Title	Relevance of the urine bacterial culture performed before transurethral resection of the bladder for post-operative febrile urinary tract infection prevention: a non-inferiority randomized controlled trial
Acronym	RUPTURE
NCT number	NCT07463963
Date of the document	13 August 2026

The Statistical Analysis Plan of the RUPTURE Study

This Statistical Analysis Plan (SAP) was written according to the guidelines proposed by Yuan et al. [1] and by Gamble et al. [2] for randomized clinical trials.

1. SAP versions, dates and reasons for revision

Version #1: August 13th, 2026

2. Trial registration number

Clinical Trials Number: NCT07463963

Research Ethics Committee Number: 2025-A01451-48 (ID-RCB French Identifier, approved on 20 March 2026)

3. Study title

Relevance of the urine bacterial culture performed before transurethral resection of the bladder for post-operative febrile urinary tract infection prevention: a non-inferiority randomized controlled trial.

4. SAP contributors with roles and responsibilities

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5. Background and rationale of study

Transurethral resection of the bladder (TURB) is a routinely performed surgery in urology (65,000/y in France). Its primary indication is the management of bladder cancer for diagnostic, prognostic, and therapeutic purposes. Currently, both French and European guidelines recommend screening for asymptomatic bacteriuria (ABU) using a urine culture (UC) before TURB. If the UC is positive, antibiotic treatment must be initiated before surgery.

Theoretically, the purpose of preoperative ABU screening before TURB is to reduce the rate of post-operative urinary tract infections (UTIs). However, there is currently a lack of high-level studies justifying this approach, despite its being a recommended practice.

The literature estimates the rate of post-TURB UTIs to be between 2% and 3.7%. In a recent French multicentre retrospective study, the rate of postoperative febrile UTI was 2.3%. This study did not find a significant association between positive pre-operative UC and a post-operative febrile UTI. No study has yet demonstrated the link between the presence of a positive preoperative UC and an increased risk of postoperative infection. The causality between preoperative UC and postoperative UTIs remains unestablished.

Therefore, we propose a non-inferiority randomized controlled trial to investigate the impact of not performing pre-operative UC before TURB on the incidence of post-TURB febrile UTIs.

6. Study type

This is a national, multicenter, prospective, comparative, non-inferiority, randomized, controlled trial in two parallel groups.

7. Objectives and related endpoints (units and calculations used to derive outcomes)

7.1. Primary objective

The primary objective is to demonstrate that not performing a systematic UC before the TURB procedure is not inferior to performing a systematic UC.

The primary outcome is the febrile UTI incidence during the first 30 postoperative days, evaluated by the proportion of patients with a symptomatic febrile UTI within 30 days following surgery.

The diagnosis of a febrile UTI will be based on clinical, biological and microbiological criteria, as defined by Bilsen et al. [3] based on an international expert consensus (Appendix #1). It should be noted that this consensus excludes catheter-associated UTIs. In case of a catheterized patient (because in the peri-operative phase of the surgical procedure or in case of hemorrhagic complications), the "symptoms and signs" criteria will not be used, and in this case, we propose the alternative following score: Definite UTI ≥ 6 points; Probable UTI 4-5 points; Possible UTI 2-3 points; No UTI 0-1 point. Febrile UTI will be characterized by “Definite UTI” or “Probable UTI”.

7.2. Secondary objectives

The secondary objectives are:

- To compare the following outcomes in the two groups:
    - The proportion of patients with postponed surgery.
    - The time to surgery (in days), defined by the number of days between the pre-operative urology consultation (inclusion visit) and the date of surgery.
    - The hospital length of stay at day 30 (in days), defined by the number of days between surgery and discharge from the hospital.
    - The proportion of patients with hospital readmission or postoperative complication within 30 days following surgery.
    - The proportion of patients with hospital readmission linked with the urinary surgical procedure within 30 days following surgery.
    - The proportion of patients with systemic UTI among patients with hospital readmission, defined as UTI complicated by sepsis (corresponding to a qSOFA > 1).
    - The proportion of patients with pre-operative antibiotic prescription for pre-operative colonization before the surgery.
    - The proportion of patients with post-operative antibiotic prescription within 30 days following surgery.
    - The time to post-TURB infection diagnosis (in days), defined by the time between surgery and the date of febrile UTI declaration (censored at day 30).
    - The overall survival time (in days), defined by the time between surgery and the date of death (censored at day 30).
- For patients with postoperative febrile UTI, we will describe the type of bacteria and type of antibiotic resistances of post-operative bacteria.
- For patients randomized in the control group (UC performed before TURB surgery), we will describe the type of bacteria and type of antibiotic resistances of pre-operative bacteria.
- To identify factors associated with post-TURB infection, among the following pre-operative, per-operative and post-operative data: age, immunodeficiency or immunosuppressive treatment, diabetes, hypertension, antithrombosis or antiplatelet agent treatment, per-operative antibiotic

