Groupe d'Etudes de Neuro-Urologie de Langue Française

PROTOCOLES EN COURS ET À VENIR SUR LES TRAITEMENTS PRÉVENTIFS DES INFECTIONS URINAIRES À RÉPÉTITION CHEZ LE PATIENT NEUROLOGIQUE

AURÉLIEN DINH

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GROUPE RECOMMANDATION SPILF

ORIGINAL ARTICLE

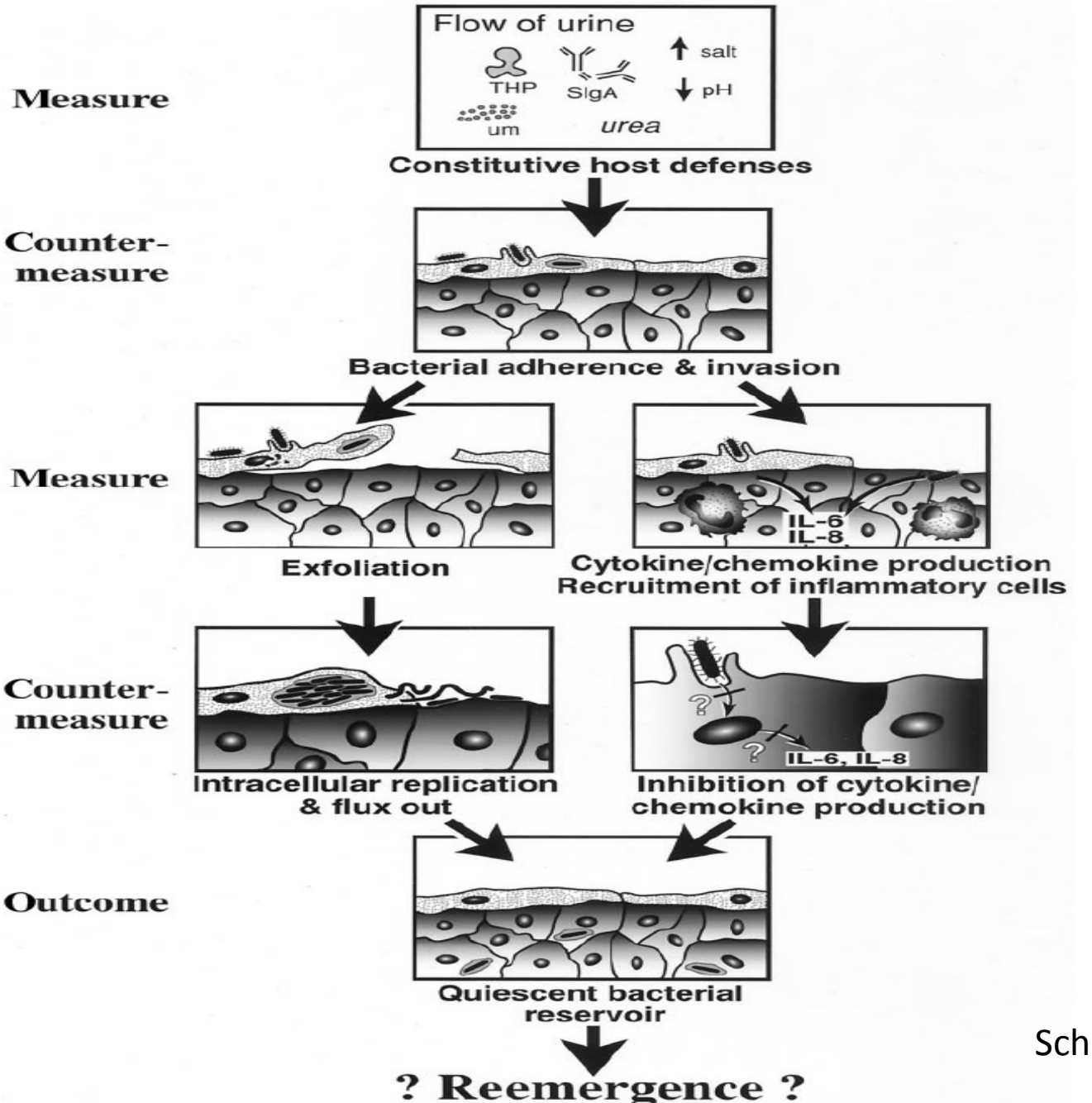
Blood stream infections due to multidrug-resistant organisms among spinal cord-injured patients, epidemiology over 16 years and associated risks: a comparative study

