The effect of rectal swab culture-guided antimicrobial prophylaxis in men undergoing prostate biopsy on infectious complications and cost of care: A randomized controlled trial in the Netherlands.

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- To assess the effectiveness of rectal culture-guided antimicrobial prophylaxis for transrectal prostate biopsy (random ultrasound-guided, targeted MRI-guided or targeted MRI-ultrasound fusion guided) on infectious complications. - To compare the...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON48812

Source
ToetsingOnline

Brief title
PRO-SWAP

Condition

- Other condition
- Bacterial infectious disorders

Synonym
infectious complications, prostate biopsy

Health condition

screening op prostaatcarcinoom (d.m.v. prostaatbiopsie)

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: ZonMw subsidie

Intervention

Keyword: Culture-guided, Infection, Prophylaxis, Prostate biopsy

Outcome measures

Primary outcome

Any registered clinical infectious complication (urinary tract infection (UTI),

pyelonephritis, sepsis, fever, acute prostatitis, acute epididymitis) within 7

days after transrectal prostate biopsy.

* UTI is defined as pyuria (>5 leucocytes per high-powered field) and

bacteriuria (*10^3 colony-forming units/ml) with symptoms of dysuria, urgency,

frequency or hematuria.

* pyelonephritis is defined as pyuria and bacteriuria with symptoms of fever,

flank pain, nausea or vomiting.

* fever is defined as a temperature *38.0°C.

* sepsis is defined as suspected infection plus at least two of the following

criteria (qSOFA score): low blood pressure (SBP*100 mmHg), high respiratory

rate (*22 breaths per min), or altered mentation (Glasgow coma scale <15).

* severe sepsis or septic shock is defined as sepsis plus organ dysfunction or

with persisting hypotension requiring vasopressors to maintain MAP *65 mmHg and to have a serum lactate level <2 mmol/L despite adequate volume resuscitation.

* acute prostatitis is defined as fever, bacteriuria and/or pyuria, and a painful prostate.

* acute epididymitis is defined as the presence of a swollen, red or warm scrotum and pain for which antibiotics are prescribed.

Secondary outcome

1. Cost of care 30 days after transrectal prostate biopsy to determine and compare overall costs of care among the intervention- and the control group.

2. Positive microbiological urine or blood culture results within 7 and 30 days after transrectal prostate biopsy.

3. Clinical infectious complications (as for primary endpoint) within 30 days after transrectal prostate biopsy.

Exploratory:

1. Hospitalization, including ICU admission and length of admission, within 30 days after transrectal prostate biopsy.

2. Overall mortality within 30 days after transrectal prostate biopsy.

3. Side effects and toxicity of used antibiotics within 30 days after transrectal prostate biopsy.

4. Prevalence of ciprofloxacin resistant GNB in local rectal flora, assessed through microbiological rectal swab cultures.

5. Overall antibiotic use within 30 days after transrectal prostate biopsy.

6. The relation between antibiotic resistance in the fecal carriage and other

determinants of infection after transrectal prostate biopsy.

7. Experiences of patients and healthcare professionals regarding barriers and facilitators (determinants) that influence the performance of the culture-guided approach in daily clinical practice.

Study description

Background summary

Transrectal ultrasound guided prostate biopsy (TRUS-PB) is a well established procedure to obtain tissue for the histological diagnosis of prostate cancer. In The Netherlands, TRUS-PB is performed in approximately 40.000 patients annually. During TRUS-PB, a spring-loaded device is used to collect multiple core biopsies, sampling tissue systematically from both sides of the gland. A variety of infectious complications may occur following transrectal prostate biopsy, ranging from asymptomatic bacteriuria or urinary tract infection (UTI) to prostatitis, bacteremia, and severe sepsis. Although no studies have clearly defined the pathophysiology of TRUS-PB related infectious complications, the cause appears to be direct inoculation of bacteria from the rectal mucosa by the biopsy needle into the prostate, blood vessels, or urinary tract.
Several classes of antibiotics are proven effective for prophylaxis during TRUS-PB, reducing infectious complications to less than 1% in case of susceptible rectal flora. Ciprofloxacin has been best studied and is recommended as first choice prophylaxis in American, European en Dutch urology guidelines, although no clear recommendations are made on the duration of prophylaxis. In the Netherlands, therefore, various prophylactic ciprofloxacin schedules are used, of which 2 to 3 days regimens are most common. Prolonged duration of prophylaxis in TRUS-PB is not proven to be more effective than a 1-day regimen, but it is more likely to select more fluoroquinolone (FQ) resistance
Due to increasing FQ resistance in gram negative bacilli (GNB) (currently more than 20% in E. coli), a significant increase up to 6% in infectious complications after TRUS-PB procedures was recently noticed. Antibiotic treatment of these infections and hospitalization may account for increased health care associated costs and will contribute to the further development of antibiotic resistance.
Directed antibiotic prophylaxis based on resistance data of individual rectal cultures may be an effective strategy to overcome the problem of increasing fluoroquinolone (FQ) resistance and reduce infectious complications after transrectal prostate biopsy. Previous studies already showed promising results but had retrospective designs, did not use control groups, used unclear