prescription for pre-operative colonization before the procedure, duration of surgery, single immediate post-operative intravesical instillation of chemotherapy, tumor specimen weight, tumor (T) classification, duration of immediate post-operative bladder catheterization (= time from beginning of surgery to removal of catheterization), duration of bladder irrigation (= time from beginning of surgery to end of irrigation), per- or post-operative bladder perforation (preceding the post-TURB infection), removal of post-operative bladder clots (preceding the post-TURB infection).

- To assess the agreement between UTI defined according to Bilsen's classification (primary outcome) and UTI declared by the clinician.

8. Inclusion criteria

- Adult patients (≥18 years).
- Scheduled to have a TURB procedure for a suspected or confirmed diagnosis of bladder tumor.
- Patients benefiting from a Social Security system or benefiting from it through a third party.
- Having given their informed consent.

9. Non-inclusion criteria

- Patients with active UTI.
- Planned combined surgery (example: TURB and TURP).
- Patient previously included in this research protocol.
- Pregnant or breastfeeding women, women of childbearing age who do not have effective contraception (hormonal/mechanical: per os, injectable, transcutaneous, implantable, intrauterine device, or surgical: tubal ligation, hysterectomy, total oophorectomy).
- Persons benefiting from enhanced protection, namely minors, persons deprived of their liberty by a judicial or administrative decision, patients staying in a health or social institution, adults under legal protection, and patients in emergency situations.

10. Post-randomization exclusion criteria

- Non-operated patient (anaesthesiologic contraindication after the randomization, occurrence of intercurrent event prohibiting the surgery, cancelled surgery, etc.).
- Consent withdrawal.

11. Definition of the two compared groups

- The experimental group is defined by:
    - No UC performed before TURB. No other preoperative management will be carried out.
    - Surgery and follow-up will be managed according to usual care.
- The control group is defined by:
    - A systematic UC performed before TURB.
    - In case of positive UC, patients will be treated by antibiotic therapy according to the current guidelines.
    - Surgery and follow-up will be managed according to usual care.

12. Randomization details

The randomization list was established by a methodologist of the Platform for Methodology Biostatistics and Data-Management. A document describing the randomization procedure will be kept confidential by the methodologist who established the list.

Randomization sequence is stratified by center using random block sizes. The patients are randomly allocated to experimental or control arm in a 1:1 ratio. Randomization is performed by the investigator through a dedicated, password-protected website.

13. Sample size calculation

The rate of febrile UTI after TURB procedure is estimated at 2,3% in France [4]. The literature estimates the rate of post-TURB febrile UTIs in-between 2% and 3.7% [5]. We considered our experimental intervention would be deleterious if we observe a rate of febrile UTI superior to 3.7% (upper bound of the rate of post-TURB febrile UTI). Therefore, we set the absolute non-inferiority margin to 1.5% as the difference between the estimated rate of febrile UTI in France and the upper bound of the rate of febrile UTI in the literature.

Considering a one-sided type I error of 5% and a power of 80%, the minimum sample size is 2470 patients (1235 per group). We add 5% to this number in case of consent withdrawal, missing outcomes, patients lost to follow-up or post randomization exclusions (low rate of non-operated patients expected), which increases the total sample size to 2600 (1300 per group).

14. Interim analysis (timing, person, adjustment of the significance level)

No interim analysis is planned.