A Dinh[1], M Saliba[1], D Saadeh[2], F Bouchand[3], A Descatha[4], AL Roux[5], B Davido[1], B Clair[6], P Denys[7], D Annane[6], C Perronne[1] and L Bernard[1,8]

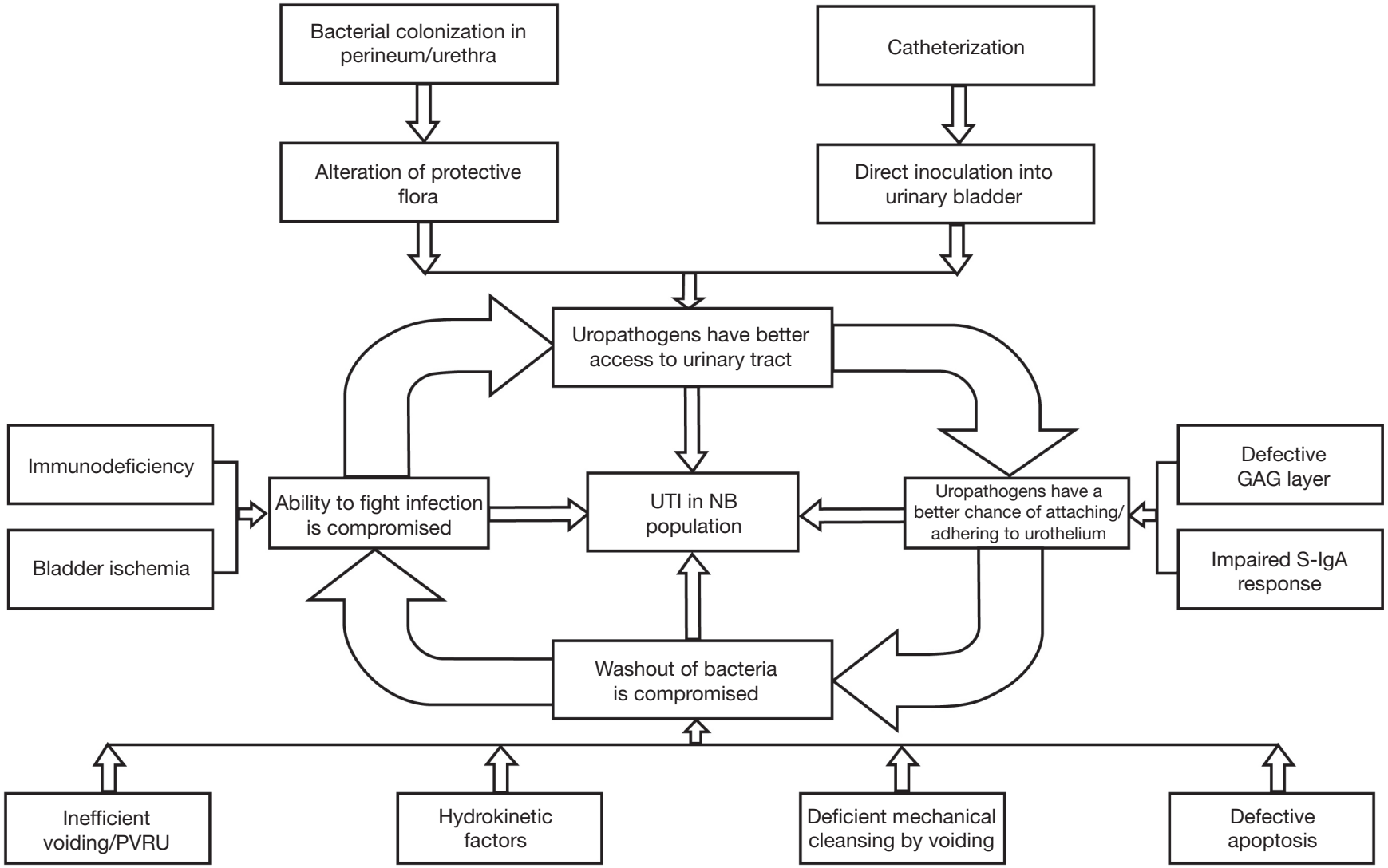
	Non-MDRO (n = *189; 59%*)	*MDRO* (n = *129; 41%*)	P-*value*
Age (mean ± s.d.)	49.97 ± 17.01	52.12 ± 17.06	0.270
Male *(n, %)*	140 (74.1)	92 (71.9)	0.665
Paraplegic *(n, %)*	119 (63.0)	72 (55.8)	0.297
Tetraplegic *(n, %)*	67 (35.4)	55 (42.6)	

