results [66]. For each comparison, two review authors (AP and CA) will independently rate the quality of evidence for each outcome as 'high', 'moderate', 'low', or 'very low' using GRADEproGDT; discrepancies will be resolved by consensus, or, if needed, by arbitration by a third review author (SM, TA or RP) For each comparison, we will present a summary of the evidence for the main outcomes in a 'Summary of findings' table, which provides key information about the best estimate of the magnitude of the effect, in relative terms and absolute differences for each relevant comparison of alternative management strategies; numbers of participants and studies addressing each important outcome; and the rating of the overall confidence in effect estimates for each outcome [67, 68]. If meta-analysis is not possible, we will present results in a narrative 'Summary of findings' table.

Acknowledgements

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Contributions of authors

Contributions of authors will be stated in agreement with the publications rules set by the peer reviewed journal that will accept this systematic review.

Declaration of interest

Declaration of interest will be stated in agreement with the publications rules set by the peer reviewed journal that will accept this systematic review.

Administrative Aspects

Literature Search

The literature search will be carried out by Cathy Yuan using the search criteria specified in Appendix 1. Cathy Yuan and Adrian Pilatz will delete the duplicates to provide the final list of abstracts to be reviewed.

Study abstracts identified by the literature search will be reviewed by Adrian Pilatz, Benjamin Pradere, Robert Pickard, and Temitope Adewuyi. Steven MacLennan will provide methodological supervision following the procedures described in Appendix 2.

Data Collection, Management and Quality Control

Data on patient and disease characteristics, treatment and patient outcome will be extracted (collected) for each study by Adrian Pilatz, Benjamin Pradere, Robert Pickard, and Temitope Adewuyi.

Data will be stored in Excel files on Dropbox.

Basic quality control checks will be carried out on the database from each study in order to assess the quality of the data. A separate analysis will be done for each study and compared to the results in the original publication of the study.

Data Quality Control Committee

Data quality control will be assured by Robert Pickard, Frank Bruyère, and Mete Çek.

Steering Committee

EAU Urological Infections Guidelines Panel.

Writing Committee

EAU Urological Infections Guidelines Panel in conjunction with reviewers involved in this systematic review.

Publication of the Results and Authorship

Publication of results will be in a peer reviewed journal and authorship will be decided based on amount of contribution from each actively involved party.

Timelines

Literature search will be conducted in May 2015, Abstract screening from May 2015 to June 2015, fulltext screening from June 2015 to July 2015, data extraction from July 2015 to August 2015 and summary analysis and drafting of systematic review article from July 2015 to November 2015.

Finances

This systematic review will be conducted through altruistic donation of time and knowledge from involved parties.

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Appendix 1: Literature Search Strategy

The following databases will be searched using the provided search strategy:

1. Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>;
2. Database (Ovid): Embase <1974 to Present>;
3. Cochrane library databases (Cochrane reviews and other reviews, CENTRAL, technology assessments) <inception date to Present>
4. LILACS for not indexed Spanish and Portuguese studies
5. Pubmed (A simple search for studies that not indexed by Medline in Pubmed before the end of the review).
6. Hand search trial registries: Clinicaltrials.gov (<https://clinicaltrials.gov/>) and WHO ICTRP (<http://www.who.int/ictip/en/>)
7. Grey literature www.opengrey.eu/; <http://www.oclc.org/oaister.en.html>

Search strategies:

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

-
1. exp Prostate/
 2. exp Prostatic Neoplasms/
 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 Anti-Infective Agents/
 10. exp Quinolones/
 11. exp Metronidazole/
 12. exp Gentamicins/
 13. exp Carbapenems/
 14. exp Trimethoprim/
 15. exp Piperacillin/
 16. exp Clavulanic Acids/
 17. exp Netilmicin/
 18. exp Cefuroxime/
 19. exp Norfloxacin/
 20. exp Ciprofloxacin/
 21. exp Ofloxacin/