15. Guidelines for an early stop of the study

The study may be prematurely suspended in the event of unexpected adverse events. On the same token, in the event of unexpected developments or new information and showing that the objectives of the study or the clinical program are unlikely to be reached, the sponsor may be persuaded to prematurely suspend the study.

No statistical discontinuation criteria have been drawn up.

16. Timing of final analysis

- Inclusion period: 48 months
- Follow-up of the participant: maximum 90 days
- Data base locking: 3 months
- Finalization of data analyses: 6 months (after the integration of the comments of all the contributors).

17. Timing for assessing each collected parameter

	Inclusion Pre-operative urology consultation (V0)	TURB surgery (V1)	Phone contact (V2)	End of the study (V3)
	Day -60 to -5	Day 0	Day 7	Day 30
Informed consent	X			
Inclusion	X			
Physical examination and medical history	X	X		

Imagery suspecting the diagnosis of bladder tumor	X			
Randomization	X			
Prescription for UC (control group only)	X			
Surgery		X		
Delivery of patient notebook[1]		X		
Interview for complications and infections			X	X
Anatomopathological results				X
Adverse events		X	X	X

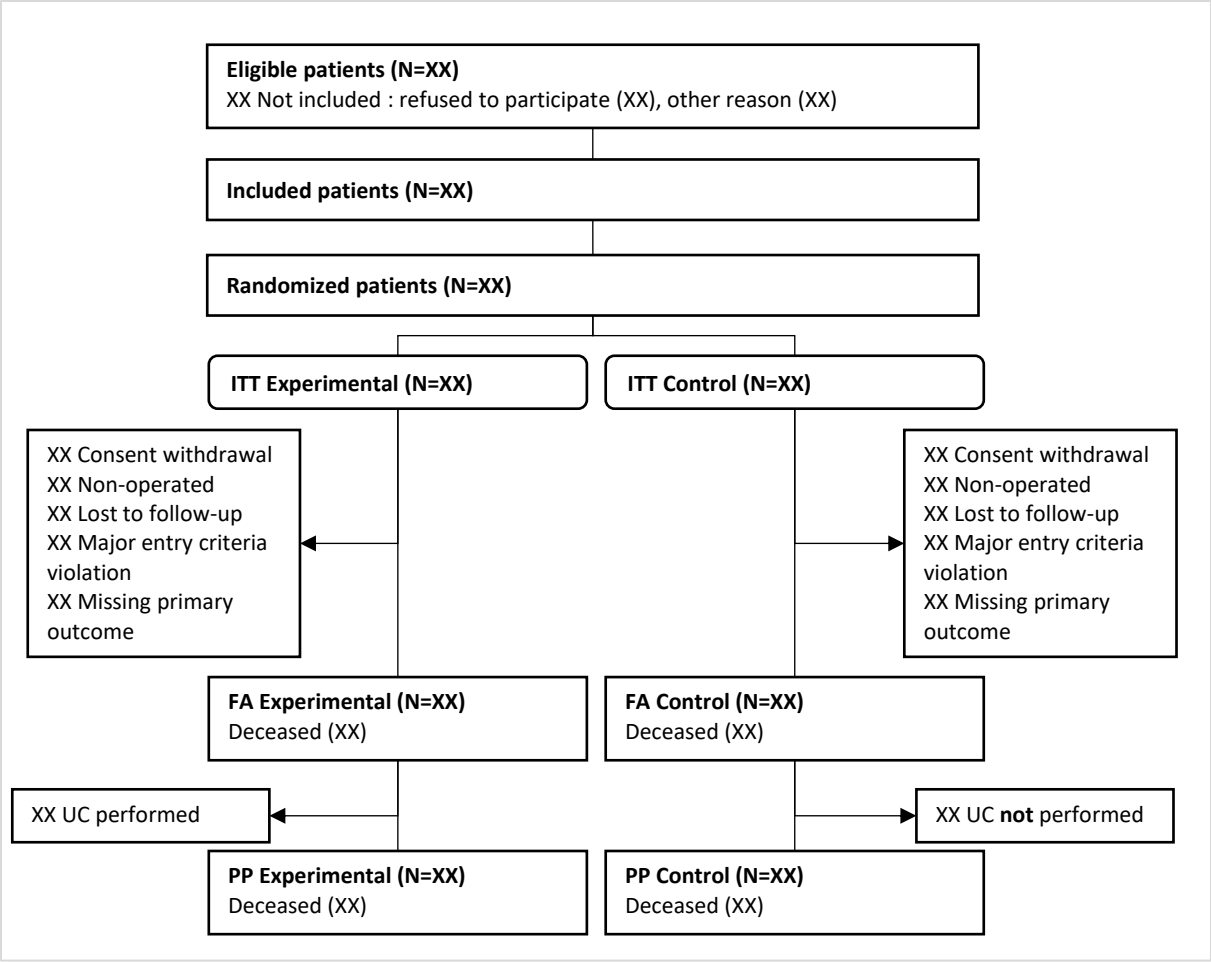
TURB: Transurethral resection of the bladder. UC: Urine culture.