STRATÉGIE NATIONALE 2022-2025 DE PRÉVENTION DES INFECTIONS ET DE L'ANTIBIORÉSISTANCE

SANTÉ HUMAINE



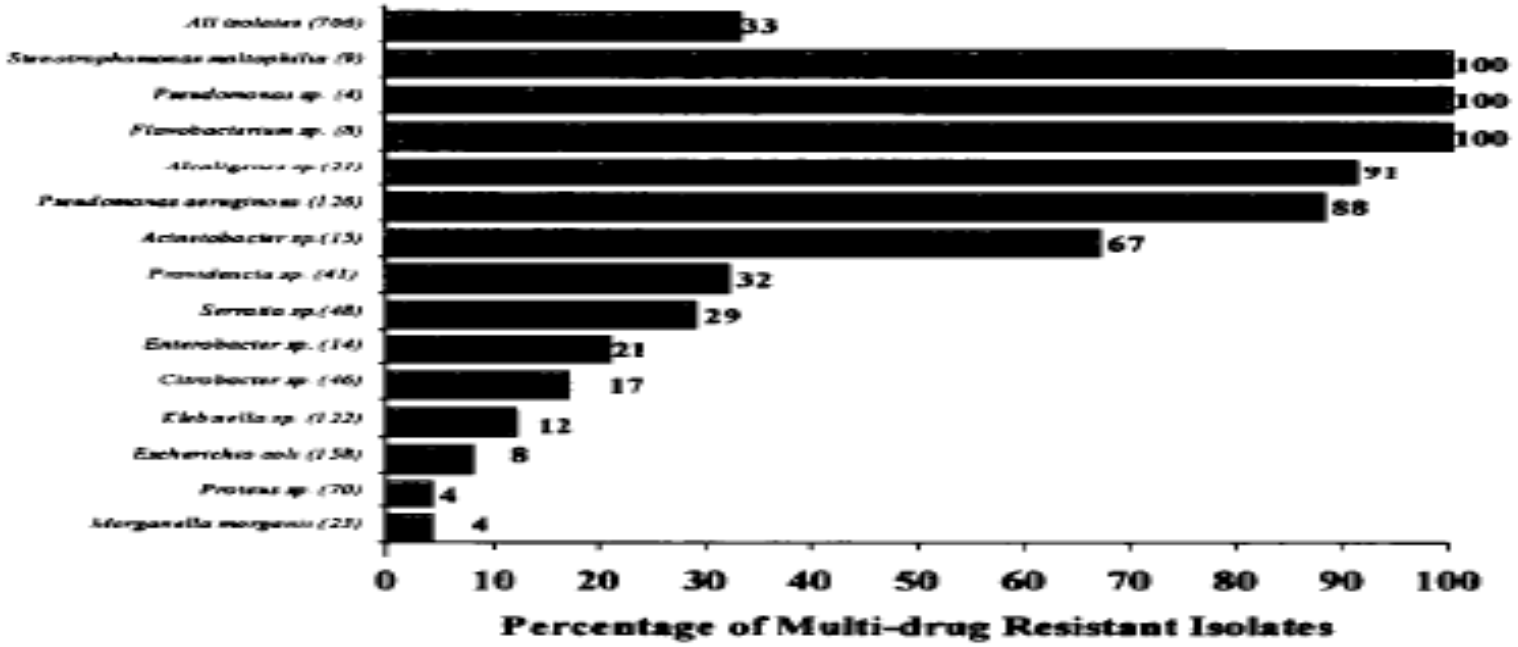
Schilling *et al*. *Urology* 2001


Bacterial colonization in perineum/urethra
Catheterization
Alteration of protective flora
Direct inoculation into urinary bladder
Uropathogens have better access to urinary tract
Immunodeficiency
Bladder ischemia
Ability to fight infection is compromised
UTI in NB population
Uropathogens have a better chance of attaching/ adhering to urothelium
Defective GAG layer
Impaired S-IgA response
Washout of bacteria is compromised
Inefficient voiding/PVRU
Hydrokinetic factors
Deficient mechanical cleansing by voiding
Defective apoptosis