22. exp Tinidazole/
23. exp Ceftriaxone/
24. exp Sulfonamides/
25. exp Aminoglycosides/
26. exp Cephalosporins/
27. exp beta-Lactamase Inhibitors/
28. exp Disinfection/ or exp Disinfectants/
29. (antibiotic* or antibacterial or anti bacterial or antiseptic* antimicrobial* or anti infect* or antiinfect* or disinfectant* or disinfection).tw.
30. (fluoroquinolone* or quinolone* or quinolinone* or gentamicin* or metronidazole or flagyl).tw.
31. (Carbapenem* or trimethoprim or sulphamethoxazole or Co-amoxiclav).tw.
32. (clavulanic acid* or sulfonamide* or aminoglycoside* or cephalosporin* or piperacillin or cefuroxime or norfloxacin).tw.
33. (ciprofloxacin or ofloxacin or tinidazole or cephtriaxon or ceftriaxone or netilmicin or netromycine).tw.
34. (cotrimoxazole or co-trimoxazole or sulfamethoxazole or (beta lactamase adj2 (inhibitors* or antagonist*))).tw.
35. (povidone iodine or betadine or iodophor or povidone).tw.
36. exp povidone/ or exp Iodophors/
37. or/9-36
38. 8 and 37
39. exp Pre-Exposure Prophylaxis/
40. exp Antibiotic Prophylaxis/
41. exp Primary Prevention/
42. (prophylaxis or prophylactic or prevent* or reduce* or reduction or reducing).tw.
43. (pre-biopsy or prebiopsy or pre-biopsies or prebiopsies).tw.
44. (pre-operativ* or pre-intervention or pre-procedure* or preoperativ* or preintervention or preprocedure*).tw.
45. (before or prior).tw.
46. or/39-45
47. 38 and 46
48. ((rectal or rectum) adj3 (swab or cleaning or washing or preparation* or sterilization)).tw.
49. exp Enema/ or enema.tw.
50. ((transrectal or trans-rectal) and perineal).tw.
51. (fusion adj3 (guided or guidance or guide or guiding)).tw.
52. (needle adj3 (size or dwell time or (number adj2 cores))).tw.
53. exp Anesthetics, Local/ or ((local or topical) adj2 (anaesthetic* or anesthetic*)).tw.
54. (dipstick urinalysis or midstream specimen of urine).tw.
55. (technical modification* or technical alternation*).tw.
56. or/48-55
57. 8 and 46 and 56
58. 47 or 57

Database: Embase <1974 to present>

Search Strategy:

1. exp prostate/
2. exp prostate tumor/
3. (prostatic or prostate).ti,ab,kw.
4. or/1-3
5. exp biopsy/
6. (biopsy or biopsies).ti,ab,kw.
7. or/5-6
8. 4 and 7
9. exp antiinfective agent/
10. exp quinolone derivative/
11. exp metronidazole/
12. exp gentamicin/
13. exp carbapenem/
14. exp trimethoprim/
15. exp sulfamethoxazole/
16. exp cotrimoxazole/
17. exp amoxicillin plus clavulanic acid/
18. exp clavulanic acid/
19. exp piperacillin/
20. exp netilmicin/
21. exp cefuroxime/
22. exp norfloxacin/
23. exp ciprofloxacin/
24. exp ofloxacin/
25. exp tinidazole/
26. exp ceftriaxone/
27. exp sulfonamide/
28. exp aminoglycoside/
29. exp cephalosporin/
30. exp beta lactamase inhibitor/
31. exp disinfection/ or exp disinfectant agent/
32. (antibiotic* or antibacterial or anti bacterial or antiseptic* antimicrobial* or anti infect* or antiinfect* or disinfectant* or disinfection).tw.
33. (fluoroquinolone* or quinolone* or quinolinone* or gentamicin* or metronidazole or flagyl).tw.