screenings techniques or were underpowered. In addition, expensive and time-consuming bacterial culture methods were performed. Moreover, the majority of these studies used intravenous antibiotics in case of FQ resistance. Oral alternatives to FQ, if available, are preferred over intravenous prophylaxis, because they are cheaper and more comfortable for the patient.

In the Radboudumc, MRI-guided or MRI-ultrasound fusion guided prostate biopsies are performed in almost all patients instead of TRUS-PB. MRI of the prostate is capable of detecting clinically relevant prostate cancer. Therefore patients with a normal MRI of the prostate may not need to undergo transrectal prostate biopsy. Moreover, MRI-guided or MRI-ultrasound fusion guided lesion targeting, allows urologist to progress from blind, systematic biopsies with 12 core samples to more accurate targeted biopsies with only 2 till 4 core samples. Because less core samples are taken with these techniques, the amount of infectious complications after MRI-guided or MRI-ultrasound fusion guided prostate biopsies might be reduced compared to TRUS-PB. However, there is no literature available on this subject.

Study objective

- To assess the effectiveness of rectal culture-guided antimicrobial prophylaxis for transrectal prostate biopsy (random ultrasound-guided, targeted MRI-guided or targeted MRI-ultrasound fusion guided) on infectious complications.
- To compare the cost-effectiveness of empirical antimicrobial prophylaxis (ciprofloxacin) to rectal culture-guided antimicrobial prophylaxis for transrectal prostate biopsy.
- To assess experiences of patients and professionals regarding barriers and facilitators (determinants) that influence the performance of the culture-guided approach in daily clinical practice.

With a culture-guided antibiotic prophylaxis strategy we aim to contribute to the control of antibiotic resistance by reducing infectious complications (less use of therapeutic antibiotics), prescription of prophylaxis based on rectal microbiome data and reducing duration of antibiotic prophylaxis to 24 hours (except for pivmecillinam/augmentin prophylaxis). Moreover, we will be able to compare the difference of infectious complications after random transrectal ultrasound-guided, targeted MRI and MRI-ultrasound fusion guided prostate biopsy.

Study design

Prospective, randomized, open-label, comparative, multi-center trial with two study arms (intervention group and control group).

Intervention

Patients will be randomized into two groups of 809 patients each with stratification for study site and type of prostate biopsy (random ultrasound-guided, targeted MRI-guided, targeted MRI-ultrasound fusion guided):

Control group: empirical prophylaxis strategy (standard of care) (ciprofloxacin 500 mg orally 2 hours before and 12 hours after the procedure).

Intervention group: culture-guided oral antibiotic prophylaxis strategy. Men whose rectal swabs do not show ciprofloxacin-resistant bacteria (estimated at 75-80%) will receive ciprofloxacin prophylaxis (similar to the control group), and men whose swabs do show ciprofloxacin-resistant bacteria will receive alternative oral antibiotics based on the culture results (in the following order):

* trimethoprim/sulfamethoxazole (SXT) 960 mg orally 2 hours before the procedure and again 12 hours later, or
* fosfomycin 3 g orally 2 hours before the procedure, or
* pivmecillinam/amoxicilline/clavulaanzuur respectively 400 mg and 500/125 mg 2 hours before biopsy, followed by 2 days with three divided doses each day after biopsy

Study burden and risks

At three moments during the study period patients have to fill in a few questionnaires:
- Baseline (approximately 7 days prior to prostate biopsy): questionnaire about demographic parameters, use of medication (including antibiotics), medical history, allergies and other parameters which might intervene with the study outcome, EQ-5D-5L (to assess health status), iMTA PCQ (to assess productivity loss).
- At approximately 7 days and 30 days after prostate biopsy: questionnaire about the study measurements, EQ-5D-5L, iMTA PCQ.