LES BACTÉRIES MULTIRÉSISTANTES

- 444 ECBU (706 bactéries) chez 287 BM **communautaires**

  33% des bactéries sont résistantes à au moins 2 familles d'antibiotique



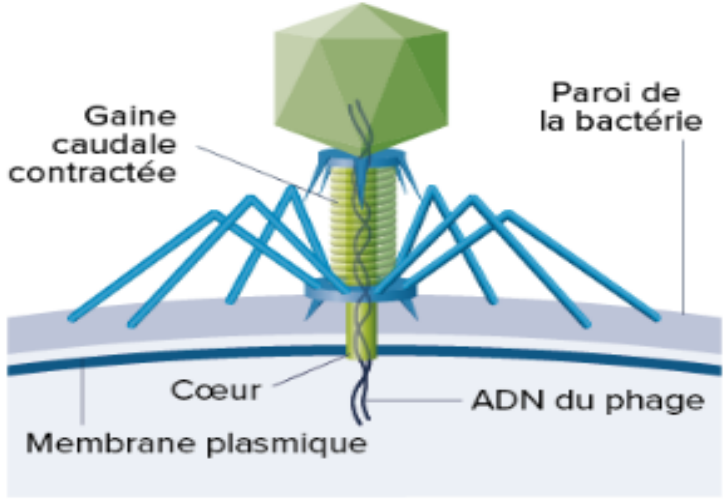
Waites KB et al. *Arch Phys Med* 2000

PHAGOTHÉRAPIE

- Expériences IOA
- Phages : effets collatéraux/difficultés ciblage, individualisation/délai obtention/ fabrication à façon
- Expérience prévention IU
- PK/PD
- 2 projets : E coli et KI pn

PHAGOTHÉRAPIE : QU'EST-CE QUE C'EST ?

- **Virus naturels** des bactéries
- **Spécifiques** de chaque bactéries
- Phages lytiques **incapables d'infecter une cellule eucaryote** donc inoffensif pour les humains, les animaux, les plantes. Ils ne se multiplient que dans les cellules procaryotes.



- **Considérés comme « agents biologiques non susceptibles de provoquer une maladie chez l'homme » selon décret n°94-352 du 4 mai 1994 relatif à la protection des travailleurs contre les risques résultant de leur exposition à des agents biologiques.**

Journal of Medical Microbiology (2011), **60**, 1697–1700 DOI 10.1099/jmm.0.029744-0

Case Report

Bacteriophage therapy for refractory *Pseudomonas aeruginosa* urinary tract infection

A. Khawaldeh,[1]† S. Morales,[2] B. Dillon,[1] Z. Alavidze,[3] A. N. Ginn,[1] L. Thomas,[1] S. J. Chapman,[1] A. Dublanchet,[4] A. Smithyman[2] and J. R. Iredell[1,5]

- Patiente de 67 ans, amputation périnéale pour adéno K
- Double J bilatérales
- *Pseudomonas aeruginosa* traité par genta, ceftazidime, CPF, mero
- Pdt 2 ans !!
- Administration pyophage 051007 intravésical x2/j pdt 10j
- Mero + Coli à J6
- Pas de récidive à 1 an

