JN 22es Journées Nationales d'Infectiologie
Montpellier
et la région Occitanie - Méditerranée
LE CORUM, Montpellier
du lundi 30 août 2021
au mercredi 1er septembre 2021

# Efficacy of 7 days versus 14 days of antibiotic therapy for acute pyelonephritis in kidney transplant recipients, a multicentre randomized non-inferiority trial.

## Essai SHORTCUT (PHRC-19-0193)

Dr Matthieu LAFAURIE
U2i
Maladies Infectieuses
Hôpital Saint-Louis, Paris

Hôpitaux Universitaires
SAINT-LOUIS
LARIBOISIÈRE
FERNAND-WIDAL

# Conflits d’interêt

Y a pas

**Coordinating Investigator**: Dr Matthieu Lafaurie
Infectious Diseases
Saint Louis Hospital, Paris

**Scientific Director:** Dr Aurélien Dinh
Infectious Diseases
Raymond Poincaré Hospital, Garches

**Sponsor**: AP-HP
and by delegation: Clinical Research and Innovation Delegation (DRCI)
Saint-Louis Hospital, Paris

Methodologist : Pr Sylvie Chevret
URC (Clinical Research Unit), Saint Louis hospital, Paris

DRCI-URC project advisor and monitoring of the study: Pr Matthieu RESCH-RIGON
URC (Clinical Research Unit) Saint Louis hospital, Paris

**Budget:** 535000 euros

# Background

- Duration of antimicrobials treatment in immunosuppressed population?
- Most time excluded from studies.
- Need to reduce antibiotic consumption in kidney transplant recipients at high risk of developing infections due to resistant pathogens.

# Main objective

To show that a 7 day-antibiotic therapy is not inferior to a 14 day-antibiotic therapy in the treatment of acute pyelonephritis in kidney transplant (APN) recipients.

**Primary endpoint**: Clinical cure and microbiological eradication and no additional antibiotic treatment since the end of antibiotic treatment up to the main evaluation at day 30.

- Clinical cure is defined as T <38°C and no symptoms of UTI.
- Microbiological eradication is defined as uropathogen ≤ 10.3 CFU/mL in urine culture

# Secondary objectives

- To compare between both arms:
  - Clinical and microbiological efficacy at day 90 and day 180
  - Tolerance and safety of antibiotics
  - Hospitalization length stay
  - Antibiotic consumption during total follow up
  - Rectal carriage of antibiotic resistant *Enterobacteriaceae*
  - Kidney graft function at day 90 and day 180
  - The total costs
- To evaluate risk factors for failure and relapse.

# Design of the trial

- Multicenter, controlled, randomized, non-inferiority, open-label clinical trial with 2 parallel groups (1:1): 7 days versus 14 days of antibiotic treatment.
- The randomization will be stratified by date of renal transplantation (< or > 1 year), center and sex

# Inclusion criteria

- Age >18 years KTR
- APN defined by: fever (T°≥38°C) (with or without clinical signs and/or symptoms of UTI) and pyuria (≥10.4 white blood cells/mL) and positive urine culture (single uropathogen ≥10.3 CFU/mL susceptible to the empirically administrated antibiotic)
- No confirmed or suspected febrile non urinary infection
- No urologic/renal complication at baseline imaging (abscess, obstruction...)
- Early response after 48h of antibiotic treatment defined by: T°<38°C and improvement or complete resolution of any symptoms and/or signs of UTI if present at baseline

# Main exclusion criteria

- Severe or complicated APN
- Any rapidly progressing disease or immediately life-threatening illness (septic shock, current or impeding respiratory, acute heart or liver failure)
- Admission or stay in intensive care unit at baseline
- Obstruction of the urinary tract
- Renal, perinephric or prostatic abscess
- Dual therapy (only 1 dose of aminoglycoside is allowed before randomization)
- First month post transplantation
- Current indwelling catheter (including bladder catheter, ureteral stents, percutaneous nephrostomy tubes)
- Neurogenic bladder/Enterocystoplasty
- Immunodeficiency or immunosuppressive therapy not related to kidney transplantation (hematologic malignancy, cancer, asplenia, <500 PNN/$mm^3$)