34. (Carbapenem* or trimethoprim or sulphamethoxazole or Co-amoxiclav).tw.
35. (clavulanic acid* or sulfonamide* or aminoglycoside* or cephalosporin* or piperacillin or cefuroxime or norfloxacin).tw.
36. (ciprofloxacin or ofloxacin or tinidazole or cephtriaxon or ceftriaxone or netilmicin or netromycine).tw.
37. (cotrimoxazole or co-trimoxazole or sulfamethoxazole or (beta lactamase adj2 (inhibitors* or antagonist*))).tw.
38. (povidone iodine or betadine or iodophor or povidone).tw.
39. exp povidone iodine/ or exp povidone/ or exp iodophor/
40. or/9-39
41. 8 and 40
42. exp prophylaxis/
43. exp prevention/
44. (prophylaxis or prophylactic or prevent* or reduce* or reduction or reducing).tw.
45. (pre-biopsy or prebiopsy or pre-biopsies or prebiopsies).tw.
46. (pre-operativ* or pre-intervention or pre-procedure* or preoperativ* or preintervention or preprocedure*).tw.
47. (before or prior).tw.
48. or/42-47
49. 41 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 perineal).tw.
53. (fusion adj3 (guided or guidance or guiding or guide)).tw.
54. (needle adj3 (size or dwell time or (number adj2 cores))).tw.
55. exp local anesthetic agent/ or ((local or topical) adj2 (anaesthetic* or anesthetic* or anesthesia or anaesthesia)).tw.
56. (dipstick urinalysis or midstream specimen of urine).tw.
57. (technical modification* or technical alternation*).tw.
58. or/50-57
59. 8 and 48 and 58
60. 49 or 59

Cochrane library databases

ID	Search
#1	MeSH descriptor: [Prostate] explode all trees

- #2 MeSH descriptor: [Prostatic Neoplasms] explode all trees
- #3 prostatic or prostate:ti,ab,kw (Word variations have been searched)
- #4 #1 or #2 or #3
- #5 MeSH descriptor: [Biopsy] explode all trees
- #6 biopsy or biopsies:ti,ab,kw (Word variations have been searched)
- #7 #5 or #6
- #8 #4 and #7
- #9 MeSH descriptor: [Anti-Infective Agents] explode all trees
- #10 MeSH descriptor: [Quinolones] explode all trees
- #11 MeSH descriptor: [Metronidazole] explode all trees
- #12 MeSH descriptor: [Gentamicins] explode all trees
- #13 MeSH descriptor: [Carbapenems] explode all trees
- #14 MeSH descriptor: [Trimethoprim] explode all trees
- #15 MeSH descriptor: [Piperacillin] explode all trees
- #16 MeSH descriptor: [Clavulanic Acids] explode all trees
- #17 MeSH descriptor: [Netilmicin] explode all trees
- #18 MeSH descriptor: [Cefuroxime] explode all trees
- #19 MeSH descriptor: [Norfloxacin] explode all trees
- #20 MeSH descriptor: [Ciprofloxacin] explode all trees
- #21 MeSH descriptor: [Ofloxacin] explode all trees
- #22 MeSH descriptor: [Tinidazole] explode all trees
- #23 MeSH descriptor: [Ceftriaxone] explode all trees
- #24 MeSH descriptor: [Sulfonamides] explode all trees
- #25 MeSH descriptor: [Aminoglycosides] explode all trees
- #26 MeSH descriptor: [Cephalosporins] explode all trees
- #27 MeSH descriptor: [beta-Lactamase Inhibitors] explode all trees
- #28 antibiotic* or antibacterial or anti bacterial or antiseptic* antimicrobial* or anti infect* or antiinfec* or disinfection or disinfectant*:ti,ab,kw (Word variations have been searched)
- #29 fluoroquinolone* or quinolone* or quinolinone* or gentamicin* or metronidazole or flagyl:ti,ab,kw (Word variations have been searched)
- #30 Carbapenem* or trimethoprim or sulphamethoxazole or Co-amoxiclav:ti,ab,kw (Word variations have been searched)
- #31 clavulanic acid* or sulfonamide* or aminoglycoside* or cephalosporin* or piperacillin or cefuroxime or norfloxacin:ti,ab,kw (Word variations have been searched)
- #32 ciprofloxacin or ofloxacin or tinidazole or cephtriaxon or ceftriaxone or netilmicin or netromycine:ti,ab,kw (Word variations have been searched)