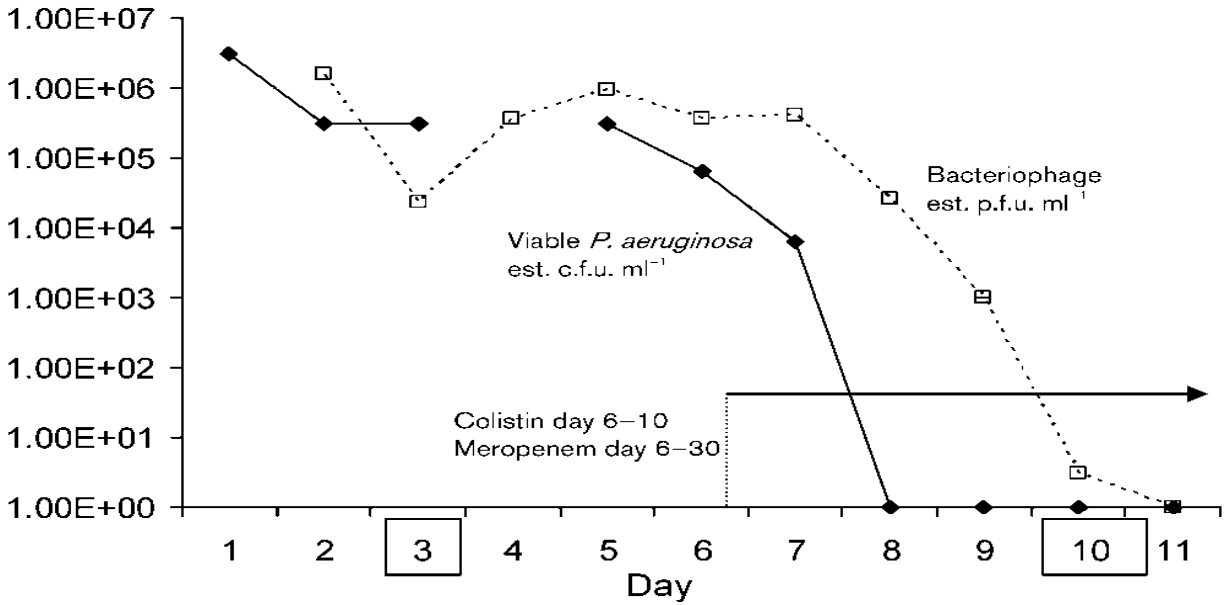


Fig. 1. Logarithmic plot of early morning urine viable *P. aeruginosa* (c.f.u. ml^{-1}) and bacteriophage (p.f.u. ml^{-1}) counts. Antibiotic administration and catheter change and removal (days 3 and 10, respectively; boxed) are indicated.

Intravesical bacteriophages for treating urinary tract infections in patients undergoing transurethral resection of the prostate: a randomised, placebo-controlled, double-blind clinical trial

Lorenz Leitner, MD • Aleksandre Ujmajuridze, MD • Nina Chanishvili, PhD • Marina Goderdzishvili, PhD • Irina Chkonia, PhD • Sophia Rigvava, PhD • et al. Show all authors

Leitner *et al. BMC Urology* (2017) 17:90
DOI 10.1186/s12894-017-0283-6

BMC Urology

STUDY PROTOCOL Open Access

Bacteriophages for treating urinary tract infections in patients undergoing transurethral resection of the prostate: a randomized, placebo-controlled, double-blind clinical trial

Lorenz Leitner[1,2], Wilbert Sybesma[1], Nina Chanishvili[3], Marina Goderdzishvili[3], Archil Chkhotua[4], Aleksandre Ujmajuridze[4], Marc P. Schneider[1], Andrea Sartori[1], Ulrich Mehnert[1], Lucas M. Bachmann[5] and Thomas M. Kessler[1*]

- **Pre RTUP si CFU ≥ 104/mL**
- **Randomisation : Pyo bacteriophage/placebo/ATB (7j)**
- **Critère d'évaluation : SF IU/bactériurie/nécessité ATB**

Synopsis

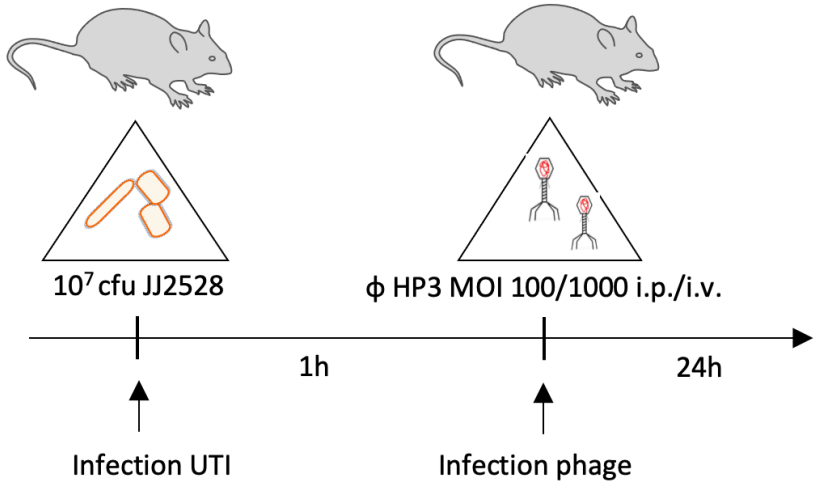
Title:	**A Phase I study to assess the pharmacokinetic and safety of phages in patients with recurrent *Escherichia Coli* urinary infections due to post-traumatic neurogenic bladder**
Study product	Bacteriophages anti-*E. coli* PP970, PP1002, PP1151, PP2000
Protocol No.:	PP-EC-001
Sponsor:	**PHERECYDES PHARMA**
Participating Country/Countries	France