[1]Patient notebook: when the patient is discharged from the hospital, a notebook will be delivered to the patient in order to track the occurrence of any potential urinary tract infection.

18. Reporting the representativity of the studied population

A flowchart will be decomposed according to the following sets. The effectives and the related differences in-between two consecutive sets will be reported. The causes of the related differences will also be listed.

- The screened set. The patients having signed the informed consent.
- The intention-to-treat (ITT) set. The patients who were randomized according to their allocated group, regardless of their adherence to the entry criteria, regardless of the intervention they received, and regardless of subsequent withdrawal from intervention or deviation from the protocol.
- The full analysis (FA) set. The previous ITT population, excluding participants who failed to meet major entry criteria [6] and participants with no data post-randomization (including patients without surgery, that we expect very low) or with missing outcome.
- The per-protocol (PP) set. The previous FA population, excluding participants who did not receive the allocated intervention (i.e. patients randomized in control group who did not perform UC before TURB and patients randomized in experimental group who performed UC before TURB).



19. Withdrawals and follow-up data

Patients may be withdrawn early from the clinical investigation for several reasons, including but not limited to consent withdrawal, lost to follow-up, death, non-operated patients. The investigator will document the reasons for premature study discontinuation. The withdrawals will be exhaustively described in the flowchart.

20. Definition of the studied population

All the analyses will be performed based on the per-protocol (PP) set. According to the non-inferiority design, analyses will also be performed on the full analysis (FA) set.

If a patient withdraws consent, he/she will be asked for permission to use data obtained prior to withdrawal and to collect the primary outcome. If this is achieved, the patient will be included in the final analyses. If the patient declines, all data from that patient will be destroyed (except for safety data).

21. Level of statistical significance (p-values, confidence intervals, one- or two-sided)

For the primary objective, statistical significance will be achieved for p-value < 5% by using one-sided alternative hypothesis and two-sided 90% confidence interval.

For secondary objectives, statistical significances will be achieved for p-values < 5% by using two-sided alternative hypotheses and two-sided 95% confidence intervals.

22. Plan and rationale for controlling the type I error (multiplicity of tests)

We will not consider the inflation of the type I error. The level of the proof will be the higher for the primary outcome. The statistical analyses related the secondary outcomes will be consider as exploratory results with a risk of false positive.

23. Sub-group analyses and/or tests of interactions

No sub-group analyses or tests of interactions are planned.

24. Description of baseline patient characteristics

Demographic variables and other baseline characteristics will be summarized for the PP set (main analyses) and for the FA set (secondary analyses). No imputation will be performed because the percentage of missing data on the outcomes is expected very low.

The means, the standard deviations and the number of missing values will be presented for each arm and marginally for the following quantitative variables: age (years), body mass index (kg/m²), previous HBA1C (in %), tobacco consumption (in pack/years).

The effectives, the percentages of patients in each category and the number of missing values will be presented for each arm and marginally for the following categorical variables: gender (male/female), ASA class (class I to IV), current smoking status (non-smoker/former smoker/current smoker), immunodeficiency or immunosuppressive treatment (yes/no), diabetes (yes/no), hypertension (yes/no), long-term indwelling urinary catheter (yes/no), UTI during the past 12 months (yes/no), history of ischemic cardiopathy (yes/no), rhythmic cardiopathy (yes/no), voiding lower urinary tract symptoms (yes/no), chronic kidney disease (yes/no).