# Statistical analysis

- Sample sizes of 235 in each group
- achieve 80% power
- to detect a non-inferiority margin difference between the group proportions of -0.05.
- The power was computed for the case the actual treatment group proportion is 0.90. The test statistic used is the one sided Z test (unpooled).
- The significance level of the test is 0.05

# Duration of the trial…

- Length of Inclusion period: 36 months
- Total study duration: 42 months
- Number of sites: 10

# Centres

| Name | Town, Country | Hospital |
|---|---|---|
| **Péraldi** | Paris, France | CHU Saint-Louis |
| **Scemla** | Paris, France | CHU Necker |
| **Matignon** | Créteil, France | CHU Mondor |
| **Snanoudj** | Paris, France | CHU Kremlin-Bicêtre |
| **Delahousse** | Boulogne, France | Hôpital Foch |
| **Kamar** | Toulouse, France | CHU Toulouse |
| **Kaminski** | Bordeaux, France | CHU Bordeaux |
| **Levi** | Lyon, France | CHU Lyon |
| **Giral** | Nantes, France | CHU Nantes |
| **Hazzan** | Lille, France | CHRU Lille |

JN 22es Journées Nationales d'Infectiologie
Montpellier
et la région Occitanie - Méditerranée
LE CORUM, Montpellier
du lundi 30 août 2021
au mercredi 1er septembre 2021

# A randomized, double-blind, multicenter study to compare the efficacy of Fosfomycin-trometamol (FT) to Ciprofloxacin(CIPRO) single dose as prophylaxis for transrectal ultrasound-guided biopsy of the prostate (TRUBP): **PROFOSFO** (PHRC-19-0261)

Dr Matthieu LAFAURIE
U2i
Maladies Infectieuses
Hôpital Saint-Louis, Paris

Hôpitaux Universitaires
SAINT-LOUIS
LARIBOISIÈRE
FERNAND-WIDAL

**Coordinating Investigator**: Pierre MONGIAT-ARTUS

Urology ward, Saint-Louis Hospital, Paris

**Scientific Director**: Matthieu LAFAURIE

Infectious Diseases Unit, Saint-Louis Hospital, Paris

**Sponsor**: Assistance Publique – Hôpitaux de Paris (AP-HP) and by delegation: Direction de la Recherche Clinique et de l'Innovation – DRCI, Saint-Louis Hospital, Paris

**Methodologist** : Sylvie Chevret

URC (Clinical Research Unit), Saint Louis hospital, Paris

**DRCI-URC project advisor and monitoring of the study**: Matthieu RESCH-RIGON

URC (Clinical Research Unit) Saint Louis hospital, Paris

# Background

- In France, 150000 TRUBP every year.

- Resistance rate to FQ (FQR) and ESBL *Enterobacteriacae* infections keep increasing, leading to a lower efficacy of FQ as prophylaxis before TRUBP and to difficulties to treat adequately patients with urinary tract infection (UTI) after TRUBP.

# Fosfomycin-trometamol (FT) or fluoroquinolone (FQ) as single-dose prophylaxis for transrectal ultra sound-guided prostate biopsy (TRUS-PB): A prospective cohort study (Delory et al), Int J Infect Dis, 2021 Jan;102:269-274

Prevalence and incidence of primary and secondary clinical endpoints.