- #33 cotrimoxazole or co-trimoxazole or sulfamethoxazole or (beta lactamase near/2 (inhibitors* or antagonist*)):ti,ab,kw (Word variations have been searched)
- #34 MeSH descriptor: [Disinfectants] explode all trees
- #35 MeSH descriptor: [Disinfection] explode all trees
- #36 povidone iodine or betadine or iodophor or povidone:ti,ab,kw (Word variations have been searched)
- #37 MeSH descriptor: [Povidone] explode all trees
- #38 MeSH descriptor: [Iodophors] explode all trees
- #39 #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23
- #40 #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38
- #41 #39 or #40
- #42 #8 and #41
- #43 MeSH descriptor: [Antibiotic Prophylaxis] explode all trees
- #44 MeSH descriptor: [Pre-Exposure Prophylaxis] explode all trees
- #45 prophylaxis or prophylactic or prevent* or reduce* or reduction or reducing:ti,ab,kw (Word variations have been searched)
- #46 pre-biopsy or prebiopsy or pre-biopsies or prebiopsies:ti,ab,kw (Word variations have been searched)
- #47 MeSH descriptor: [Primary Prevention] explode all trees
- #48 pre-operativ* or pre-intervention or pre-procedure* or preoperativ* or preintervention or preprocedure*:ti,ab,kw (Word variations have been searched)
- #49 before or prior:ti,ab,kw (Word variations have been searched)
- #50 #43 or #44 or #45 or #46 or #47 or #48 or #49
- #51 #42 and #50
- #52 (rectal or rectum):ti,ab,kw and (swab or cleaning or washing or preparation* or sterilization):ti,ab,kw (Word variations have been searched)
- #53 MeSH descriptor: [Enema] explode all trees
- #54 enema:ti,ab,kw (Word variations have been searched)
- #55 transrectal or trans-rectal:ti,ab,kw and perineal:ti,ab,kw (Word variations have been searched)
- #56 fusion:ti,ab,kw and guided or guidance or guide or guiding:ti,ab,kw (Word variations have been searched)
- #57 needle:ti,ab,kw and size or dwell time or (number near/2 cores):ti,ab,kw (Word variations have been searched)

- #58 MeSH descriptor: [Anesthetics, Local] explode all trees
- #59 local or topical:ti,ab,kw and anaesthetic* or anesthetic*:ti,ab,kw (Word variations have been searched)
- #60 dipstick urinalysis or midstream specimen of urine:ti,ab,kw (Word variations have been searched)
- #61 technical modification* or technical alternation*:ti,ab,kw (Word variations have been searched)
- #62 #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61
- #63 #8 and #50 and #62
- #64 #51 or #63

It is noted that for some studies there is a time lag between the date published in PubMed and collected by Medline (OvidSP). we will perform a simple search for studies that not indexed by Medline in Pubmed; before the end of the review,.

De-duplication of Identified Studies

Search results will be combined and duplicates removed by Cathy Yuan and Adrian Pilatz.

Appendix 2: Review of Studies Identified by the Literature Search and Searching Meeting Abstracts

The abstracts of studies that are identified by the literature search will be reviewed by a review team including:

Robert Pickard (Corresponding)

Frank Bruyère (Senior)

Metek Çek (Senior)

Adrian Pilatz (Associate)

Benjamin Pradere (Associate)

Temitope Adewuyi (Research Fellow)

The studies identified by the literature search will be divided among reviewers such that the abstract of each study is independently reviewed by two different reviewers.

Review of Studies Identified by the Literature Search

A separate Study Eligibility Form will be used as an aide in identifying eligible studies. It will be filled out by each reviewer for all studies that are identified as being potentially eligible or for which the eligibility is unclear based on their review of the abstract. Associates will primarily retrieve the fulltext of the studies identified as potentially relevant. On those cases, where a fulltext access is not possible, the form will be e-mailed to the EAU Guideline Office to request the full publication.

The unclear and potentially eligible studies will be entered into an Excel database by the reviewer in order to keep track of the study's status and final disposition. The Excel file will include information on whether or not the study is eligible and if not, the reason for exclusion. Excel sheets from the various reviewers will be combined after collection from all reviewers.

Final Assessment of Study Eligibility

Disagreements between reviewers on study eligibility should be worked out between the reviewers whenever possible. The list of studies proposed as being eligible and the studies for which agreement between the reviewers could not be reached will be reviewed by at least one senior or corresponding member.