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)

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Conflits d’intérêt

Y a pas
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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/mm³)
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

<table>
<thead>
<tr>
<th>Name</th>
<th>Town, Country</th>
<th>Hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Péraldi</td>
<td>Paris, France</td>
<td>CHU Saint-Louis</td>
</tr>
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<td>Scemla</td>
<td>Paris, France</td>
<td>CHU Necker</td>
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<td>Matignon</td>
<td>Créteil, France</td>
<td>CHU Mondor</td>
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<td>Snanoudj</td>
<td>Paris, France</td>
<td>CHU Kremlin-Bicêtre</td>
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<td>Delahousse</td>
<td>Boulogne, France</td>
<td>Hôpital Foch</td>
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<td>Kamar</td>
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<td>Kaminski</td>
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<td>Hazzan</td>
<td>Lille, France</td>
<td>CHRU Lille</td>
</tr>
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</table>
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)

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

Budget: 663000 euros
Background

• In France, 150000 TRUBP every year.

• Resistance rate to FQ (FQR) and ESBL Enterobacteriaceae 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

<table>
<thead>
<tr>
<th>Clinical endpoints $^b$</th>
<th>FQ-arm n= 116</th>
<th>FT-arm n= 81</th>
<th>Total n= 197</th>
<th>RR$^a$</th>
<th>95%CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-TRUS-PB UTI</td>
<td>17/116 (15%) (95%CI, 10–17%)</td>
<td>7/81 (9%) (95%CI, 5–13%)</td>
<td>24/197 (12%) (95%CI, 8–17%)</td>
<td>0.55</td>
<td>(0.22–1.40)</td>
<td>0.209</td>
</tr>
<tr>
<td>Post-TRUS-PB microbiologically documented UTI</td>
<td>6/116 (5%) (95%CI, 2–8%)</td>
<td>1/81 (1%) (95%CI, 0–3%)</td>
<td>7/197 (4%) (95%CI, 1–6%)</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-TRUS-PB antibiotic intake</td>
<td>14/116 (12%) (95%CI, 8–17%)</td>
<td>7/81 (9%) (95%CI, 5–13%)</td>
<td>21/197 (11%) (95%CI, 6–15%)</td>
<td>0.70</td>
<td>(0.27–1.82)</td>
<td>0.462</td>
</tr>
<tr>
<td>Post-TRUS-PB hospitalization (all causes)</td>
<td>13/116 (11%) (95%CI, 7–16%)</td>
<td>3/81 (4%) (95%CI, 1–6%)</td>
<td>16/197 (8%) (95%CI, 4–12%)</td>
<td>0.30</td>
<td>(0.08–1.11)</td>
<td>0.071</td>
</tr>
<tr>
<td>Post-TRUS-PB hospitalization (due to UTI)</td>
<td>9/116 (8%) (95%CI, 4–11%)</td>
<td>1/81 (1%) (95%CI, 0–3%)</td>
<td>10/197 (5%) (95%CI, 2–8%)</td>
<td>0.15</td>
<td>(0.02–1.20)</td>
<td>0.073</td>
</tr>
<tr>
<td>Post-TRUS-PB adverse events</td>
<td>36/116 (31%) (95%CI, 25–37%)</td>
<td>28/81 (36%) (95%CI, 28–41%)</td>
<td>64/197 (32%) (95%CI, 26–39%)</td>
<td>1.17</td>
<td>(0.64–2.15)</td>
<td>0.602</td>
</tr>
</tbody>
</table>
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°C ≥ 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 ≥ 10³/mL (single uropathogen)
    - and leucocyturia ≥ 10⁴/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
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
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:
  o Fever (temperature ≥ 38°C)
  o and at least one of the following:
    - dysuria, frequency of urination, urgency of urination, hematuria
    - perineal, flank or suprapubic pain
    - pain on rectal examination
  o and leukocyturia ≥ 10/ mm³
• 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/mm³)
- 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 $\geq 10^3$/mL

Inclusion

Day 3-4
- Urine culture positive
- Single uropathogen ($\geq 10^3$/mL)
- Susceptible to: 3rd generation cephalosporins, nal acid and FQ
- No prostate abscess
- Post-void residue $<100$ mL
- No fever ($<38^\circ$C)
- Possible oral route

Antibiotic therapy
- Ofloxacin 200 mg bd (IV or per os)
- Ceftriaxone 1 g od (IV or IM)
- Cefotaxime 1 g td (IV or IM)

Day 3-4
- Oral ofloxacin
- Placebo

Week 6
Main assessment

Week 12
Secondary assessment

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

Yes
To all items
Randomisation
Randomization

- **Randomization criteria: Day 3-4**
  - positive urine culture with a single uropathogen (≥10³ 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)
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 endpoints**

- 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

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

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

→ **deleterious effect of 7-day vs 14-day antibiotic therapy**
## Adverse events related to antimicrobials

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