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

SHORTCUT

INTERVENTIONAL RESEARCH PROTOCOL INVOLVING HUMAN PARTICIPANTS CONCERNING A MEDICINAL PRODUCT FOR HUMAN USE

Version N°3.0 of 26/10/2023
Project Code: APHP200020 /ID-RCB n°: 2021-A02581-40/ Eudract 2022-002319-43

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PROTOCOL SIGNATURE PAGE

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

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The study will be carried out in accordance with the protocol, with current good practices and with statutory and regulatory requirements.

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1 SUMMARY

Full title	Efficacy of 7 days versus 14 days of antibiotic therapy for acute pyelonephritis in kidney transplant recipients, a multicentre randomized non-inferiority trial.
Acronym	SHORTCUT
Coordinating Investigator	Dr Matthieu Lafaurie, Infectious Diseases, Saint Louis hospital, Paris
Sponsor	Assistance Publique-Hôpitaux de Paris
Scientific justification	Infections are a major cause of morbidity and mortality in solid organ transplant recipients. In kidney transplant recipients (KTR) urinary tract infection (UTI) represent 45–72% of all infections, and 30% of all hospitalizations for sepsis. Acute transplant pyelonephritis are the most common complications occurring in more than 20% of patients, mainly in the first year after transplantation. They are associated with an increased risk of acute kidney rejection and long-term kidney graft dysfunction. Gram-negative bacteria, mainly *E. coli*, account for more than 70% of UTI in KTR. As those infections are favored by urinary tract modifications/defects and immunosuppression, they are often recurrent and necessitate repeated courses of antibiotics. Selective pressure due to antibiotic consumption, along with frequent hospital admissions and immunosuppression, are well known risk factors for the development of antibiotic resistant infections. Multidrug (MDR)- or extensively (XDR)- drug resistant *Enterobacteriaceae* including ESBL- or carbapenemase-producing organisms, are thus increasingly observed in transplant units and represent a global threat as very few new antibiotics are expected in the next decade. One main strategy to limit antimicrobial resistance is to reduce the duration of antibiotic treatment. A 7 day-course is recommended for simple acute pyelonephritis (APN) treated with fluoroquinolones or parenteral B-lactams, prolonged up to 10 or 14 days in the presence of underlying disease at risk of complications. Most KT teams treat patients between 14–21 days as recommended by American guidelines. However, the need to extend treatment duration in immunosuppressed patients is a poorly defined concept and the optimal duration of treatment for APN in KTR is not known as these patients are excluded from most studies.

	As there is an urgent need to reduce antibiotic consumption in this population at high risk of developing infections due to resistant pathogens, the hypothesis is that a 7 day-treatment is sufficient to cure APN with good clinical response after 48h of treatment in KTR and is as effective as 14 days.
Main objective and primary endpoint	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 recipients. *Primary endpoint*: Clinical cure and no additional antibiotic treatment since the end of antibiotic treatment up to the main evaluation at day 30. Clinical cure is defined as fever <38°C and no symptoms of UTI.
Secondary objectives and endpoints	To compare between both arms: -Clinical cure at day 90 and day 180 -Microbiological cure at day 30, 90 and 180 -Tolerance and safety of antibiotics -Hospitalization length stay -Antibiotic consumption during total follow up -Acquisition of antibiotic resistant *Enterobacteriaceae* -Kidney graft function and transplant rejection at day 90 and day 180 - The total costs. To evaluate risk factors for failure and relapse/recurrence. To evaluate efficacy of the antibiotic treatment at the end of treatment (D7 for experimental arm and D14 for control group) *Secondary endpoints*: - Clinical cure at day 90 and 180 - Microbiological cure *at day 30, 90 and 180 - Incidence of relapse /recurrence between day 30 and day 90 - Incidence of adverse events imputable to antibiotic treatment - Kidney function assessed according to MDRD (Modification of Diet in Renal Disease) or CKD (Chronic Kidney Disease - Epidemiology Collaboration) epi - Hospitalization length stay defined by the delay between the date of inclusion and the date of hospital discharge - Antibiotic consumption - Rectal carriage of antibiotic resistant *Enterobacteriaceae* at inclusion and day 30

	**Microbiological cure is defined as a sterile urine or uropathogene ≤ 10^3 CFU/mL in urine culture.*
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 (≤ 1 year and > 1 year), center and sex (potential confounders).
Population of trial subjects	KTR with acute pyelonephritis
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 or ≥10/mm^3) and positive urine culture (uropathogen ≥10^3 CFU/mL susceptible to the empirically administrated antibiotic) -No confirmed or suspected febrile non urinary bacterial infection -No urologic/renal complication at baseline imaging (abscess, obstruction...) - Favourable early response to antibiotic treatment:(48 to 60 hours after the first dose of antibiotic effective against the causative uropathogen) defined by: T°<38°C and improvement (or resolution) of signs and/or symptoms of urinary tract infection if present at diagnosis. - Written informed consent
Exclusion criteria	Patients with any of the following conditions: -Severe or complicated condition - Any rapidly progressing disease or immediately life-threatening illness, including, but not limited to, septic shock, current or impeding respiratory failure, acute heart or liver failure - Admission or stay in intensive care unit at baseline - Obstruction of the urinary tract - Renal, perinephric or prostatic abscess - prior inclusion in this study - current participation to another interventional study -Dual antibiotic therapy ((prophylactic antibiotic such as cotrimoxazole allowed))(only 1 dose of aminoside 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, including hematologic

	malignancy, cancer, asplenia, neutropenia<500 neutrophils/mm^3, -Pregnancy, breastfeeding -Hypersensitivity or previous severe adverse drug reaction to the antibiotic therapy -Unable or unwilling, in the judgment of the investigator, to comply with the protocol -Life expectancy<1 month -Patient under legal guardianship or without healthcare coverage -Homeless patient -Women with childbearing potential not using adequate contraception
Comparator treatment	Standard (14 days) antibiotic duration
Interventions added for the trial	2 swabs for bacterial resistance rectal carriage study and 1 follow-up consultation will be added to the standard procedure
Risks added by the trial	UTI could relapse more frequently in the short duration arm if non inferiority is not demonstrated. This will require a new antibiotic treatment for the patient.
Scope of the trial	Phase IV trial
Number of subjects included	470
Number of sites	10
Duration of the trial	Length of participation to the study: 6 months Length of Inclusion period: 36 months Total study duration: 42 months
Number of enrolments expected per site and per month	1-2
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 reference group proportion is 0.95. The treatment group proportion is assumed to be 0.90 under the null hypothesis of inferiority. 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
Sources of funding for the trial	Ministry of Health
Trial will have a Data Monitoring Committee	yes

2 SCIENTIFIC JUSTIFICATION FOR THE STUDY

2.1 Hypothesis for the study

As there is an urgent need to reduce antibiotic consumption in Kidney Transplant Recipients (KTR), a population at high risk of developing infections due to resistant pathogens and antibiotic-induced *Clotridioides difficile* Infections (CDI), our hypothesis is that a 7 day-treatment is sufficient to cure Acute Pyelonephritis (APN) with good clinical response after 48h of treatment and is as effective as 14 days of treatment.

2.2 Description of knowledge relating to the condition in question

Infections are a major cause of morbidity and mortality in solid organ transplant recipients. In KTR urinary tract infections (UTI) represent 45–72% of all infections, and 30% of all hospitalizations for sepsis (1). APN are the most common complications occurring in more than 20% of patients, mainly in the first year after transplantation. They are associated with an increased risk of acute kidney rejection and long-term kidney graft dysfunction (2,3). Gram-negative bacteria, mainly *E. coli*, account for more than 70% of UTI in KTR. As those infections are favored by urinary tract modifications/defects and immunosuppression, they are often recurrent and necessitate repeated courses of antibiotics. Selective pressure due to antibiotic consumption, along with frequent hospital admissions and immunosuppression, are well known risk factors for the development of antibiotic resistant infections. Multidrug (MDR)- or extensively (XDR)- drug resistant *Enterobacteriaceae* including ESBL- or carbapenemase-producing organisms, are thus increasingly observed in transplant units and represent a global threat as very few new antibiotics are expected in the next decade (4). This highincidence of multidrug-resistant microorganisms is associated with increased mortality and graft failure and favors the recurrence of UTI (2).

Antibiotic use has also been associated with CDI risk, especially in immunucompromized patients such as renal transplant population (5). Antibiotic use for UTI has been identified as an independent risk factor for CDI (AOR = 4.17, 95% CI = 1.12-15.54, P = .034) (6).

One main strategy to limit antimicrobial resistance and the risk for CDI is to reduce the duration of antibiotic treatment (7).

The optimal duration of antibiotic treatment of UTI in KTR is poorly known and investigated. Early recognition of the morbidity and mortality associated with allograft pyelonephritis, especially in the first 4-6 weeks following transplantation, led to recommendations in the 1980s to treat UTI with as long as a 6-week course of antimicrobials (9). Since the early 2000's, morbidity and mortality associated with UTI after kidney transplantation has decreased (10) leading to less prolonged treatment. According to KDIGO transplant recipient's guidelines (2009), KTR with kidney allograft pyelonephritis should be hospitalized and treated with intravenous antibiotics, at least initially (9). In the absence of a kidney abscess, a 14 days-course is usually recommended. However, due to the absence of evidence from randomized control studies, at present there is no consensus on the duration of antibiotic treatment. The recently updated US guidelines for example, suggest that *transplant pyelonephritis or urosepsis warrants longer treatment, for example, 14-21 days* and a switch to oral treatment after the resolution of symptoms(4).

2.3 Summary of relevant pre-clinical and clinical trials

At present all relevant clinical data concern non-complicated or complicated UTI in non-immunocompromised patients. KTR are thus excluded from those studies.

Several randomized control trials (RCT) have shown that7 days is safe and non-inferior to longer antibiotic duration to treat acute non-complicated pyelonephritis in those patients (8). The efficacy of this short duration of treatment has been well demonstrated for oral fluoroquinolones and parenteral B-lactams (11-14).

Data on short duration antibiotic treatment efficacy for complicated UTI are scarce and most studies include both patients with complicated cystitis or pyelonephritis (15). Immunocompromised patients are excluded, apart from diabetes, that isno more considered as a risk factor for complications (8). The study by Sandberg*et al.* in 2012 included 282 women with APNincluding 9% of complicated pyelonephritis and 27% of bacteremia. Ciprofloxacin for 7 days was non inferior to ciprofloxacin 14 days in terms of clinical and microbiological efficacy (14).

A meta-analysis on 8 RCT, including 3 RCT with more than 20% of patients with urogenital abnormalities, comparing 7 days or less versus longer treatment for APN and septic urinary tract infection showed no difference between the short and long treatment arms regarding clinical failure at end of treatment, even in a small subgroup of bacteraemic patients (16).