| Clinical endpoints[b] | FQ-arm n= *116* | FT-arm *n= 81* | Total *n= 197* | RR[a] | 95%CI | p-value |
|---|---|---|---|---|---|---|
| Post-TRUS-PB UTI | 17/116 (15%) (95%CI, 10–17%) | 7/81 (9%) (95%CI, 5–13%) | 24/197 (12%) (95%CI, 8–17%) | 0.55 | (0.22–1.40) | 0.209 |
| Post-TRUS-PB microbiologically documented UTI | 6/116 (5%) (95%CI, 2–8%) | 1/81 (1%) (95%CI, 0–3%) | 7/197 (4%) (95%CI, 1–6%) | – | | |
| Post-TRUS-PB antibiotic intake | 14/116 (12%) (95%CI, 8–17%) | 7/81 (9%) (95%CI, 5–13%) | 21/197 (11%) (95%CI, 6–15%) | 0.70 | (0.27–1.82) | 0.462 |
| Post-TRUS-PB hospitalization (all causes) | 13/116 (11%) (95%CI, 7–16%) | 3/81 (4%) (95%CI, 1–6%) | 16/197 (8%) (95%CI, 4–12%) | 0.30 | (0.08–1.11) | 0.071 |
| Post-TRUS-PB hospitalization (due to UTI) | 9/116 (8%) (95%CI, 4–11%) | 1/81 (1%) (95%CI, 0–3%) | 10/197 (5%) (95%CI, 2–8%) | 0.15 | (0.02–1.20) | 0.073 |
| Post-TRUS-PB adverse events | 36/116 (31%) (95%CI, 25–37%) | 28/81 (36%) (95%CI, 28–41%) | 64/197 (32%) (95%CI, 26–39%) | 1.17 | (0.64–2.15) | 0.602 |

# Main objective and primary endpoint

- To demonstrate that FT is non inferior to CIPRO for the prophylaxis of post-TRUBP UTI within 4 weeks from TRUBP.

- Occurrence of UTI within 4 weeks from TRUBP, defined as follows:

  - at least one among the following *clinical signs*:
    - Fever (T°≥ 38°C, on 2 consecutive occasions ≥ *1 hour apart)*
    - Shaking and chills
    - Urinary signs including urinary burn, pain, urgency
    - Orchitis/Epidydimitis

  - and *microbiologically confirmed infection:*
    - bacteriuria $\geq 10^3$/mL (single uropathogen)
    - and leucocyturia $\geq 10^4$/mL
    - and/or bacteremia

# Secondary objectives and endpoints

- If non-inferiority of FT vs CIPRO is demonstrated, *to demonstrate superiority of FT over CIPRO* for the prophylaxis of post-TRUBP UTI.
- To compare between FT and FQ, 4 weeks after TRUBP

  - The antibiotic use (dose, duration and indication (UTI or other infection) after TRUBP;

  - The rate of adverse events related to antibiotic prophylaxis;

  - The rate of hospital admissions with a focus on admissions due to post TRUBP UTI;

  - The all-causes mortality;

  - The rate of FQ and FT-resistance of pathogens involved in post-TRUBP UTI;

  - The acquisition of rectal carriage of resistant bacteria to FQ, FT and ESBL-producing *Enterobacteriaceae*;

  - The total costs.

# Design of the study

- Randomized, double blind, non-inferiority, multicenter clinical trial:

Cipro 500 mg + placebo vs fosfo 3 g + placebo: single dose 2 hours before TRUBP

- The randomization will be stratified by center

# Inclusion criteria

- Man
- ≥18 years
- Recommended to undergo a prostate biopsy as part of standard of care
- Signed informed consent

# Exclusion criteria

- < 3 months-life expectancy
- **Severe renal failure (defined as creatinine clearance ≤ 20 ml/min)**
- G6PD deficiency
- Non-controlled epilepsy
- History of FQ associated tendinopathy, aortic aneurysm or dissection
- History of cardiac valvular insufficiency
- Marfan syndrome/Ehlers-Danlos syndrome
- History of FQ or FT allergy
- **Hepatic cytolysis (ASAT/ALAT ≥ 5N)**
- Myasthenia gravis
- History of severe psychiatric disorders
- Galactose intolerance, lactase deficiency, glucose or galactose digestive malabsorption
- Tutorship or guardianship
- No health insurance

# Sample sizes

- The rate of the primary endpoint (UTI post-TRUBP) in the FQ arm (control group) is estimated at 5%.