Investigational Product/ Treatment:	**Name of the compound:** Bacteriophages anti-*E. coli* PP970, PP1002, PP1151, PP2000 **Pharmaceutical form:** 2 mL of sterile suspension of a single anti-E. *coli* phage – type PP970 or PP1002 or PP1151 or PP2000 at 10^9 PFU/mL in buffer solution (into 3 mL glass vial). **Dose per administration: between 10 mL (5 vials of one single phage administered) up to 40 mL (for the 4 phages administered)** of suspension of bacteriophages diluted in solution of NaCl 0.9% for a total volume of 100 mL. **Timing for administration:** Once in the morning, at 8:00 am, by self-catheterization, once the subject has already empty the bladder by a previous self-catheterization. Depending on the pharmacokinetic (and safety) data collected, the schedule of administration may be increased to two administrations (at 8:00 am and 8:00 pm) and up to three administrations (at 8:00 am, 4:00 pm and midnight). The subject will empty the bladder before each additional administration. Decision will be taken by the sponsor in agreement with the PI.
Number of Patients	36 patients **Sample size justification** This number should be sufficient to provide robust data on the quantification of phages in the urine.

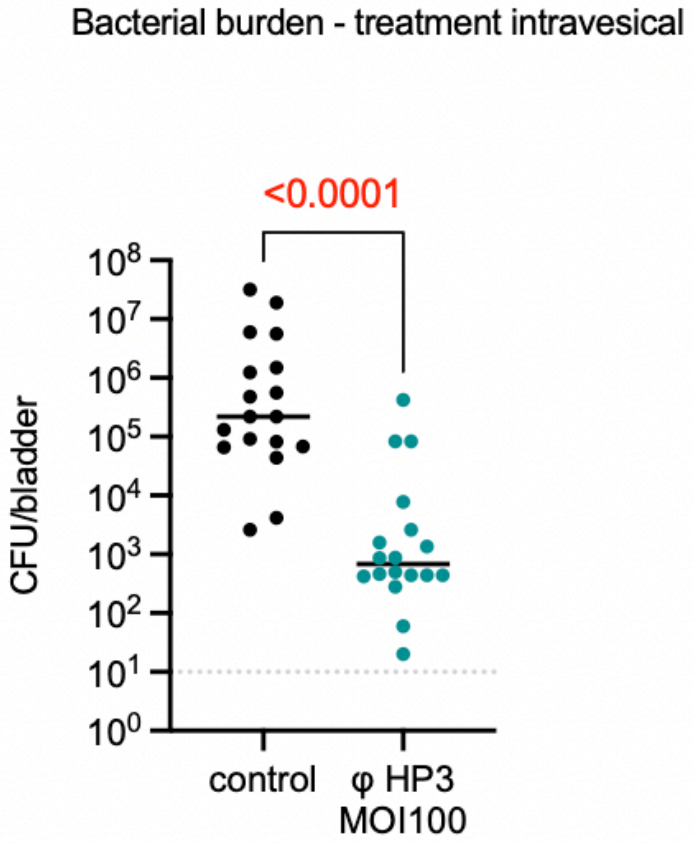
Main Evaluation Criteria:	**1.1.1. Primary endpoint** Quantification of phages in the urine. For the first group treated with a single administration, urine samples will be collected at T0 (pre-treatment), T4H, T8H and T24H. Patients will be informed to avoid additional bladder emptying between T0-T4H and between T4H-T8H. In case of urgent urination during these periods, additional urinary samples will be collected for pharmacokinetic analysis, as well as during any bladder emptying between T8H and T24H. Urinary pH and volume will be documented at each time point. In case of twice daily administrations, urinary collection timepoints will remain identical (T0 (pre-treatment), T4H, T8H and T24H), with an additional T12H collection, before the second administration. Patients will be informed to avoid additional bladder emptying between T0-T4H, T4H-T8H and T8H-T12H. In case of urgent urination during these periods, additional urinary samples will be collected for pharmacokinetic analysis, as well as during any bladder emptying between T12H and T24H. In case of three times daily administration, urinary collection timepoints will be T0 (pre-treatment), T4H, T8H (before the second administration), T16H (before the third administration) and T24H. Patients will be informed to avoid additional bladder emptying between T0-T4H and T4H-T8H. In case of urgent urination during these periods, additional urinary samples will be collected for pharmacokinetic analysis, as well as during any bladder emptying between T8H-T16H and T16H-T24H. **1.1.2. Secondary endpoints** 1. Safety parameters: adverse events, physical examination, biological tests as hematology and biochemistry during the whole study 2. <u>Microbiology</u>: - Urine : *E.Coli* quantification (CFU and qPCR) at T0, T4H, T8H, T24H 3. <u>Immunology:</u> - Serum: anti-*E. coli* phage antibodies, cytokine IL-6 at T0 and T24H - Urine : anti-*E. coli* phage antibodies at T0, T4H, T8H and T24H 4. Post-treatment outcomes: - Recurrence of infection at M1, M3 and M6 - Antibiotherapy requirement in case of recurrence - Duration of hospitalization in case of recurrence 5. Metagenomic analysis of urinary bacterial samples