No p-value will be reported. The balance diagnostics of baseline covariates between the two arms will be achieved by estimating standardized mean differences (SMD) [7]. Unbalances will be considered for absolute SMD values higher than 10%.

Underlined covariates are baseline potential risk factors for primary outcome and analyses will be adjusted on these factors (section 26).

25. Description of the outcomes

The outcomes of the patients will be compared for the PP set (main analyses) and for the FA set (secondary analyses). No imputation will be performed because the percentage of missing data on the outcomes is expected very low.

For the hospital length of stay (in days) and the time to surgery (in days), we will present means, standard deviations and the number of missing values for each treatment arm and marginally. Student t-test will be performed to obtain the p-value. The overall survival and the infection-free survival curves will be obtained with Kaplan-Meier estimator for each treatment arm. Confidence intervals will be obtained using Greenwood's formula. Log-rank test will be performed to obtain the related p-values. The effectives, the percentages of patients in each category and the numbers of missing values will be presented for each arm and marginally for the following binary outcomes: febrile UTI incidence within 30 days (primary outcome), systemic UTI among hospitalized patients, postponed surgery, rehospitalizations or postoperative complications within 30 days following surgery, hospital readmission linked with the urinary surgical procedure within 30 days following surgery, antibiotic prescription for pre-operative colonization before the surgery, antibiotic prescription within 30 days following surgery. For the primary outcome, two-proportions z-test will be performed to obtain the p-value (one-sided). For secondary binary outcomes, Pearson's Chi2 tests will be performed to obtain the p-values. Only when at least one theoretical effective under the null assumption will be lower than 5, a Fisher exact test.

For the sample of patients with post-TURB febrile UTI in the FA set, the type of bacteria will be presented for ECBU and for hemoculture separately. We will present the effectives, the percentages of patients in each category (absence/presence) and the number of missing values for the following post-operative bacteria: *Acinetobacter baumanii, Actinotignum schaalii, Citrobacter freundii, Citrobacter koseri, Corynebacterium urealyticum, Enterobacter cloacae, Enterococcus faecalis, Escherichia coli, Klebsiella aerogenes, Klebsiella pneumoniae, Morganella morganii, Proteus mirabilis, Providencia stuartii, Pseudomonas aeruginosa, Raoultella ornithinolytica, Serratia marcescens, Staphylococcus aureus, Staphylococcus saprophyticus, Streptococcus agalactiae (groupe B), Ureaplasma urealyticum*. For each bacteria, we will also describe the percentages of patients with multidrug-resistant bacteria. The same description will be presented for the pre-operative bacteria in the sample of patients randomized in the control group in the FA set.

For the FA set, we will identify factors associated with post-TURB infection using BIC minimization in a multivariate logistic regression.

Agreement between febrile UTI as defined in the primary outcome ("Definite UTI" or "Probable UTI" according to Bilsen's classification) and febrile UTI assessed by the clinician will be estimated with Cohen's kappa coefficient. We will consider the guidelines proposed by Landis and Koch [8] to interpret the magnitude of agreement (values > 0.8 indicating almost perfect agreement, > 0.6 substantial agreement, > 0.4 moderate agreement, > 0.2 fair agreement). In addition to the definition of febrile UTI considered for the primary outcome, we will also consider others dichotomizations of Bilsen's classification and estimate agreement with febrile UTI assessed by the clinician (sensitivity analyses). First, we will consider the definition of febrile UTI as "Definite UTI". Second, we will consider the definition of febrile UTI as "Definite UTI" or "Probable UTI" or "Possible UTI".

26. Adjustments and estimands

The following analyses will be performed for both the PP (main analyses) and FA (secondary analyses) populations to compare the clinical outcomes between randomized groups.

Ignoring stratification factors in the analysis leads to incorrect confidence intervals [9]. More generally, adjusted analyses on the risk factors of the outcome may increase power and give correct type I error rates [10]. We will use G-computation to estimate the average treatment effect (ATE).