- Sample sizes of 326 in FT-arm and 326 in Group FQ-arm
- 90% power
- to detect a non-inferiority margin difference between the group proportions of 0.05.
- The intervention group proportion is assumed to be 10% under the null hypothesis of inferiority.
- The significance level of the test is 0.05.

- Duration of enrolment period : 18 months
- Length of participation for participants : 8 weeks
- Total study duration : 20 months
- Participating sites: 10

# Centres

- Service d’urologie, CHU Rennes
- Service d'Urologie  Hôpital Bicêtre Le Kremlin-Bicêtre
- Service d'Urologie  Institut Mutualiste Montsouris Paris
- Service d’Urologie: Clinique beausoleil, Montpellier
- Service d'Urologie  Hôpital Saint-Louis, Paris
- Service d’Urologie  Hôpital Bretonneau Tours
- Service d'Urologie  Clinique La Croix du Sud  Quint Fonsegrives
- Service d’Urologie et Transplantation Rénale CHRU de Besançon
- Service d'Urologie  Hôpital Tenon Paris
- Service d’Urologie, andrologie et transplantation rénale Hôpital Rangueil Toulouse

JN 22es Journées Nationales d'Infectiologie
Montpellier
et la région Occitanie - Méditerranée
LE CORUM, Montpellier
du lundi 30 août 2021
au mercredi 1er septembre 2021

# Efficacy of 7 versus 14 days of antibiotic therapy in male with febrile urinary tract infection due to fluoroquinolone susceptible organisms. PROSTASHORT: a randomized clinical trial.

Dr Matthieu LAFAURIE

U2i, Maladies Infectieuses
Hôpital Saint-Louis, Paris
31/08/2021

Hôpitaux Universitaires
SAINT-LOUIS
LARIBOISIÈRE
FERNAND-WIDAL

Scientific manager: Pr Agnes Lefort, Hôpital Beaujon

Methodology/Monitoring: Pr S. Chevret, Hôpital Saint-Louis
Analysis: Kristell Desseaux

# Study design, methods

- **Randomized, double-blind, placebo-controlled, non-inferiority multicenter trial**.

- Assuming that a **non inferiority margin of 10%** (14 days vs. 7 days) reflects acceptable non inferiority
- **Necessary number of patients : 284 (142 per arm)** with a first-species risk (one-sided) of 2.5% and a power of 80%.