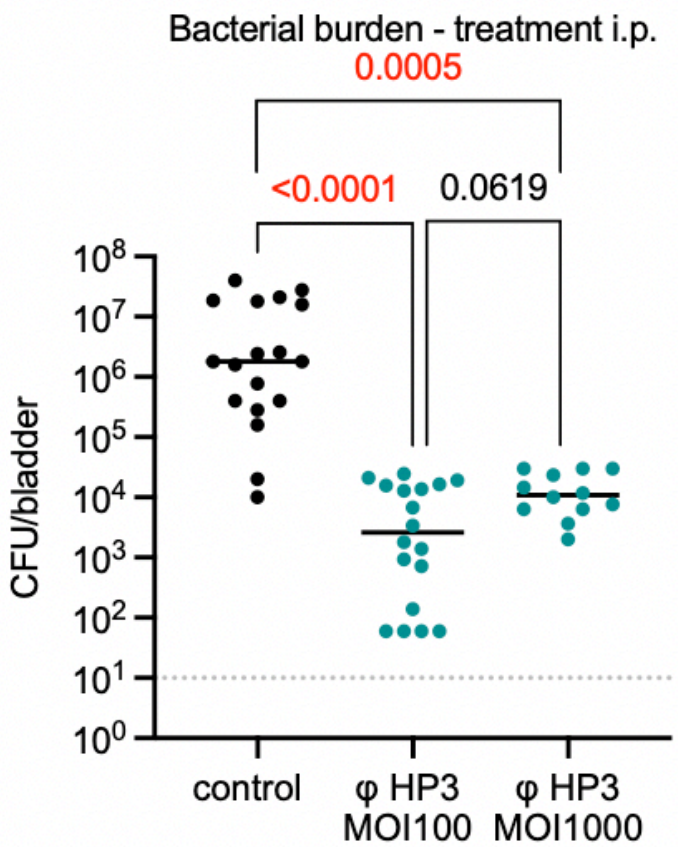
Main Selection Criteria:	**Inclusion Criteria :** 1. Male or female ≥ 18 years 2. Post-traumatic neurogenic bladder due to spinal cord injury 3. Well-balanced bladder without any element in favour of a reflux 4. History of recurrent monomicrobial *E. coli* urinary infections (> 2 in the last year) 5. Without diagnosis of superinfection due to another pathogen on the last urinary collection 6. Without active (symptomatic) urinary infection in the past month defined by absence of any of the following symptoms: autonomous hyperreflexivity, spasticity, leakages, contracture, pyuria, fever, shivers. 7. No recurrence between the screening visit and the first administration of phages 8. Without of evidence of lithiasis on a bladder echography performed within the last year 9. Females of childbearing potential/Sexually active males with partner of childbearing potential: commitment to consistently and correctly use an

Modèle in vivo de réduction de la charge bactérienne après phagothérapie (*E. Coli*)



Bacterial & phage burden bladder





Modèle murin de phagothérapie pour infection urinaire avec des souches *K. pneumoniae BLSE* provenant des patients avec des vessies neurologiques en impasse thérapeutique (R. Calin/M. Ingersoll/R. Tournebize)