Firstly, we will estimate the outcome models. Among the potential predictors, we will consider the stratification factors (recruitment center) and the potential risk factors highlighted in the section 24. No interaction between the randomization arms and the predictors will be tested. For each outcome, the BIC minimization will be used to select the covariates to consider for adjustment. Binary outcomes will be modeled with logistic regressions. Continuous outcomes (hospital length of stay and time to surgery) will be modeled with linear regressions. Time-to-event outcomes (overall survival and infection-free survival) will be modeled with proportional hazards models, using Breslow's method to estimate the baseline hazard function [11].

Secondly, based on the outcome models, we will predict the outcomes if all participants were assigned to the experimental arm and then if all participants were assigned to the control arm. For each outcome, the ATE will be defined as the difference between the two adjusted predictions: difference of the proportions for binary outcomes, difference of the means for continuous outcomes, and for time-to-event outcomes we will consider the difference of the restricted mean survival times and the difference of the restricted mean infection-free survival times.

To avoid the exclusion of patients with missing values on the baseline predictors, multivariate imputation by chained equations will be performed 5 times. For each complete sample, 1,000 bootstrap samples will be generated. The confidence intervals of the ATE estimations will be non-parametrically estimated from the 5,000 imputed bootstrap samples [12].

27. The assumptions of the statistical methods, and alternative methods if they are false

There is no reason to suppose that the missing values of the baseline predictors will not be missing at random in such a randomized clinical trial. Therefore, the only assumption is the good specification of the outcome models.

The respect of the linearity and log-linearity assumptions will be assessed by comparing the Akaike information criterion (AIC) of the univariate model where the variable is not transformed versus the AIC of the model with B-splines transformation. If the criterion is lower for the model with B-splines, this transformation will be used in the multivariate model.

We will use Schoenfeld's residuals to evaluate the respect of the proportional hazards assumption for the proportional hazards model. If it does not hold, an interaction with time or stratification will be used to relax this assumption.

28. References

[1] Yuan I, Topjian AA, Kurth CD, Kirschen MP, Ward CG, Zhang B, et al. Guide to the statistical analysis plan. Paediatr Anaesth. mars 2019;29(3):237-42

[2] Gamble C, Krishan A, Stocken D, Lewis S, Juszczak E, Doré C, et al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. JAMA. 19 déc 2017;318(23):2337-43.

[3] Bilsen MP, Conroy SP, Schneeberger C, Platteel TN, Van Nieuwkoop C, Mody L, et al. A reference standard for urinary tract infection research: a multidisciplinary Delphi consensus study. Lancet Infect Dis. 2024 Mar;S1473309923007788.

[4] Kutchukian S, Gondran-Tellier B, Dinh A, et al. Asymptomatic Bacteriuria and Urological Surgery: Risk Factor or Not? Results From the National and Multicenter TOCUS Database. J Urol. 2024;212(3):461-469.

[5] Bausch K, Halbeisen FS, Aghlmandi S, Sutter SU, Ewald H, Appenzeller-Herzog C, et al. Antimicrobial Prophylaxis for Postoperative Urinary Tract Infections in Transurethral Resection of Bladder Tumors: A Systematic Review and Meta-Analysis. J Urol. 2021 Apr;205(4):987–98.

[6] Fergusson D, Aaron SD, Guyatt G, Hébert P. Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. BMJ. 2002 Sep 21;325(7365):652-4.

[7] Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med. 10 nov 2009;28(25):3083-107.

[8] Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977 Mar;33(1):159-74.

[9] Kahan BC, Morris TP. Reporting and analysis of trials using stratified randomisation in leading medical journals: review and reanalysis. BMJ. 14 sept 2012;345:e5840.