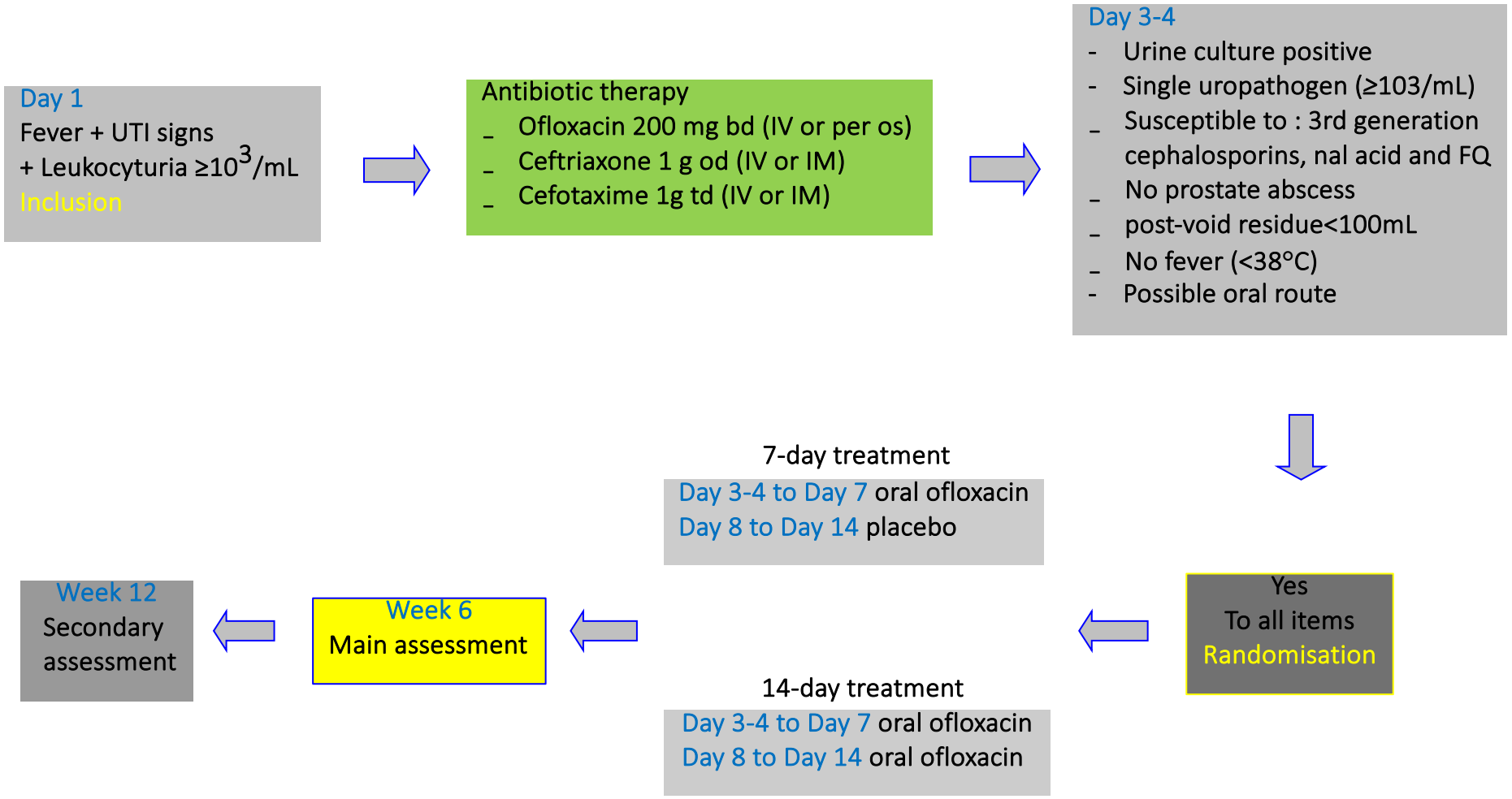
- **Missing data considered as failures**, pointwise and with 95% confidence interval calculated by the exact method.
- Sensitivity analysis for recoding missing data performed.

# Eligibility criteria

- Male
- Aged 18 years or older
- **Febrile urinary tract infection** , defined as :
    - Fever (temperature ≥ 38C° )
    - and at least one of the following :
        - dysuria, frequency of urination, urgency of urination, hematuria
        - perineal, flank or suprapubic pain
        - pain on rectal examination
    - and leukocyturia ≥ 10/ $mm^3$
- **Duration of symptoms for less than 3 months**

# Exclusion criteria

- Septic shock or sepsis
- Nosocomially acquired urinary tract infection
- Prior urinary tract infection treatment within 12 months
- Indwelling urinary catheter
- Neutropenia (polynuclear count of less than 500/$mm^3$)
- Fluoroquinolone or aminoglycoside within 72 hours prior antibiotic treatment
- Creatinine clearance ≤ 20 ml/min
- Severe disease with a high probability of death at 3 months
- Allergy or contraindication to fluoroquinolones and/or cephalosporins
- Known G6PD deficiency
- Major cognitive impairment
- History of tendinopathy with a fluoroquinolone
- ASAT/ALAT ≥ 5N,
- Myasthenia gravis/galactose intolerance, Lapp lactase deficiency or glucose/galactose malabsorption syndrome.
- Guardianship, curatorship or no social security coverage
- Absence of written consent from the patient