At two moments during the study period a rectal swab is performed (at home by self-sampling approximately 14 days prior to prostate biopsy and immediately before prostate biopsy by the urologist). Utility of a rectum swab culture is a minimally invasive method to provide information on patients' rectal flora.

At baseline, some patients (phase 1) will be approached for an in-depth interview (approximately 5-10 patients per center, for approximately 1 hour per patient) as part of an analysis of determinants that influence the performance of the culture-guided approach in daily clinical practice. Interviews will take place at a with the patient agreed upon moment and location. Based upon these results, a questionnaire will be developed to assess barriers and facilitators experienced. Thereafter (phase 2), approximately 50-100 patients per center will be asked to fill in an extra questionnaire at baseline (approximately 15 minutes).

According to the laws and regulations associated with research with a medicinal product, the study medication must be provided from the Clinical Trial Units of the hospital pharmacies of the participating centers. Therefore, participants can not obtain the antimicrobial prophylaxis at their home pharmacy. Participants will be offered two choices: to obtain the antimicrobial prophylaxis in the days before prostate biopsy at the hospital pharmacy (consequence: extra trip to the hospital) or to be present in the hospital two hours prior to prostate biopsy and then obtain the antimicrobial prophylaxis at the hospital pharmacy (and take the antimicrobial prophylaxis immediately). No extra other (study-related) hospital visits are required.

Risks associated with participation:
The risks associated with participation in the study are negligible. Utility of a rectum swab culture is a minimally invasive and safe method to provide information on a participant*s rectal flora. It is already routine procedure for patients, admitted to Dutch hospitals, that are at risk for carriage of multidrug resistant bacteria (HRMO screening or methicillin-resistant Staphylococcus aureus (MRSA).
The alternative antibiotics which may be prescribed in case of FQ resistance are all registered in the Netherlands and good, logical alternatives as antimicrobial prophylactic around prostate biopsy. We do not expect additional risks compared to the use of the standard antibiotic prophylaxis with ciprofloxacin and besides already registered adverse effects. In addition, it should be mentioned that it concerns antibiotic prophylaxis, which means that the antibiotics are used only for a short period (mostly only for up to 24 hours).

Benefit:
We expect that the intervention group (with rectal swab culture-guided antimicrobial prophylaxis) will have a lower risk of post-biopsy infectious complications compared to the control group (estimated at respectively 0.8% and 2.6%).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Subject undergoes a transrectal prostate biopsy as part of the standard care in one of the participating (study) centers (because of suspicion of prostate cancer).
- Subject is able and willing to sign the Informed Consent Form.

Exclusion criteria

- Inability to receive ciprofloxacin prophylaxis for any reason (e.g. documented history of sensitivity to medicinal products or excipients similar to those found in the antibiotic prophylaxis, relevant history or presence of cardiovascular disorders (specific relevant QTc time prolongation), relevant drug interaction).
- Inability to receive either co-trimoxazole, fosfomycin and pivmecillinam/augmentin prophylaxis for any reason (e.g. documented history of sensitivity to medicinal products or excipients similar to those found in the antibiotic prophylaxis, relevant drug interaction).
- Inability to understand the nature of the trial and the procedures required.
- Individuals with an urinary tract infection or acute prostatitis within 14 days prior to transrectal prostate biopsy.
- Individuals who received antibiotics within 14 days prior to transrectal prostate biopsy.
- Individuals who fail to send a rectum swab to the microbiology laboratory.
- Individuals whose rectal swab shows no growth on a Colombia blood agar (CBP)

(growth control)

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-04-2018
Enrollment:	1618
Type:	Actual

Medical products/devices used

Generic name:	Eswab of the rectum
Registration:	Yes - CE intended use
Product type:	Medicine
Brand name:	Augmentin
Generic name:	Amoxicillin/clavulanic acid
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Ciproxin
Generic name:	Ciprofloxacin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Co-trimoxazole
Generic name:	Trimethoprim//sulfamethoxazole

Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Monuril
Generic name:	Fosfomycin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Selexid
Generic name:	Pivmecillinam
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	14-12-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-02-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-03-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-07-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-10-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-12-2018
Application type:	Amendment

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-02-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-02-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-03-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-04-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-07-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-07-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2017-002938-23-NL
ClinicalTrials.gov	NCT03228108
CCMO	NL63566.091.17

Study results

Date completed:	26-09-2021
Actual enrolment:	1538