Based on those studies, a 7 day-course is recommended for non-complicated APN treated with fluoroquinolones or parenteral B-lactams, prolonged up to 10 or 14 days in the presence of underlying disease at risk of complications (8). Most KT teams treat patients between 14–21 days as recommended by American guidelines (4). However the need to extend treatment duration in immunosuppressed patients is a poorly defined concept and the optimal duration of treatment for APN in KTR remain to be defined.

2.4 Description of the population to be studied and justification for the choice of subjects

The trial will include KTR treated for an acute graft pyelonephritis. Patients with early APN (1st month) post transplantation and/or with current indwelling catheter will be excluded because the presence of indwelling catheter in the first month post-transplant or after could compromise the efficacy of a short duration treatment.

2.5 Identification and description of the investigational medication or medications

Initial empirical treatment for acute pyelonephritis in KTR (antibiotic and dose) will be left at the discretion of the patient's physician.

The decision to prescribe the experimental treatments (antibiotics) is independent of the inclusion of the patient in the research.

For definitive antibiotic therapy after microbiological results, guidelines will be provided to participating ward physicians. In accordance to French recommendations for APN (8) antibiotic with high kidney concentrations, such as parenteral B-lactams, fluoroquinolones or cotrimoxazole, will be recommended depending of antimicrobial susceptibility test results and

patient known antibiotic allergy or side effects history. Prescription of antibiotics with low kidney concentration such as oral cephalosporins will be discouraged.

2.6 Description and justification of the dosage, route of administration, administration schedule and treatment duration

As stated, the ward physicians will have the responsibility of antibiotic prescription. However, guidelines will encourage prescriptions according to the current French recommendations for non KTR patients

The choice of the prescribed ICD, of the posology, the route and mode of administration is independent of the research but depend on the characteristics of the pathogen, of the national and local recommendations, of renal function and other parameters' characteristic of the patient

For each of the ICD any of the specialities of a generic group (or speciality considered as equivalent by local COMEDIMS) are susceptible to be prescribed.

Acceptable contraceptive measures

In accordance with CTFG recommendation, acceptable contraceptive methods are:

-Progesterone-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action;
- Male or female condom with or without spermicide 5;
- Cap, diaphragm with spermicide 5
A combination of male condom with either, cap, diaphragm or sponge with spermicide are also considered acceptable.

2.7 Summary of the known and foreseeable benefits and risks for the study participants

To our knowledge, after reviewing published literature and ongoing trials registered, SHORTCUT will be the first randomized double blind trial that could provide scientific evidence of the efficacy and safety of a short antibiotic regimen duration for acute pyelonephritis in KTR. The results of SHORTCUT may change national and international guidelines, by providing high quality evidence demonstration that a short duration treatment is safe in KTR.
The originality of SHORTCUT is that its design is pragmatic and fits to the requirements of usual nephrology process in KTR with APN.

Expected patient benefit
Shorten the duration of antibiotic treatment has many advantages for the patient. It decreases the risk of treatment-related adverse events, and the risk of *C. difficile* infection and emergence of resistant strain in the intestinal microbiota. As immunosuppression enhances the risk of MDR/XDR infection due to Extended spectrum betalactamase- (ESBL)/carbapenemase-producing *Enterobacteriaceae* (CPE) this point is crucial for KTP. Urinary tract infections (mostly due to *Enterobacteriaceae*) are indeed the more frequent infection in KTP. MDR/XDR UTI are more difficult to treat and enhance the duration of hospitalization because parenteral

antibiotic treatment is almost always needed due to the lack of effective oral antibiotics. CPE UTI enhances the mortality compared to UTI due to non-resistant bacteria.

Risk for the study participant

Urinary tract infection could relapse more frequently in the short duration arm if non inferiority is not demonstrated. This will require a new antibiotic treatment for the patient

3 OBJECTIVES

3.1 Primary 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 recipients with good clinical response after 48h of treatment.

3.2 Secondary objectives

To compare between both arms:

- Clinical cure at day 90 and day 180
- Microbiological cure at day 30, 90 and 180
- Tolerance and safety of antibiotics
- Hospitalisation length stay
- Antibiotic consumption during total follow up
- Acquisition of antibiotic resistant *Enterobacteriaceae*
- Kidney graft function and transplant rejection at day 90 and day 180
- The total costs

To evaluate risk factors for failure and relapse/recurrence.
To evaluate efficacy of the antibiotic treatment at the end of treatment (D7 for experimental arm and D14 for control group)

4 STUDY DESIGN

4.1 Concise description of the primary and secondary endpoints

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

Clinical cure is defined as fever <38°C and no symptoms of UTI.

Secondary endpoints

- Clinical cure at day 90 and 180
- Microbiologicalcure * at day 30, 90 and 180
- Incidence of relapse /recurrence between day 30 and day 90
- Incidence of adverse events imputable to antibiotic treatment
- Kidney function will be assessed according to MDRD (Modification of Diet in Renal Disease) or CKD (Chronic Kidney Disease - Epidemiology Collaboration) epi at day 90 and day 180. MDRD definition could be find in the following reference: Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999 Mar 16;130(6):461–70. CKD-EPI definition could be find in the following reference: A New Equation to Estimate Glomerular Filtration Rate. Andrew S. Levey, MD; Lesley A. Stevens, MD, MS;

Christopher H. Schmid, PhD; Yaping (Lucy) Zhang, MS; Alejandro F. Castro III, MPH; Harold I. Feldman, MD, MSCE; John W. Kusek, PhD; Paul Eggers, PhD; Frederick Van Lente, PhD; Tom Greene, PhD; and Josef Coresh, MD, PhD, MHS, for the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). Annals of Internal Medicine 2009;150(9):604-613.

- Hospitalisation length stay defined by the delay between the date of inclusion and the date of hospital discharge
- Antibiotic consumption
- Rectal carriage of antibiotic resistant bacteria at inclusion and at day 30

4.2 Research methodology

Design of the trial

Phase IV 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 open design was selected because of the heterogeneity of microorganisms responsible for APN in KT and thus the multiplicity of antibiotics that will be prescribed, making a blind trial unfeasible.

Number of participating sites

10

Identification of the subjects

The subjects participating in this study will be identified as follows:

Site number (3 digits) - Sequential selection number for the site (4 digits) - surname initial - first name initial

This reference number is unique and will be used for the entire duration of the trial.

A treatment number will be also assigned when the participant is allocated to a treatment arm.

Randomiation

Randomization will be performed in a centralized fashion, on line via the e-CRF, by secure internet connexion (CleanwebTélémédecine).

The randomization

- 1:1 between the two parallel arms of
- Experimental group: short duration; 7 day-duration antibiotic treatment
- Control group: standard duration; 14 day-duration antibiotic treatment
- centralized, carried out using a computerized system, CleanWeb®
- stratified according to date of renal transplantation (≤1 year and> 1 year), center and sex (potential confounders). This will result in 4 distinct randomization lists in each of the 10 centres. Each of those 40 lists will be based on permutation blocks to insure equilibrium, the size of which will be kept unknown to the investigators. They will be established by the Clinical and Biostatistics research unit of Saint-Louis Hospital before the beginning of the study according to a method based on permutation block whose size will be kept confidential

As soon as the trial is implemented in a center and when the form of functions delegation (FFD) is filled and signed by all investigator team participants to the trial in the center, the monitoring CRA will forward the request for center opening to Telemedecine. Telemedecine will send by e-mail only, a login and password to each participant (according to their profile) in the center. This e-mail will also contain the internet link allowing to login into the e-CRF.
Experimental treatment numbers will be generated automatically by Cleanweb.

5 IMPLEMENTATION OF THE STUDY

Whose consent must be obtained	**Who informs the individuals and collects their consent**	**At what point the individuals are informed**	**At what point the consent is obtained**
The individual participating in the study;	The principal investigator or collaborating physician declared and trained in the study	Day 1 or 2 or 3	The day before the randomization (day 2 or 3)

Any patient that will be eligible and has given his/her consent will be included in the study.

5.1 Baseline and randomization visits

- **Day 1**:**Baseline**. Patients with clinical signs of APN will be assessed by their physician. As recommended for APN in KRT, at least 1 blood culture, urine analysis (UA), blood cell count, creatinine clearance (CC), liver tests, C reactive protein (CRP), urinary tract and renal imaging (ultrasound or CT scan) will be performed. Empirical antibiotic treatment will be started (antibiotic and dose left at the discretion of the patient's physician) and the patient will be either hospitalized or will be treated on an outpatient basis.
- **Day 3: Inclusion/Randomization**. The investigator in the KT unit will assess the patient, verify early response after 48h of treatment and that all inclusion criteria and none non-inclusion criteria are met. After information and consent signature, eligible patients will be randomly assigned to receive a total of 14 days or 7 days treatment. UA, blood cell count, CC, CRP, urine beta-HCG and rectal swab for faecal resistance study will be done. Randomization will be done if early response 48h to 60 hours after the first administration of effective antibiotic treatment is verified (i.e T°<38°C and improvement or complete resolution of any symptoms and/or signs of UTI if present at baseline) and no later than 5 days after the start of the antibiotic treatment (at D3, D4 or D5). If a change of antibiotic is necessary due to the results of the antibiogram, D0 becomes the day of the first administration of the effective antibiotic.

5.2 Follow-up visits

- **Day 14** (or D15 or D16) (end of treatment in standard duration group): this visit can be made on site at the hospital (inpatient or outpatient) or by telephone. Antibiotic compliance,

occurrence of adverse events, fever and/or new urinary signs of infection since the hospital discharge will be assessed.

- **Day 30** (+/- 3 days) (*main evaluation visit*): assessment for clinical cure and microbiological cure (as defined) and inquiry about any additional antibiotic since the end of antibiotic treatment. UA, blood cell count, CC and CRP. Rectal swab for faecal resistance study.
- **Day 90 (+/- 7 days) and Day 180 (+/- 7 days)**: clinical assessment, inquiry about any UTI and/or additional antibiotic treatment and/or hospitalization since the end of antibiotic treatment. UA, CC.

In case of adverse events, patients can either contact a doctor or a nurse from the transplant department directly by phone, or come to the hospital emergency room or to the transplant consultation, or see their GP, depending on the severity of the adverse effects and the follow-up habits of the departments.