Day 1
Fever + UTI signs
+ Leukocyturia ≥10$^3$/mL
Inclusion
Antibiotic therapy
_ Ofloxacin 200 mg bd (IV or per os)
_ Ceftriaxone 1 g od (IV or IM)
_ Cefotaxime 1g td (IV or IM)
Day 3-4
- Urine culture positive
- Single uropathogen (≥103/mL)
_ Susceptible to : 3rd generation cephalosporins, nal acid and FQ
_ No prostate abscess
_ post-void residue<100mL
_ No fever (<38°C)
- Possible oral route
Yes
To all items
Randomisation
7-day treatment
Day 3-4 to Day 7 oral ofloxacin
Day 8 to Day 14 placebo
14-day treatment
Day 3-4 to Day 7 oral ofloxacin
Day 8 to Day 14 oral ofloxacin
Week 6
Main assessment
Week 12
Secondary assessment

# Randomization

- Randomization criteria: Day 3-4
  - positive urine culture with a single uropathogen ($\geq 10^3$ UFC/ml)
  - uropathogen susceptible to nalidixic acid, FQ and 3rd generation cephalosporins
  - possibility of oral treatment
  - temperature <38° C on ceftriaxone, cefotaxime or ofloxacin initiated empirically at diagnosis
  - No prostatic abscess and post-void residue > 100 ml on ultrasound

- Stratification by:
  - study site
  - urinary tract-related comorbidities
  - age (<50 years/≥50 years)

# Primary end-point

**Cure of the UTI 6 weeks after initiation of active antibiotic therapy** and defined as follows:

- **Negative urine culture** (except contaminants *i.e.* alpha-hemolytic streptococci, *Lactobacillus*, *Corynebacteria*, *Gardnerella* or coagulase negative Staphylococci)
- **No fever** (T<38° or T ≥38° not related to UTI)
- **No antibiotic treatment** whose spectrum includes the causative uropathogen

# Secondary end-points

- Adverse events related to antibiotic treatment
- Intestinal carriage of antimicrobial-resistant gram-negative bacilli
- Infectious and urological complications during treatment and follow-up

# Primary outcome

| Analysis | Patients | % (95%CI) | 14-day antibiotic therapy | % (95%CI) | 7-day antibiotic therapy | % (95%CI) | Absolute Difference (95%CI) |
|---|---|---|---|---|---|---|---|
| Per-protocol | 225 | | 117 | | 108 | | |
| **Cure** | **160** | **71.1% [64.7;76.9]** | **96** | **82.1% [73.9;88.5]** | **64** | **59.3% [49.4;68.6]** | **-22.8% [-34.2;-11]** |
| Intention to treat | 240 | | 125 | | 115 | | |
| Cure | 161 | 67.1% [60.7;73] | 97 | 76.6% [69.3;84.6] | 64 | 55.7% [46.1;64.9] | - 21.9 %[-33.3;-10.1] |

→ non-inferiority 7-day vs 14-day not demonstrated

→ deleterious effect of 7-day vs 14-day antibiotic therapy

# Adverse events related to antimicrobials

| | | Total | | 14-day antimicrobial therapy | | 7 day-antimicrobial therapy | |
|---|---|---|---|---|---|---|---|
| | | N=13 | | N=9 | | N=4 | |
| Adverse events | Headache | 1 | 8% | 1 | 11% | 0 | 0% |
| | Diarrhea | 3 | 23% | 2 | 22% | 1 | 25% |
| | Tendon and joint pain | 5 | 39% | 3 | 33% | 2 | 50% |
| | Rash | 4 | 31% | 3 | 33% | 1 | 25% |
| Grade | 1 | 9 | 69% | 7 | 78% | 2 | 50% |
| | 2 | 2 | 15% | 1 | 11% | 1 | 25% |
| | 3 | 2 | 15% | 1 | 11% | 1 | 25% |
| Stopping antibiotic treatment | Yes | 2 | 15% | 1 | 11% | 1 | 25% |