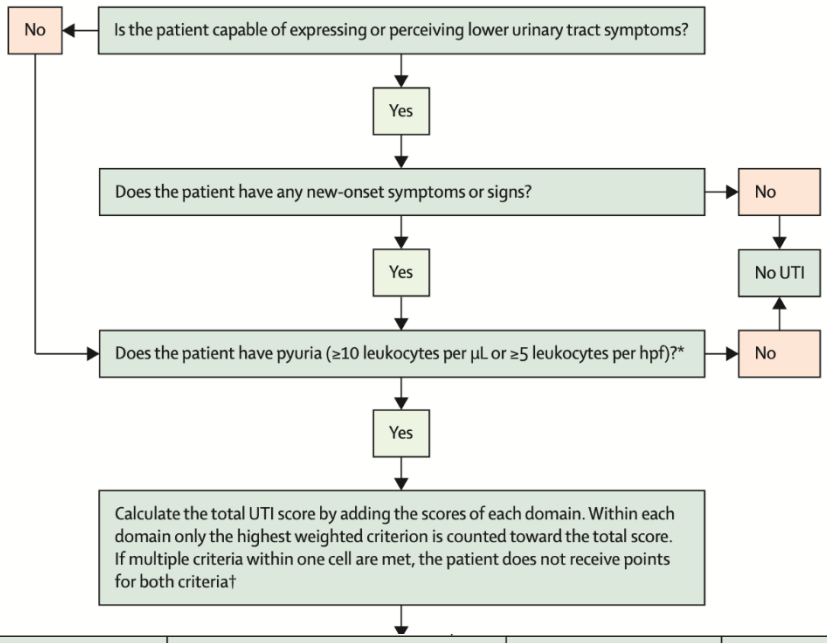
[10] Morris TP, Walker AS, Williamson EJ, White IR. Planning a method for covariate adjustment in individually randomised trials: a practical guide. Trials. 18 avr 2022;23(1):328.

[11] Lin DY. On the Breslow estimator. Lifetime Data Anal. 2007 Dec;13(4):471-80.

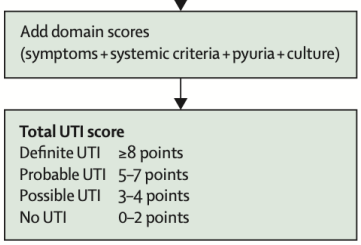
[12] Schomaker M, Heumann C. Bootstrap Inference When Using Multiple Imputation. Stat Med. 30 juin 2018;37(14):2252-66.

Appendix #1: Bilsen's algorithm for UTI classification

Algorithm proposed by Bilsen et al. [3] to classify UTIs.



Domain	Specifics	3 points	2 points	1 point	0 points
Symptoms and signs	**Major** Dysuria Urinary urgency Urinary frequency **Minor** Suprapubic pain or tenderness Flank pain or tenderness Perineal pain or painful prostate exam Urinary incontinence Macroscopic haematuria Recognition of symptoms	Two or more new-onset major symptoms Add 1 point if woman aged ≥65 years	One new-onset major symptom or two new-onset minor symptoms	One new-onset minor symptom or inability to express or experience symptoms (eg, delirium, dementia, or spinal cord injury)	
Systemic criteria	Fever (≥38·0°C or 100·4°F)‡ C-reactive protein concentration ≥50 mg/L‡ Procalcitonin concentration ≥0·5 ng/mL‡ White blood cell count ≥12×10^9 per L‡ Bacteraemia (same pathogen as urine culture)		One or more new-onset systemic criteria		No systemic criteria
Pyuria	In either midstream urine or single catheterised sample	≥200 leukocytes per µl or ≥50 leukocytes per hpf	10–200 leukocytes per µl or 5–50 leukocytes per hpf Subtract 1 point if woman aged ≥65 years		
Culture results	Uropathogens: Enterobacterales, *Pseudomonas aeruginosa*, and *Staphylococcus saprophyticus*	One or two uropathogens: for midstream urine ≥10^4 CFU/mL, for *Escherichia coli* ≥10^3 CFU/mL is sufficient; for single catheter ≥10^3 CFU/mL Subtract 1 point if woman aged ≥65 years Or Bacteraemia (same pathogen as urine culture)		Mixed flora or Other pathogen or No growth, but pretreated with antimicrobials	No growth, not pretreated with antimicrobials or Urine culture not performed



UTI with systemic involvement if ≥1 criterion
- Fever without other cause
- Flank pain or costovertebral angle tenderness
- Systolic blood pressure <90 mm Hg without other cause
- Elevated inflammatory levels without other cause
- Bacteraemia (same pathogen as urine culture)
- Renal abscess
- Pyonephrosis