During the follow-up consultations of the patients in the framework of the protocol, the possible occurrence of adverse effects, their intensity and the treatment received will be accurately recorded in the source file and in the e-CRF

5.3 Expected length of participation, chronology and duration of the study.

5.4

Length of Inclusion period: 36 months

Duration of participation for each subject, of which:

- Treatment period: 7 to 14 days
- Follow-up period:6 months

Total study duration: 42 months

5.5 Table summarising the chronology of the study

Actions	**Baseline** Day 1	**Inclusion/ Randomization** Day 3, 4 or 5	Day14	**Main evaluation** Day 30	Day 90	**End of study** Day 180
Signature of the consent form		X				
Past medical history		X				
Questionning about any UTI signs and fever			X	X		
Clinical exam	X	X		X	X	X
Urine analysis	X	X		X	X	X
Beta-HCG urine test		X				
Blood culture(s)	X					
Blood test: blood cell count, C reactive protein	X	X		X		
Blood liver tests	X					
Creatinine clearance	X	X		X	X	X
Renal imaging (ultrasound or CT scan)	X					
Rectal swab for faecal resistance study		X		X		
Dispensation of treatments	X	X				
Compliance to antibiotic therapy inquiry	X	X	X			
Adverse events		X	X	X	X	X

5.6 Distinction between standard care and research

TABLE: "Standard care" vs. "added interventions" required specifically for the study

Procedures and treatments to be provided during the study	**Procedures and treatments associated with standard care**	**Procedures and treatments added for the study**
Treatments	X	short duration of antibiotic therapy
Follow-up visits	X	Additional (phone) D14 consultation
Blood samples	X	
Urine analysis (ECBU)	X	Additional sample at D3
Rectal flora analysis		Rectal swab and bacterial analysis all additional at D3 and D30
Renal imaging	X	

5.7 Biological samples

Collection

Samples for screening of rectal carriage of resistant bacteria *Enterobacteriaceae*

Rectal swabswill be processed at day 3and day 30. They will be placed in transport media ESwab™ (Copan) and sent, immediately after collection, in a triple-packaged envelope by post, to the laboratory of Microbiology of Saint-Louis Hospital, under the supervision of Pr Berçot, head of the Microbiology department. After receipt in the Bacteriology laboratory, they will be frozen at -80° pending their analysis.

Collections of bacteria responsible for urinary tract infection

Urines will be collected at day 1, day 3, day 30, day 90 and day 180.
The bacteria responsible for UTI at day 1 (and throughout the follow-up in case of UTI relapse/recurrence) will be identified using mass spectrometry (VitekMS, Biomerieux), the antibiotic susceptibility test will be performed. Then, the bacteria will be frozen at -80°C for further analysis by whole genome sequencing in the local laboratory. At the end of the study, all samples will be sent in one batch in the centralized Laboratory of Microbiology (Saint-Louis hospital) in dry ice.

Bacterial collections (from rectal flora and urine) will be stored (either frozen or in deep agar) until the end of the study and will be destroyed after microbiological analysis.

Microbial analyses

Cultures

The tubes will be processed by batch. The 2 tubes of the same patient (day 3 _ and day 30) will always be thawed at the same time in order to avoid the impact of thawing on the bacterial families and the microbiota.

Bacteria cultures will be performed using rectal sampling on culture medium UriSelect™4 (BIO-RAD), Carb/OXA biplate, CHROMID® BLSE agar (BioMérieux, Marcy l'Etoile, France) and UriSelect™4 (BIO-RAD) containing antibiotics targeted for the study as ciprofloxacin 1 mg/L). Cascading dilutions up to 10^{-5} will be performed from the liquid of the transport medium ESwab™ and each dilution will be inoculated on selective and non-selective agars for *Enterobacteriaceae* counting. The Colony-Forming Unit count of strains isolated on specific medium compared to the non-selective medium count will determine the relative fecal abundance of resistant strains compared to the overall population of *Enterobactericeae* as previously described (17).

Phenotypes

Resistant colonies will be identified using the spectrometry of mass (VitekMS, Biomerieux) and their antibiotic susceptibility test performed to characterize their resistance phenotypes. The molecules recommended for the management of urinary tract infections will be tested: ampicilin, cefoxitin, piperacillin-tazobactam, pivmecillinam, amoxicillinin clavulanic acid, cefepime, cefotaxime, ertapenem, amikacin, gentamicin, nalidixic acid, ciprofloxacin, trimethoprim-sulfametaxazole, temocillin, fosfomycin and furan. The antibiotic susceptibility test and determination of MICs for fosfomycin, cefotaxime, nalidixic acid and ciprofloxacin will be performed by E-test (bioMérieux, Marcy l'Etoile, France) on Mueller Hignton agar (Bio-rad). Categorization into Resistant/Susceptible/Intermediate will be performed according to the interpretation criteria of the CA-SFM/EUCAST (18).

Genotypes and analysis of molecular determinant

Whole genome sequencing (WGS) and bioinformatic analysis of fecal *Enterobacteriaceae* with a resistance pattern to FQ and/or ESBL on rectal swab at day 3, and day 30 will be performed. Briefly, DNA will be extracted using Wizard Genomic DNA Purification Kit (Promega, Madison, United States (US)), and DNA libraries will be prepared with Nextera XT (Illumina, San Diego, US). De novo assembly will be performed using SPAdes software version 3.13.0 [4]. Quality Assessment Tool for Genome Assemblies (QUAST) software version 5.0.2 will showed the assembly of the genome and the number of contigs [5]. WGS data will be analysed *in silico*to determine the sequence types. Additional resistance markers were sought using ResFinder version 3.1.1 (https://cge.cbs.dtu.dk/services/ResFinder/) and the plasmid content of the strains using (PlasmiFinder)

Description and interpretation

The relative fecal abundance of resistant strains compared to the overall population of *Enterobactericeae* could be determined. The results obtained will allow a comparison resistance 30 days after the basal step at the inclusion.

In addition, the intrinsic resistance mechanism of the bacteria could be highlight by the determination of the content of bacteria in antibiotic resistance genes as well as the clonality of the strains.

Declaration and responsibility for the collection

The collection of samples and bacteria isolated from these samples will be kept at -80°C until the publication of the study under the responsibility of Professor Béatrice Bercot.

At the end of the study, the samples may be used for further analysis not described in the initial protocol but which may be useful for investigation of the condition in light of advances in scientific knowledge, provided the participant is informed and does not oppose this, as stated in the information note/consent form.If the samples are kept at the end of the study, the sample collection will be declared to the ministry of research [and to the director of the competent regional healthcare authority (Article L. 1243-3 of the *Code de la Santé Publique* [French Public Health Code]).

6 ELIGIBILITY CRITERIA

6.1 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 or ≥10/mm^3) and positive urine culture (uropathogen ≥10^3 CFU/mL susceptible to the empirically administrated antibiotic)
- No confirmed or suspected febrile non urinary bacterial infection
- No urologic/renal complication at baseline imaging (abscess, obstruction)
- Favourable early response to antibiotic treatment: 48 to 60 hours after the first dose of antibiotic effective against the causative uropathogen, T°<38°C and improvement (or resolution) of signs and/or symptoms of urinary tract infection if present at diagnosis.
- Written informed consent

6.2 Exclusion criteria

Patients with any of the following conditions:

- Severe or complicated condition
  - Any rapidly progressing disease or immediately life-threatening illness, including, but not limited to, septic shock, current or impeding respiratory failure, 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 antibiotic therapy (prophylactic antibiotic such as cotrimoxazole allowed) (only 1 dose of aminoside is allowed before randomization)
- First month post transplantation

- Current indwelling catheter (including bladder catheter, ureteral stents, percutaneous nephrostomy tubes)
- Prior inclusion in this study
- current participation to another interventional study
- Neurogenic bladder
- Enterocystoplasty
- Immunodeficiency or immunosuppressive therapy not related to kidney transplantation including hematologic malignancy, cancer, asplenia, neutropenia<500 /mm3
- Pregnancy, breastfeeding
- Hypersensitivity or previous severe adverse drug reaction to the antibiotic therapy
- Unable or unwilling, in the judgment of the investigator, to comply with the protocol
- Life expectancy<1 month
- Patient under legal guardianship or without healthcare coverage
- Homeless patient
- Women with childbearing potential not using adequate contraception

6.3 Recruitment methods

In most investigating centers, in case of febrile infection KTR seek for medical attention in the hospital where they are followed by their nephrologist. This process will allow to systematic screen all KTR with APN.
All 10 centers participating to the trial have answered to a feasibility survey and given the number of patients they intend to include. Total foreseeable number of patients is 620, quite higher than number of patient needed to be included.

Total number of subjects to be included	470
Number of sites	10
Enrolment period (months)	36
Number of subjects/site	47
Number of subjects/site/month	1-2

6.4 Termination and exit rules

6.4.1 Criteria and procedures for prematurely terminating the study treatment

- Several situations are possible

- Temporary suspension of the treatment , the investigator must document the reason for suspending and resuming the treatment in the participant’s source file and the case report form (CRF)
- Premature discontinuation of the treatment but the participant remains enrolled in the study until the end of their participation
- Premature discontinuation of study-related treatment , and withdrawal from the study

- The investigator must:
    - Document the reason(s)
    - Collect all the assessment criteria at the moment the subject exits from the study, if the participant agrees.
    - Schedule further follow-up visits for the participant, especially in case of a serious adverse event.

- In the case of severe adverse events, the investigator must notify the sponsor and follow up the participant for 1 months following the premature discontinuation of treatment. Notification of a serious adverse event must be sent by email (eig-vigilance.drc@aphp.fr) to the sponsor. The serious adverse event will be monitored until it is resolved. If a Data Safety Monitoring Board has been created, the committee can specify and/or validate the follow-up methods.

6.4.2 Criteria and procedure for premature withdrawal of a participant from the study

- Participants may exit the study at any time and for any reason.
- If, during the course of his/her participation in the study, the participant presents one of the following exclusion criteria, then the study product/procedure must be discontinued but the participant will continue to be monitored for the study.
    - List the relevant exclusion criteria
- The investigator can temporarily or permanently withdraw a participant from the study for any safety reason or if it is in the participant's best interests.
- Participant lost to follow-up: the participant cannot be located. The investigator must make every effort to reconnect with the participant (and document his attempts in the source file), at least to determine whether the participant is alive or dead

If a participant exits the study prematurely or withdraws consent, any data collected prior to the date of premature exit may still be used.

- If a participant exits the study prematurely, and if the participant agrees, state the procedure and schedule for collecting the data required by the protocol (primary endpoint, secondary endpoints, safety assessment) (NB: this must be stated in the information and consent form)
- State how premature exit from the study will affect the participant's ongoing care (state exactly what the participant will be offered).
- In case of serious adverse events, see the corresponding section on vigilance

The case report form must list the various reasons why the participant has discontinued the study:

- ☐ Lack of efficacy
- ☐ Adverse reaction
- ☐ Another medical issue
- ☐ Personal reasons of the participant
- ☐ Explicit withdrawal of consent
- ☐ Lost to follow-up

6.4.3 Follow-up of participants following premature withdrawal from the study

If a participant discontinues the study, this will in no way affect their usual care for their condition.

In the event of serious adverse events following premature discontinuation of treatment and participation of the patient in the study; see section 6.4.1

6.4.4 Full or partial cancellation of the study

AP-HP (the sponsor) or the Competent Authority (ANSM) can prematurely discontinue all or part of the trial, temporarily or permanently, further the recommendation of the Data safety Monitoring Board in the following situations:

- first, if suspected unexpected serious adverse reactions (SUSARs) are observed in one of the treatment arms or if there is a discrepancy in the serious adverse reactions between the two treatment arms, requiring a reassessment of the benefit-risk ratio for the trial
- if an interim analysis confirms the efficacy of one of the treatment arms or, alternatively, the lack of efficacy
- similarly, AH-HP, as the sponsor, or the Competent Authority (ANSM) may prematurely decide to discontinue the trial due to unforeseen issues or new information about the product, in light of which the objectives of the study or clinical programme are unlikely to be achieved.
- AP-HP, as the sponsor, reserves the right to permanently suspend enrolment at any time if the inclusion objectives are not been met.

If the study is prematurely discontinued for safety reasons, the decision and justification will be provided by the sponsor (AP-HP) to the Competent Authority (ANSM) and the CPP within 15 days, along with recommendations from the Data Safety Monitoring Board in case of substantial modification.

7 TREATMENT ADMINISTERED TO STUDY PARTICIPANTS

As explained in chapter 2 (2.5 and 2.6), patients will receive antibiotics according to the standard care process. All antibiotics will be delivered by the pharmacy (either hospital and/or community) as routinely. Posology, adjusted to creatinine clearance and route of administration will follow standard guidelines to treat urinary tract infections.

Given that the information contained in marketing authorizations of drugs is likely to change, at the time of the prescription, investigators are advised to ensure the respect in particular of contraindications, warnings and precautions for use, as well as drug interactions.

Investigators can refer:

- to information available on the Public Drug Database, accessible via the Internet at the following address: http://base-donnees-publique.medicaments.gouv.fr/,

- to information available on drug interaction ANSM thesaurus, accessible via the Internet at the following address: https://ansm.sante.fr/documents/reference/thesaurus-des-interactionsmedicamenteuses-1

- Letters to the healthcare professionals about warnings and precautions for use of fluoroquinolones are available on the ANSM's website:

- Risk of regurgitation/heart valve failure :
https://ansm.sante.fr/informations-de-securite/antibiotiques-de-la-famille-des-fluoroquinolonesadministres-par-voie-systemique-et-inhalee-risque-de-regurgitation-insuffisance-des-valvescardiaques

- Risk of disabling, long-lasting an potentially irreversible side effects and restrictions on use
https://ansm.sante.fr/informations-de-securite/antibiotiques-de-la-famille-des-quinolones-etfluoroquinolones-administres-par-voie-systemique-ou-inhalee-risque-deffets-indesirables-invalidantsdurables-et-potentiellement-irreversibles-et-restrictions-dutilisation

- Risk of occurrence of aneurysm and aortic dissection:
https://ansm.sante.fr/informations-de-securite/fluroquinolones-par-voie-systemique-ou-inhaleerisque-de-survenue-danevrisme-et-de-dissection-aortique

In the context of the academic study with no commercial purpose, the drugs are prescribed and used strictly under the conditions entitling them to reimbursment (the duration of treatment in the experimental arm being less than that used in the SOC) Thus, under article L1121-16-1 of the CSP, the sponsor will neither provide nor finance the antibiotics used but will delegate teheir supply and fincing to each of the centers

As patients will be treated with different kinds of antibiotics according to the physician, to the causative germ and the history of patients, no specific labelling or packaging will be forecasted.

However, regarding traceability the sponsor will organize and monitor the following data for each administration: ICD, name of speciality dayly posology, administration route and compliance. These data will be collected in the eCRF. In the context of this study traceability of the batches used will not be implemented (the management of quality complaints / recalls is part of the pharmaceutical processes implemented in each hospital as part of the care).

8 EFFICACY ASSESSMENT

- Clinical cure, defined as fever <38°C and no symptoms of UTI will be assessed through an appropriate history and physical examination by the physician taking care of the patients.

- Microbiological eradication defined as uropathogen ≤ 10.3 CFU/mL in urine culture will be assessed with urine analysis (culture and, if positive, antimicrobial susceptibility test).
- New urinary infection or relapse of the urinary infection will be assessed using the same clinical and microbiological parameters.
- Incidence of adverse events imputable to antibiotic treatment will be recorded during the follow-up.
- Antibiotic consumption (indication, dose and duration) throughout the follow-up will be recorded.
- Rectal carriage of antibiotic resistant bacteria at the end of treatment (day 14) and at day 30 will be analysed (see for details in chapter 5.6).

9 SPECIFIC COMMITTEES FOR THE TRIAL

9.1 Scientific Committee

- Members of the committee:

Pr AC CREMIEUX, Infectious Diseases Unit, Hôpital Saint-Louis, Paris.
Pr PERALDI, Nephrology Department, Hôpital Saint-Louis, Paris.
Dr SCEMLA, Nephrology Department, Hôpital Necker, Paris.
Pr BERCOT, microbiology, Hôpital Saint-Louis, Paris.
Dr DINH, Infectious Diseases, Hôpital Raymond Poincaré, Garches.

- Missions:

To validate the antibiotic guidelines for treating APN
To validate the e-CRF that will be implemented
To regularly take stock of the trial and to inform the Data Safety Monitoring Board in case of any difficulty during the course of the trial (low-rate recruitment…)

- Operating procedures:

One meeting every 12 months or more frequently, if necessary.

9.2 Data Safety Monitoring Board (DSMB)

A Data Safety Monitoring Board (DSMB) will be established by the sponsor for this trial. Its primary mission is to monitor safety data.
The DSMB will hold its first meeting before the first participant is enrolled and ideally before the protocol is submitted to the competent authority (ANSM) and the CPP (Research Ethics Committee).
The DSMB will operate in accordance with the sponsor's procedures. The DSMB works in an advisory capacity only and the sponsor retains all decision-making authority.

- Members of the DSMB:

Three independent expert in kidney transplantation and/or infectious disease and/or microbiology were nominated plus an expert in Public Health.
To ensure their independency with the study team, they are not issued from centres participating in the study. Also, they will be thanked but not listed as authors in the publications.

- Dr Evangéline Pillebout,(nephrology, Saint Louis Hospital)
- Dr Francois Camelina,(microbiology, Saint Louis Hospital)
- Dr Geoffroy Liégeon, (infectious deases, Saint Louis Hospital)
- Dr Tristan Delory, (Public Health)

- Missions:

- On demand of the coordinator of the study, to ensure the recruitment by delivering advices to improve the inclusion-rate in the trial, to open new investigator centres, to simplify the procedure to facilitate inclusions…
- Data safety monitoring: to ensure that there is no increased risk during the course of the trial, for the patients randomized in the short duration arm (7 days) compared to the standard duration arm (14 days) by asking, if judged necessary, crude results and if neededresults per arm (without disclosing)
- An intermediate analysis will be systematically performed after 200 pateints have been randomized.
- To suggest study cessation in case of safety issue.

- Operating procedures:

Operating procedures are defined in the DSMB charter.
A minimum of one meeting every 6 months is planned and or more frequently, if necessary.

9.3 Validation Committee

- Members of the Committee

Dr Julien COUSSEMENT, nephrologist, Dr Raphael LEPEULE, infectious disease specialist and Dr Vincent Cattoir, bacteriologist.

- Mission and Operating procedures

At the end of the follow up of the last included patient, the committee will blindly evaluate the primary end points of all patients.

After reviewing the e-CRF data they will classify patients into 4 categories, as follows:

- Cure: 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 fever <38°C and no symptoms of UTI. Microbiological eradication is defined as uropathogen ≤ 10.3 CFU/mL in urine culture.
- Relapse: recurrence of urinary tract infection due to the same microorganism. Clinical and microbiological criteria are the same than those used to establish the initial diagnostic of KT pyelonephritis. However, relapse infections will be divided into 2 groups: febrile (APN) and afebrile (cystitis).
- Reinfection: new urine tract infection episode due to a different pathogen than initial causing the APN. Clinical and microbiological criteria are the same as those used to establish the initial diagnostic of KT pyelonephritis. Reinfections will be divided into 2 groups: febrile (APN) and afebrile (cystitis).
- Urinary colonization: bacteriuria with a single pathogen, whatever the threshold, with no signs of UTI and no fever.

10 SAFETY ASSESSMENT - RISKS AND RESTRICTIONS ADDED BY THE STUDY

10.1 Definitions

According to Article R1123-46 of the French Public Health Code:

- **Adverse event**

Any untoward medical occurrence in a study participant, which does not necessarily have a causal relationship with the study or with the product subject to the study.

- **Adverse reaction**

Adverse event occurring in a person enrolled in a study involving human participants, when this event is related to the study or to the product being studied.

- **Adverse reaction to an investigational medicinal product**

Any untoward and unwanted reaction to an investigational medication regardless of the dose administered.

- **Serious adverse event or reaction**

Any adverse event or reaction that results in death, threatens the life of the research participant, requires hospitalisation or prolongs hospitalisation, causes a serious or long-term disability or handicap, or results in a congenital abnormality or deformity.

- **Unexpected adverse reaction to an investigational medicinal product**

Any adverse reaction to the product whose nature, severity, frequency or outcome is inconsistent with the standard safety information described in the summary of the product characteristics, or in the investigator's brochure if the product is not authorised.

According to Article R.1123-46 of the Code de la Santé Publique and the guidelines for clinical trial sponsors (ANSM):

- **Emerging safety issue**

Any new information may lead to a reassessment of the risk/benefit ratio of the trial or of the product under investigation, modifications in the investigational medicinal product use the conduct of the clinical trial or the clinical trial document, or a suspension, interruption or modification of the research trial or of similar trials.

For studies involving the first administration of a health product in healthy volunteers: any serious adverse reaction.

Examples:

a) any clinically significant increase in the frequency with which of an expected serious adverse reaction;

b) suspected unexpected serious adverse reactions in patients who have terminated their participation in the clinical trial which have been notified by the investigator to the sponsor as well as potential follow-up reports;

c) any new fact relating to the conduct of the clinical trial or the development of the investigational medicinal product, if the new fact is likely to affect participant safety

Examples:

- a serious adverse event that may be related to the trial's interventions and diagnostic procedures and which may impact the conduct of the clinical trial, if this event could affect the safety of the participants,
- a significant risk for the trial participants such as a lack of efficacy of the investigational medicinal product used in the treatment of a life-threatening disease,
- significant safety results from a recently completed research on animals (such as a carcinogenicity research),
- the premature termination, or temporary suspension for safety reasons, of a trial conducted in another country by the same sponsor using the same investigational medicinal product
- a serious adverse event related to a auxiliary medicinal product required to conduct the trial and without interaction with the investigational medicinal product, if this event could affect the safety of the participants

d) recommendations from the Data Safety Monitoring Board (DSMB), wherever applicable, if they are relevant to the safety of the participants

e) any unexpected serious adverse reaction with the IMP reported to the sponsor by spontaneous notifications, by publications or health authorities, if this adverse reaction could affect the safety of the participants of the clinical trial conducted by the sponsor.

10.2 The role of the investigator

The investigator must **assess the seriousness criteria of each adverse event** and record all serious and non-serious adverse events in the case report form, (eCRF)
The investigator must **document** serious adverse events **as thoroughly as possible** and provide a definitive medical diagnosis, if possible.

The investigator must **assess the severity** of the adverse events by using general terms:

- *Mild: tolerated by the patient, does not interfere with daily activities*
- *Moderate: sufficiently uncomfortable to affect daily activities*
- *Serious: preventing daily activities*

The investigator must **assess the causal relationship between** a serious adverse events and interventions/procedures added by the study

The method used by the investigator is based on following causality terms:

- Reasonnable possibility
- No reasonnable possibility

Serious adverse events that require a notification without delay by the investigator to the sponsor

As per article R.1123-49 of the French Public Health Code (CSP), the investigator must notify the sponsor **without delay on the day when the investigator becomes aware**of any serious adverse event which occurs during a trial as described in Article L.1121-1(1) CSP, except those which are listed in the protocol and, as not requiring a notification without delay.
A serious adverse event is any untoward medical occurrence that:

1- results in death 2- is life-threatening to the participant enrolled in the study 3- requires hospitalisation or prolongation of existing hospitalisation 4- results in persistent or significant disability/incapacity 5- is a congenital anomaly/birth defect

Specific features of the protocol

Other events that require the investigator to notify the sponsor without delay

- Adverse events deemed “medically significant”

New Urinary tract infection or relapse of the initial urinary tract infection

The investigator must notify the sponsor without delay on the day the investigator becomes aware of these adverse events, in the same manner and within the same deadline as for serious adverse events (see above).

- ***In utero*** **exposure**

The investigator must notify the sponsor without delay on the day the investigator becomes aware of any pregnancy that occurs during the study, even if it is not associated with an adverse event.

10.2.1.1 Serious adverse events that do not require the investigator to notify the sponsor without delay

These serious adverse events are simply recorded in the case report form.

- Normal and natural course of the condition:
  Any adverse outcomes related to non-infectious complication of the kidney transplant

- Special circumstances
  − Hospitalization for a pre-existing illness or condition
  − Hospitalization for a medical or surgical treatment arranged prior to the trial
  − Admission for social or administrative reasons Adverse events during the trial

- *Adverse events during the trial possibly related to treatments prescribed as part of the patient's standard care (including ATB, immunosupressant,). The SAE related to antibiotherapy that is not related with the research procedure must be transmitted to the relevant regional pharmacovigilance centre, Centre Régional de Pharmacovigilance (CRPV) and not to sponsor (excluding those leading to death)*

The investigator must report these events to his Centre Régional de Pharmacovigilance (CRPV).

10.2.1.2 Period during which the investigator must send notificationof SAEs to the sponsor without delay

The investigator must notify the sponsor without delay of any serious adverse events as defined in the corresponding section:

- from the date the consent form is signed
- throughout the D30 visit
- Indefinitely, if the SAE is likely to be due to interventions added by the study (short duration of antibiotherapy) according to the investigator

10.2.1.3 Procedures and deadlines for notifying the sponsor

The initial notification of an SAE must be provided in a written report signed by the investigator using a SAE notification form specific to the study and intended for this purpose (in the case report form).

Each item in this form must be completed by the investigator so that the sponsor can carry out the appropriate analysis.

The initial notification to the sponsor of a serious adverse event must be quickly followed by an additional detailed written report (or reports) so that the case outcome may be monitored by the Safety Department or to provide further information.

Whenever possible, the investigator will provide the sponsor with any documents that may be useful for medical assessment of the case (medical reports, laboratory test results, results of additional examination, etc.). These documents must be non identifying. In addition, the documents must include the following: study acronym and the number and participant initials..

Any adverse event will be monitored until fully resolved (stabilisation at a level considered acceptable by the investigator, or return to the previous state) even if the subject has left the study..

The initial notification, the SAE follow-up reports and all other documents must be sent to the sponsor's Safety Department by email (eig-vigilance.drc@aphp.fr). It should be noted that it is possible to send SAE reports to the Safety Department by fax to +33 (0)1 44 84 17 99, only in the event of a failed attempt to send the SAE report by email (in order to avoid duplication).

For studies which use e-CRFs

- the investigator completes the SAE report form in the e-CRF, then validates, prints and signs the form before sending it by email;
- If it is not possible to connect to the e-CRF, the investigator should complete, sign and send the SAE report form to the safety Department. As soon as the connection is restored, the investigator must complete the SAE report form in the e-CRF.

The investigator must respond to all requests for additional information from the sponsor.
For all questions relating to an adverse event report, the safety Department can be contacted via email at vigilance.drc@aphp.fr.

For cases of *in utero* exposure, the investigator will complete the "report and follow-up form for pregnancy during participation in a study".
The investigator must monitor the pregnant woman throughout her pregnancy or until the pregnancy is terminated, and must notify the sponsor of the outcome of the pregnancy using this form.
If the outcome of the pregnancy falls within the definition of a serious adverse event (miscarriage, pregnancy termination, foetal death, congenital abnormality, etc.), the investigator must follow the procedure for reporting SAEs.
The initial pregnancy notification, the SAE follow-up reports, and any other documents will be sent to the sponsor according to the same procedures specified herein

10.3 Role of the sponsor

The sponsor, represented by its Safety Department, continuously, throughout the trial, assesses participant safety throughout the study.

Analysis and declaration of serious adverse events

The sponsor assesses:

- the **seriousness** of all the adverse events reported
- the **causal relationship** with each specific intervention/procedure/examination added by the study,
  All serious adverse events which the investigator and/or the sponsor believe could have a causal relationship with the *interventions/procedures/practiced examinations and/or administered products*, specifically added by the study that could reasonably be considered as having suspected serious adverse reactions.
  the **expected or unexpected** nature of the serious adverse reactions
  Any serious adverse reaction whose nature, severity, frequency or outcome is inconsistent with the safety information described in the summary of product characteristics, or in the investigator's brochure if the product is not authorised, is considered unexpected

  The sponsor, represented by its Safety Department, assesses the expected/unexpected nature of a serious adverse reaction based on the information described below**.**

❖ For serious adverse events likely to be related to the investigational medicinal product(s): refer to the SmPC for each IMP (antibiotic therapy) used

❖ The serious adverse events potentially related to the study procedure (short duration of antibiotherapy):
New Urinary tract infection or relapse of the initial urinary tract infection except those leading to life threatening and death

The sponsor will report all suspected unexpected serious adverse reactions (SUSARs), within the regulatory time frame, to the ANSM (French Health Products Safety Agency):

- The sponsor must send the initial report immediately upon learning of the unexpected serious adverse reaction if is fatal or life-threatening, or otherwise within 15 days from learning of any other type of unexpected serious adverse reaction;

- All additional, relevant information must be declared by the sponsor in the form of monitoring reports within a period of 8 calendar days starting from when the sponsor had this information.

Any suspected unexpected serious adverse reaction must also be declared electronically using the Eudravigilance European adverse drug reactions database managed by the European Medicines Agency (EMA).

The sponsor must notify all the investigators about any information that could adversely affect the safety of the trial subjects.

Analysis and declaration of other safety data

This means any new information that prompts a reassessment of the risk/benefit ratio of the trial or of the product under investigation, or which could be sufficient to consider changes to the use of the product, the trial procedures or trial documentation, or the suspension, cancellation or amendment of the research trial or of other similar trials. For trials involving the first administration or use of a health product in healthy volunteers: any serious adverse reaction.

The sponsor will inform the competent authority and the Research Ethics Committee without delay upon knowledge of any emerging safety issue and, if applicable, describe what measures have been taken.

Following the initial declaration of any emerging safety issue, the sponsor will address to competent authorities any additional relevant information about the emerging safety issue in the form of a follow-up report, which must be sent no later than 8 days after learning of the information.

Annual safety report

Once a year for the duration of the clinical study, the sponsor must produce an annual safety report (Development Safety Update Report - DSUR) which includes, in particular:

- a safety analysis for the research participants,
- a description of the patients included in the study (demographic profile etc.)
- a list of all the suspected serious adverse reactions that occurred in France in the concerned study during the period covered by the report,
- summary tables including all of the SAEs that have occurred since the start of the study.

The report must be sent no later than 60 days after the anniversary of the date on which the first ANSM authorized the trial.

10.4 10.3.4 Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) may be established by the sponsor. Its primary mission is to monitor safety data. It can have other missions, such as monitoring efficacy data (especially if the protocol includes interim analyses).
The sponsor is responsible for justifying the creation or absence of such a committee to the Competent Authority (ANSM) and to the CPP (Research Ethics Committee).

A DSMB will be established for this trial. The DSMB must hold its first meeting before the first participant is enrolled and ideally before the protocol is submitted to the competent authority and the CPP (Research Ethics Committee).
All missions as well as the specific operating procedures of the DSMB are described in the study's DSMB charter.

The DSMB members are:

- Dr Evangéline Pillebout,(nephrology Saint Louis Hospital)
- Dr Francois Camelina,(microbiology, Saint Louis Hospital)
- Dr Geoffroy Liégeon, (infectious deseases, Saint Louis Hospital)
- Dr Tristan Delory, (santé publique)

The DSMB's principle missions and their operating procedures are described in the DSMB chart of the clinical trial.
The DSMB has a consultative role. The decision concerning the conduct of the clinical trial relies on the sponsor.

The DSMB will operate in accordance with the sponsor's procedures. The DSMB works in an advisory capacity only and the sponsor retains all decision-making authority.

11 DATA MANAGEMENT

11.1 Data collection procedures

The investigator will allow the sponsor's representatives to monitor the study at the frequency defined in the contract, depending on enrolment at each center.
Case Report Forms (CRFs) and related source documents will be reviewed in detail during monitoring visits (completeness, adherence to the guidelines, accuracy compared to source documents). The sponsor's representative will also review regulatory documents, drug storage and accountability. The investigator must keep a comprehensive and centralized filing system for all study-related documents that would be suitable for inspection by the sponsor's monitors or representatives of any other regulatory agency.

11.2 Right to access data and source documents

Data access

In accordance with GCP:
- the sponsor is responsible for ensuring all parties involved in the study agree to guarantee direct access to all locations where the study will be carried out, the source data, the source documents and the reports, for the purposes of the sponsor's quality control and audit procedures.
- the investigators will ensure the persons in charge of monitoring and auditing the clinical trial and of quality control have access to the documents and personal data strictly necessary for these tasks, in accordance with the statutory and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code)

Source documents

Source documents are defined as any original document or item that can prove the existence or accuracy of a data or a fact recorded during the study. These documents will be kept in accordance with the regulations in force by the investigator or by the hospital in the case of a hospital medical file.

Data confidentiality

The persons responsible for the quality control of clinical studies (Article L.1121-3 of the French Public Health Code) will take all necessary precautions to ensure the confidentiality of information relating to the investigational medicinal products, the study, the study participants and in particular the identity of the participants and the results obtained.
These persons, as well as the investigators themselves, are bound by professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the French Criminal Code).
During and after the clinical study, all data collected about the study participants and sent to the sponsor by the investigators (or any other specialised collaborators) will be anonymised.
Under no circumstances will the names and addresses of the subjects be shown.
The sponsor will ensure that each subject has agreed in writing for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed.

11.3 Data processing and storage of documents and data

Identification of the data processing manager and the location(s)
Data management will be done in the biostatistical unit of Saint Louis hospital, Paris (Pr Chevret).

Data entry
Data will be entered electronically via a web browser.

Data processing (CNIL, the French Data Protection Authority) in France
This trial is governed by the CNIL "Reference Method for processing personal data for clinical studies" (MR-001, amended). AP-HP, the study sponsor, has signed a declaration of compliance with this "Reference Method".

11.4 Ownership of the data

AP-HP is the owner of the data. The data cannot be used or disclosed to a third party without its prior permission.

12 STATISTICAL ASPECTS

12.1 Planned statistical methods, including the timetable for any planned interim analyses

Primary analyses of the trial will be performed on the whole population of included patients, i.e. in intention to treat (ITT), independently from the treatment received, whatever the treatments received and whatever the objective of non-inferiority or superiority demonstration.

Disposition of the Study Subjects: The disposition of subjects will be described with summaries by treatment group of the number of subjects enrolled, the number of subjects treated, and the number of subjects for whom study drug was permanently discontinued (including the reasons for discontinuation).

In order to address non inferiority questions, confidence intervals at 95% of the main endpoint will be calculated and its lower threshold compared to the margin of non-inferiority (5%) planned in the trial.
For superiority questions or for secondary criteria, effect sizes will be appreciated using point estimates with a confidence interval of 95%, using statistical tests adapted to each criterion. Effects measured on right-censored criteria will be hazard ratios, the effect on proportions will be measured by relative risks and the difference between risks. These estimations will be adjusted on prognostic factors.

12.2 Hypotheses for calculating the required number of subjects, and the result

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 reference group proportion is 0.95. The treatment group proportion is assumed to be 0.90 under the null hypothesis of inferiority. The power was computed for the case when 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. Total sample size is thus 470 patients.

12.3 Anticipated level of statistical significance

All tests will be two-sided with p-values of 0.05 or less denoting statistical significance. All tests will be based on a two sided alpha risk of 0.05.
For the primary endpoint it corresponds to a unilateral test considering an alpha risk of 0.025.

12.4 Method for taking into account missing, unused or invalid data

Missing data on covariates of interest will be attributed by multiple imputation using chained equations (Multiple Imputation by Chained Equation: MICE).

12.5 Management of modifications made to the analysis plan for the initial strategy.

An amendment will be filed in case of modification of the initial statistical analysis plan (SAP).

12.6 Cost-consequence analysis

The economic evaluation will assess the costs and the efficacy /safety of reduced antibiotherapy. Costs and consequences will not be aggregated. The analysis is undertaken from the viewpoint of the healthcare system, over a 6-month period.

All healthcare resources required for the treatment of the APN will be collected prospectively. They include in-hospital and out-hospital treatments, tests, consultations, imaging and home care.

Healthcare costs will be assessed using a combination of resource-based and event-based methods. The total length of stay and discharge information (DRG) will be extracted from the hospital information system for the index admission and event-related subsequent admissions during the 180 day-follow up period. Hospital costs will be assigned based on the Severity-Diagnosis Related Groups adjusted for length of stay. The cost of each admission will be estimated from the national cost study, using the actual length of stay and the per diem cost stratified by DRG.

Out-hospital resources will be estimated from the e-CRF, medical charts (discharge prescriptions) and patient's interviews during the follow up visits. In addition to the antibiotic treatment, we will collect information on consultations, medications, laboratory tests. Out-hospital resources will be valued using the latest price/ tarif schedule. Total average cost per patient will be commuted in each group; 95%

bootstrapped interval will be estimated and costs will be compared using nonparametric tests).

Health consequences for the economic evaluation are consistent with the study's endpoints:

- Clinical cure and microbiological eradication at day 180
- Total number of relapse /recurrence at day 180
- Total antibiotic consumption at day 180

If the 7 day-treatment course is non inferior to the 14 day-course, we will undertake a budget impact analysis.

12.7 Selection of populations

Primary analyses of the trial will be performed on the whole population of included patients, i.e. in intention to treat (ITT), independently from the treatments received and whatever the objective of demonstration of superiority or non-inferiority**Erreur ! Signet non défini.**.

A secondary analysis of the non-inferiority will use the per-protocol population.

13 QUALITY CONTROL AND ASSURANCE

Every clinical study involving human participant managed by AP-HP is ranked according to the projected risk incurred by the study participants using a classification system specific to AP-HP-sponsored clinical trials.

13.1 General organisation

The sponsor must ensure the safety and respect of individuals who have agreed to participate in the trial. The sponsor must have a quality assurance system for monitoring the implementation of the study at the research centers.

For this purpose, the sponsor shall appoint Clinical Research Associates (CRA) whose primary role is to carry out regular follow-up visits at the study sites, after completing their initial visits. The purpose of monitoring the study, as defined in the Good Clinical Practices (GCP section5.18.1), is to verify that:

- the rights, safety and protection of the research subjects are met.
- the data reported are exact, complete and consistent with the source documents
- the study is carried out in accordance with the protocol in force, the GCPs and with all statutory and regulatory requirements.

Strategy for site opening

The strategy for opening the sites is determined using the tailored monitoring plan.

Scope of site monitoring
In the case of this C risk study, the appropriate monitoring level has been determined based on the complexity, the impact and the budget for the study. Therefore, the sponsor, in agreement with the coordinating investigator, has agreed on a logistical score and impact and the corresponding study monitoring level of: **High** level.

13.2 Quality control

A Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the proper running of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the DRCD and in accordance with Good Clinical Practice as well as with the statutory and regulatory requirements.

The investigator and the members of the investigator's team agree to make themselves available during regular Quality Control visits by the Clinical Research Associate. During these visits, the following elements will be reviewed depending on the monitoring level :

- written consent
- compliance with the study protocol and its procedures
- quality of the data collected in the case report forms: accuracy, missing data, consistency of the data with the "source" documents (medical files, appointment books, original copies of laboratory results, etc.)
- management of the treatments used

13.3 Case Report Form

All information required by the protocol must be entered in the case report forms. The data must be collected as and when it is obtained, and clearly recorded in these case report forms. Any missing data must be coded.
Every site will have access to the electronic case report forms via a web-based data collection system. Investigators will be given instructions for using this tool.
When the investigators complete the case report form via the internet, the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality and relevance of all the data entered. In addition, the data are immediately verified as they are entered, thanks to consistency checks. To this end the investigator must validate any changes to the values in the case report form. An audit trail will be kept of all changes. A justification can be added when applicable, as a comment.
A print-out, authenticated (signed and dated) by the investigator, will be requested at the end of the study. The investigator must archive a copy of the authenticated document that was delivered to the sponsor.

13.4 Management of non-compliances

Any events that occur as a result of non-compliance, by the investigator or any other individual involved in conducting the study, with the protocol, standard operating procedures, good clinical practice or statutory and regulatory requirements must be recorded in a declaration of non-compliance and sent to the sponsor.

These non-compliances will be managed in accordance with the sponsors procedures.

13.5 Audits/inspections

The investigators agree to accept the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits and inspections. These audits and inspections cannot be refused on the basis of medical secrecy.

An audit can be carried out at any time by independent individuals appointed by the sponsor. The aim of the audits is to ensure the quality of the study, the validity of the results and compliance with the legislation and regulations in force.

The persons who manage and monitor the trial agree to comply with the sponsor's requirements and with the competent authority regarding study audits or inspections.

The audit may encompass all stages of the study, from the development of the protocol to the publication of the results and the storage of the data used or produced as part of the study.

13.6 Principal Investigator's comitment to assume responsibility

Before starting the study, each investigator will give the sponsor’s representative a copy of his/her updated personal curriculum vitæ with his/herand RPPS number (Répertoire Partagé des Professionnels de Santé, Collective Database of Health Professionals). The CV must include any previous involvement in clinical research and related training

Each investigator will commit to comply with legislation and to conduct the trial in line with GCP, in accordance with the Declaration of Helsinki.

The Principal Investigator at each participating site will sign a declaration of responsibility (standard DRCI document) which will be sent to the sponsor's representative.
The investigators and their staff will sign a delegation of duties form specifying each person's role and will provide their CVs.

14 ETHICAL AND LEGAL CONSIDERATIONS

14.1 Methods for informing and obtaining consent from the research participants

In accordance with Article L1122-1-1 of the Code de la Santé Publique (French Public Health Code), no interventional research involving human participants can be carried out on a person without his/her freely given and informed consent, obtained in writing after the person has been given the information specified in Article L.1122-1 of the aforementioned Code.

A reflection period of 48 hours is given to the individual between the time when he or she is informed and when he or she signs the consent form.

The person’s freely-given, written, informed consent will be obtained by the principal investigator or a physician representing the investigator before the person is enrolled in the study

A copy of the information note and consent form, signed and dated by the research participant and by the principal investigator or the physician representing the investigator will
be given to the individual prior to their participation in the study. The principal investigator or the physician representing him/her will keep a copy.

At the end of the study, one copy will be placed in a tamper-proof sealed envelope containing all the consent forms. This envelope will be archived by the sponsor.

In addition, the investigator will specify in the research participant’s medical file the methods used for obtaining their consent as well as the methods used for providing information with a view to obtaining consent. The investigator will retain the original signed and dated consent form.

14.2 Prohibition of concomitant clinical studiesparticipation and exclusion period after the trial

The participant may not enroll in another interventional study protocol involving human participants for the duration of his or her participation without consulting with the physician monitoring him or her in the context of the study.

14.3 Legal obligations

Role of the sponsor

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Assistance Publique - Hôpitaux de Paris (AP-HP) is the sponsor of this study and, by delegation, the DRCI (Clinical Research and Innovation Department) carries out the study's missions in accordance with Article L.1121-1 of the Code de la Santé Publique (French Public Health Code). Assistance Publique - Hôpitaux de Paris reserves the right to halt the study at any time for medical or administrative reasons. In this case, notification will be sent to the investigator.

Request for approval from CPP (Research Ethics Committee)

Prior to starting the study, AP-HP, as sponsor, must obtain for this interventional study involving human participants concerning a medicinal product for human use, approval from the appropriate CPP (Research Ethics Committee), within the scope of its authority and in accordance with in force legislation and regulatory requirements.

Request for authorisation from the ANSM

Prior to starting the study, AP-HP, as sponsor, must obtains authorisation from the ANSM (French Health Products Safety Agency) for the interventional study involving human participants concerning a medicinal product for human use, within the scope of the ANSM's authority and in accordance with in force legislation and regulatory requirements.

Procedures relating to data protection regulation

The computer file used for this research is implemented in accordance with French (amended “Informatique et Libertés” law governing data protection) and European (General Data Protection Regulation – GDPR) regulations.

This research is governed by the CNIL (French Data Protection Agency) “Reference Methodology for processing personal data used within the scope of health research” (amended MR-001). AP-HP, as sponsor of the research, has signed a declaration of compliance with this “Reference Methodology”

Amendments to the research

Any substantial modification to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain, approval from the CPP (Research Ethics Committee) and authorisation from the ANSM within the scope of their respective authorities, before the amendment can be implemented.
The information note and the consent form can be revised if necessary, in particular in case of a substantial amendment to the study or if adverse reactions occur.

Final study report

The final report for the research involving human participants referred to in Article R1123-67 of the *Code de la Santé Publique* (French Public Health Code) is written and signed by the sponsor and the investigator. A report summary drafted according to the reference plan of the competent authority must be sent to the competent authority within a period of one year following the end of the study, i.e., the end of the participation of the last participant in the study.

14.3.7 Archiving

Specific documents for an interventional study involving human participants concerning a medicinal product for human use will be archived by the investigator and the sponsor for 15 years after the end of the research.

This indexed archiving includes, in particular:

- A sealed envelope containing the originals of all information sheets and consent forms signed by all individuals at the center who participated in the study;
- A sealed envelope for the sponsor, containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;

- "Study" binders for the Investigator and the sponsor, including (non-exhaustive list):
  - the successive versions of the protocol (identified by version no. and its date), and any appendices
  - the ANSM authorisations and CPP decisions
  - any correspondence
  - the enrolment list or register
  - the appendices specific to the research
  - the final study report
- The data collection documents

15 FUNDING AND INSURANCE

15.1 Sources of funding for the trial

PHRC

15.2 Insurance

For the duration of the study, the Sponsor will take out an insurance policy covering the sponsor's own third party liability as well as the third party liability of all the doctors involved in the study. The sponsor will also provide full compensation for any damages caused by the study to the study participant and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any collaborator. Compensation cannot be refused on the grounds of a third party act or the voluntary withdrawal of the person who initially consented to participate in the study.

Assistance Publique-Hôpitaux de Paris (AP-HP) has taken out insurance with HDI-GERLING through BIOMEDIC-INSURE, covering its own third party liability and that of any collaborator (doctor or research staff), in accordance with Article L.1121-10 of CSP.

16 PUBLICATION

16.1 Mention of the AP-HP manager (DRCD) in the acknowledgements of the text

- "The sponsor was *Assistance Publique – Hôpitaux de Paris* (Clinical Research and Development Department)"

16.2 Mention of the funder in the acknowledgements of the text

- *"The study was funded by a grant from Programme Hospitalier de Recherche Clinique - PHRC 2019 (Ministry of Health)"*

This study has been registered on the http://clinicaltrials.gov/ website under *registration number:*

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18 ADDENDUM

18.1 List of Investigators

SurName	Name	Town, Country	Hospital	Email Tel
DIVARD	Gillian	Paris, France	CHU Saint-Louis	gillian.divard@aphp.fr +33 1 42 49 96 05
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Hazzan	Marc	Lille, France	CHRU Lille	marc.hazzan-2@univ-lille2.fr +33 3 20 44 40 97

18.3 SAE Form

Direction de l'Organisation Médicale et des relations avec les Universités (DOMU) Délégation à la Recherche Clinique et à l'Innovation (DRCI)	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS **Formulaire de notification d'un Evènement Indésirable Grave (EIG) survenant au cours d'une recherche impliquant la personne humaine portant sur un Médicament ou produit assimilé**	**PARTIE RESERVEE AU PROMOTEUR** **REFERENCE VIGILANCE :** Référence GED : REC-DTYP-0192

Dès la prise de connaissance de l'EIG par l'investigateur, ce formulaire doit être dûment complété (3 pages), signé et retourné sans délai au secteur Vigilance de la DRCI par mail : eig-vigilance.drc@aphp.fr

Il est possible de transmettre les formulaires de notification d'EIG au secteur vigilance par télécopie au +33 (0)1 44 84 17 99 uniquement en cas de tentative infructueuse d'envoi par mail.

Notification initiale ☐ **Suivi d'EIG** ☐ **N° du suivi** |__|__|

1. Identification de la recherche	
Acronyme : SHORTCUT	**Date de notification :** |__|__| |__|__| |_2_|_0_|__|__| jj mm aaaa
Code de la Recherche : APHP200020	**Date de prise de connaissance de l'EIG par l'investigateur :** |__|__| |__|__| |_2_|_0_|__|__| jj mm aaaa
Risque : B	
E	**NA**

Titre complet de la recherche : **Efficacy of 7 days versus 14 days of antibiotic therapy for acute pyelonephritis in kidney transplant recipients, a multicenter randomized non-inferiority trial.**

2. Identification du centre investigateur

Nom de l'établissement :	Investigateur (nom/prénom) : .....
Ville et code postal :	Tél : ..... Email : .....
Service :	

3. Identification et antécédents de la personne se prêtant à la recherche

Référence de la personne : |__|__|__| - |__|__|__|__|__|__| - |__| - |__|
n°centre - n° ordre de sélection - initiale nom - initiale prénom

Sexe : ☐ M ☐ F	Date de naissance : |__|__| |__|__| |__|__|__|__| jj mm aaaa
Poids : |__|__|__| kg Taille : |__|__|__| cm	Age : |__|__|__|ans
Date de signature du consentement : |__|__| |__|__| |_2_|_0_|__|__| jj mm aaaa	**Antécédents médicaux-chirurgicaux/familiaux pertinents pour l'évaluation du cas (joindre un CRH anonymisé le cas échéant) :** .....
Date de randomisation : |__|__| |__|__| |_2_|_0_|__|__| jj mm aaaa	☐ Groupe expérimental (7 jours d'antibiothérapie) ☐ Groupe contrôle (14 jours d'antibiothérapie)

4. Médicament(s) expérimental(aux) (ME) ou produit(s) assimilé(s) [préciser le(s)quel(s)] avant la survenue de l'EIG
(barrer l'encadré si traitement non débuté)

Nom commercial Préciser l'antibiotique administré avec son nom commercial	Voie(1)	Posologie (préciser l'unité ex : mg/j)	Date de début *(jj/mm/aaaa)*	En cours(2)	Date de fin *(jj/mm/aaaa)*
.....	.....	.....	|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|
.....	.....	.....	|__|__| |__|__| |_2_|_0_|__|__|	☐	|__|__| |__|__| |_2_|_0_|__|__|

Acronyme :

Référence de la personne se prêtant à la recherche : |__|__|__| - |__|__|__|__| - |__| - |__|
n°centre - n° ordre de sélection - initiale nom - initiale prénom

5. Procédures et actes ajoutés par la recherche ***(ex. : biopsies, IRM …)*** ***(barrer l'encadré si procédures et actes non réalisés)***	Date de réalisation *(jj/mm/aaaa)*	Chronologie	
		Avant la survenue de l'EIG	Après la survenue de l'EIG
Arrêt de l'antibiothérapie à J7 dans le groupe expérimental	|__|__| |__|__| |_2_|_0_|__|__|	☐	☐
…… …… Après arrêt de l'antibiothérapie (pour le groupe expérimental), préciser si nécessité de reprise de l'antibiothérapie à la suite d'une nouvelle infection du tractus urinaire ou récidive de l'infection initiale…	☐ oui, date |__|__| |__|__| |_2_|_0_|__|__| (préciser dans le tableau des traitements concomitants les antibiotiques administrés à nouveau) ☐ Non ☐ NA…	☐	☐
ECBU à J3	|__|__| |__|__| |_2_|_0_|__|__|	☐	☐
Ecouvillon rectal à la recherche de bactéries multi-résistantes à J3 et J30	|__|__| |__|__| |_2_|_0_|__|__|	☐	☐

6. Médicament(s) <u>concomitant(s)</u> au moment de l'EIG, à l'exclusion de ceux utilisés pour traiter l'événement indésirable ***(compléter le tableau ci-après et si nécessaire l'annexe relative aux médicaments concomitants ou barrer l'encadré si non applicable)***

➪ **Annexe jointe au présent formulaire :** ☐ Oui ☐ Non

Nom commercial (de préférence) ou Dénomination Commune Internationale	Voie(1)	Posologie (préciser l'unité ex : mg/j)	Dates d'administration *(du jj/mm/aa au jj/mm/aa)*	En cours (2)	Indication	***Action prise*** *0 : poursuite sans modification de la posologie 1 : arrêt 2 : diminution de la posologie 3 : augmentation de la posologie 4 : ne sais pas*	***Causalité de l'EIG*** *0 : non lié au médicament 1 : lié au médicament 2 : ne sais pas*
			du |__|__| |__|__| |__|__| au |__|__| |__|__| |__|__|	☐			
			du |__|__| |__|__| |__|__| au |__|__| |__|__| |__|__|	☐			

(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser) (2) En cours au moment de la survenue de l'EIG

7. Evènement indésirable grave [EIG]

<u>Diagnostic</u> : ☐ Définitif ☐ Provisoire

……
……
……

<u>Organe(s) concerné(s)</u> :

……
……

Date de survenue des premiers symptômes : |__|__| |__|__| |_2_|_0_|__|__|
Préciser lesquels :
.....

.....
.....
.....
.....

Date d'apparition de l'EIG :
|__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa
Heure de survenue : |__||__| hh |__||__| min
☐ *donnée manquante*

Délai entre la date de la dernière administration du ME/produit assimilé ou la date de procédure/acte ajouté par la recherche et la date de survenue de l'EIG :
|__||__| / |__||__| |__||__|
jj hh min

Critères de gravité :

☐ Nécessite ou prolonge l'hospitalisation :

du |__|__| |__|__| |_2_|_0_|__|__|

au |__|__| |__|__| |_2_|_0_|__|__| ☐ *en cours*

☐ Décès
☐ Mise en jeu du pronostic vital
☐ Incapacité ou handicap important ou durable
☐ Anomalie ou malformation congénitale
☐ Autre(s) critère(s) médicalement significatif(s), préciser :
.....
.....

Degré de sévérité *) :*
☐ Léger ☐ Modéré ☐ Sévère

L'évènement a-t-il conduit à :
☐ aucune mesure prise concernant le ME
☐ diminution de la posologie du ME
☐ augmentation de la posologie du ME
☐ arrêt définitif du ME
☐ arrêt transitoire du ME, date de reprise : |__|__| |__|__| |_2_|_0_|__|__|
☐ ne sais pas

Récidive de l'EIG après ré-administration : ○ Non ○ Oui Date : |__|__| |__|__| |_2_|_0_|__|__|
○ Non applicable

L'évènement a-t-il conduit à une interruption de la procédure/acte ajouté par la recherche ?

☐ Oui Date : |__|__| |__|__| |_2_|_0_|__|__| ,
préciser :……

☐ Non

☐ Non applicable

Des mesures symptomatiques ont-elles été prises ?

☐ Non ☐ Oui Date : |__|__| |__|__| |_2_|_0_|__|__|Préciser : ……

L'évènement fait-il suite à :

- une erreur médicamenteuse ?	☐ Non	☐ Oui	Date : |__|__| |__|__| |_2_|_0_|__|__|
- un surdosage ?	☐ Non	☐ Oui	Date : |__|__| |__|__| |_2_|_0_|__|__|
- un mésusage ?	☐ Non	☐ Oui	Date : |__|__| |__|__| |_2_|_0_|__|__|
- autre (préciser) : ……	☐ Non	☐ Oui	Date : |__|__| |__|__| |_2_|_0_|__|__|

PARTIE RESERVEE AU PROMOTEUR
REFERENCE VIGILANCE :

Référence GED : REC-DTYP-0192

Acronyme :
Référence de la personne se prêtant à la recherche : |__|__|__| - |__|__|__|__| - |__| - |__|
n°centre - n° ordre de sélection - initiale nom - initiale prénom

Evolution de l'événement

☐ **Décès**
○ sans relation avec l'EIG
○ en relation avec l'EIG
Date : |__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa

☐ **Sujet non encore rétabli**, préciser :
○ Etat stable ○ Amélioration ○ Aggravation

☐ **Résolu :**
○ sans séquelles
○ avec séquelles, préciser lesquelles :
Date : |__|__| |__|__| |_2_|_0_|__|__|
jj mm aaaa
|__|__| |__|__|
hh min

☐ **Evolution inconnue**

8. Autre(s) étiologie(s) envisagée(s)

☐ Non ☐ Oui Si oui, préciser : ……
……
……

9. Examen(s) complémentaire(s) réalisé(s)

☐ Non ☐ Oui Si oui, préciser date, nature et résultats : [joindre les bilans anonymisés]……
……
……

10. Selon l'investigateur, l'événement indésirable grave est (plusieurs cases possibles)

Lié à la recherche :

☐ **Oui :**

- **Au(x) médicament(s)/produit(s) assimilé(s) de la recherche : le(s)quel(s) ?**
  …préciser le nom commercial…… ☐ **Lié** ☐ **Non lié**
  …préciser le nom commercial…… ☐ **Lié** ☐ **Non lié**
  …préciser le nom commercial…… ☐ **Lié** ☐ **Non lié**
  …préciser le nom commercial…… ☐ **Lié** ☐ **Non lié**

- **A la (aux) procédure(s)/acte(s) de la recherche :**
  Raccourcissement de la durée de l'antibiothérapie ☐ **Lié** ☐ **Non lié**

☐ **Non :** ☐ **à la progression de la maladie faisant l'objet de la recherche : (à compléter)**
☐ **à un (ou plusieurs) médicament(s) concomitant(s) administré(s), le(s)quel(s) : ……**
☐ **à une maladie intercurrente, laquelle : ……**
☐ **autre, préciser : ……**

Notificateur	**Investigateur**	Tampon du service :
Nom et fonction : Signature	Nom : Signature	

18.4 Pregnancy Form

Direction de l'Organisation Médicale et des relations avec les Universités (DOMU) Délégation à la Recherche Clinique et à l'Innovation (DRCI)	ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS ***Notification et suivi d'une grossesse apparue au cours d'une recherche portant sur un Médicament ou produit assimilé***	**PARTIE RESERVEE AU PROMOTEUR** **REFERENCE INTERNE :** Référence GED : REC-DTYP-0185

Ce formulaire doit être dûment complété (2 pages), signé et retourné sans délai au secteur Vigilance de la DRCI par télécopie au +33 (0)1 44 84 17 99

1. Identification de la recherche

Acronyme : SHORTCUT
Code de la recherche : APHP200020

Notification initiale ☐ **Suivi de notification** ☐ **N° du suivi** |__|__|

Date de notification : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Date de prise de connaissance de la grossesse par l'investigateur : |__|__| |__|__| |2|0|__|__| (jj mm aaaa)

Titre complet de la Recherche : **Efficacy of 7 days versus 14 days of antibiotic therapy for acute pyelonephritis in kidney transplant recipients, a multicentre randomized non-inferiority trial.**

2. Identification du centre investigateur

Nom de l'établissement : .....
Ville et code postal : .....
Service : .....

Investigateur (nom/prénom) : .....
Tél : Fax :

3. Identification de la personne présentant une grossesse

Référence de la personne : |__|__|__| - |__|__|__|__|__| - |__| - |__| (n°centre - n° ordre de sélection - initiale nom - initiale prénom)
Date de naissance : |__|__| |__|__| |___|___|__|__|
Date d'inclusion : |__|__| |__|__| |_2_|_0_|__|__|
Date de randomisation : |__|__| |__|__| |_2_|_0_|__|__|

Groupe de randomisation : ☐ (à compléter) ☐ (à compléter)
Date des dernières règles : |__|__| |__|__| |_2_|_0_|__|__|
Et/ou date début de grossesse : |__|__| |__|__| |_2_|_0_|__|__|

Cas particulier d'une exposition paternelle : ☐ Oui ☐ Non

Référence de la personne : |__|__|__| - |__|__|__|__|__| - |__| - |__| (n°centre - n° ordre de sélection - initiale nom - initiale prénom)
Date de naissance : |__|__| |__|__| |___|___|__|__|
Date d'inclusion : |__|__| |__|__| |_2_|_0_|__|__|
Date de randomisation : |__|__| |__|__| |_2_|_0_|__|__|
Groupe de randomisation : ☐ (à compléter) ☐ (à compléter)

Expositions au cours de la grossesse :

Tabac :	☐ non	☐ oui (préciser nombre de paquets/année) :	☐ arrêt (préciser date) :	☐ poursuite
Alcool :	☐ non	☐ oui (préciser unités OH) :	☐ arrêt (préciser date) :	☐ poursuite
Drogue :	☐ non	☐ oui (préciser substance) :	☐ arrêt (préciser date) :	☐ poursuite

Autre (préciser) :

4. Antécédents maternels

Médicaux :

Chirurgicaux :

Obstétricaux : |__|__| geste |__|__| pare

Préciser si fausse couche, grossesse extra-utérine, interruption de grossesse (médicale ou volontaire), mort *in utero*, malformation congénitale, pathologie congénitale/néonatale non malformative, … (*nombre, date et nature/raison si applicable).*

5. Médicament(s) expérimental (aux) administré(s) ou non pendant la grossesse ou s'il s'agit une exposition paternelle				
Nom commercial (de préférence) ou Dénomination Commune Internationale	Date de première administration Ou non administré	Date de dernière administration Ou en cours	Voie d'administration(1)	Posologie / 24h
	|__|__| |__|__| |_2_|_0_|__|__| ☐ Non administré	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		
	|__|__| |__|__| |_2_|_0_|__|__| ☐ Non administré	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		
(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser)				

6. Procédures et actes ajoutés par la recherche ***(Barrez l'encadré si procédures et actes non réalisés)***	Date de réalisation *(jj/mm/aaaa)*	Chronologie	
		Avant la grossesse	Au cours de la grossesse
	|__|__| |__|__| |_2_|_0_|__|__|		
	|__|__| |__|__| |_2_|_0_|__|__|		

Acronyme :

PARTIE RESERVEE AU PROMOTEUR

Référence de la personne : \|__\|__\|__\| - \|__\|__\|__\|__\|__\| - \|__\| - \|__\|
n°centre – n° ordre de sélection – initiale nom – initiale prénom

7. Médicament(s) concomitants administré(s) dans le cadre du soin ***(Cf. annexe « Liste relative aux médicaments concomitants » complétée : ☐ Oui ☐ Non applicable)***				
Nom commercial (de préférence) ou Dénomination Commune Internationale	Date de première administration	Date de dernière administration Ou en cours	Voie d'administration(1)	Posologie / 24h
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		
	|__|__| |__|__| |_2_|_0_|__|__|	|__|__| |__|__| |_2_|_0_|__|__| ☐ En cours		
(1) Voie d'administration : VO=voie orale ; IM=Intramusculaire ; IV=intraveineuse ; SC=sous-cutanée ou autre (à préciser)				

8. Suivi de la grossesse

☐ Echographiques. Date(s) et résultats à préciser *(joindre les CR anonymisés)* :

☐ Autres examens. Date(s) et résultats à préciser *(joindre les CR anonymisés)* :

9. Grossesse en cours ou issue de la grossesse ☐ (faxer un nouveau formulaire complété à l'issue de la grossesse pour le suivi de la notification initiale) ☐ (compléter ci-dessous)

Date : \|__\|__\| \|__\|__\| \|_2_\|_0_\|__\|__\| Terme : \|__\|__\| SA \|__\|__\| J

☐ Fausse couche
→ Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :

☐ Grossesse extra-utérine
→ Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :

☐ Interruption de grossesse → Raison :
→ Examen anatomo-pathologique disponible : ☐ Non ☐ Oui, précisez le résultat :

☐ Accouchement : ☐ Spontané ☐ Provoqué ☐ Voie basse ☐ Césarienne

Naissance multiple : ☐ Non ☐ Oui, précisez le nombre :

Souffrance fœtale : ☐ Non ☐ Oui, précisez :

Mort-né : ☐ Non ☐ Oui, précisez :

Placenta normal : ☐ Oui ☐ Non, précisez :

Liquide amniotique : ☐ Clair ☐ Autre, précisez :

Anesthésie : ☐ Générale ☐ Péridurale ☐ Rachianesthésie ☐ Aucune

10. Nouveau-né (Si naissance multiple, compléter les parties 1, 2, 3, 9 et 10 d'un nouveau formulaire et le faxer)

Sexe : ☐ Masculin ☐ Féminin

Poids : |__|__|__|__| grammes Taille : |__|__|__| cm Périmètre crânien : |__|__|__| cm

APGAR : 1 minute : _____ 5 minutes : _____ 10 minutes : _____

Malformation(s) congénitale(s) : ☐ Non ☐ Oui, précisez :

Pathologie(s) congénitale(s)/néonatale(s) non malformative(s) : ☐ Non ☐ Oui, précisez :

Le nouveau-né a-t-il bénéficié d'un suivi particulier à la naissance : ☐ Non ☐ Oui, précisez : ☐ Non applicable

Notificateur	**Investigateur**	Tampon du service :
Nom et fonction : Signature :	Nom : Signature :	