Ingersoll lab unpublished, Pasteur/ Institut Cochin

PRÉVENTION NON ANTIBIOTIQUIE

- Plan ATB
- NEJM Urovaxom
- OM-80
- Critère original : exposition ATB
- PIUr

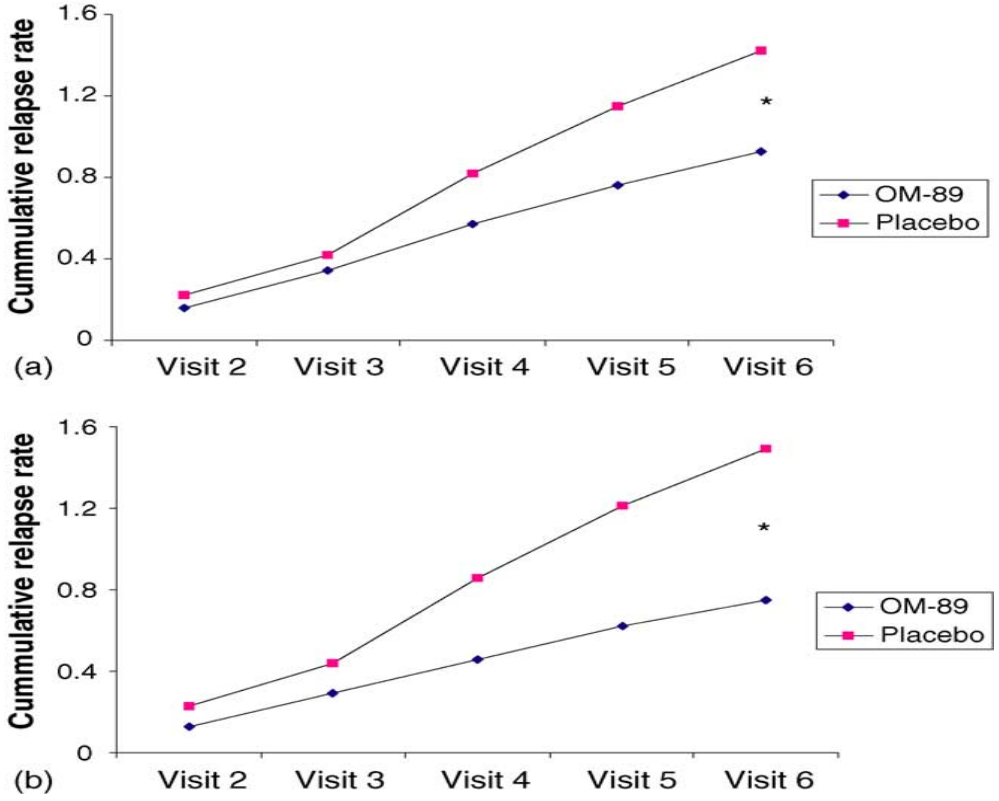
European Urology

European Urology 47 (2005) 542–548

A Long-Term, Multicenter, Double-Blind Study of an *Escherichia Coli* Extract (OM-89) in Female Patients with Recurrent Urinary Tract Infections

Hartwig W. Bauer[a], Schanaz Alloussi[b], Günther Egger[c], Hans-Martin Blümlein[d], Gabriel Cozma[e,*], Claude C. Schulman[f]
on behalf of the Multicenter UTI Study Group[1]

- Essai randomisé double aveugle vs placebo
- 453 patientes adultes
- IU à l'inclusion avec ECBU +
- OM-89 : 1 capsule/j pdt 90j
- 3 mois sans traitement
- Puis les 10ers j de M7, M8, M9
- Suivi 1 an
- Taux d'IU total : 0,84 vs 1,28
- Réduction de 34% (p<0,003)



European urology 2005

J Korean Med Sci 2010; 25: 435-9

ISSN 1011-8934
DOI: 10.3346/jkms.2010.25.3.435

A Prospective Multi-center Trial of *Escherichia coli* Extract for the Prophylactic Treatment of Patients with Chronically Recurrent Cystitis

- Essai avant après
- 42 patientes au moins 2 Iu dans les 6 derniers mois
- Traitement capsule 1/j pdt 3 mois
- Suivi 6 mois
- IU : 0.35 vs. 4.26, *P* <0.001

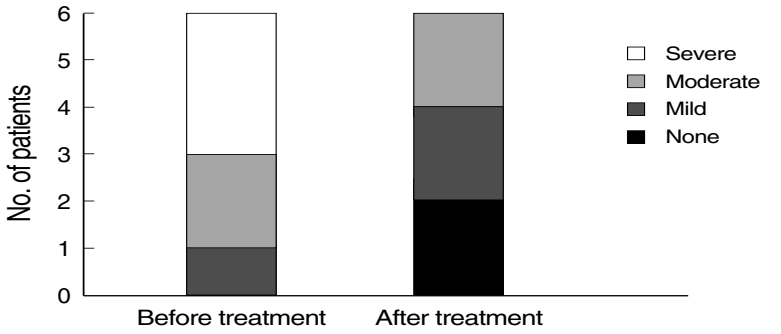


Fig. 1. Changes of urgency in recurred patients (n=6).

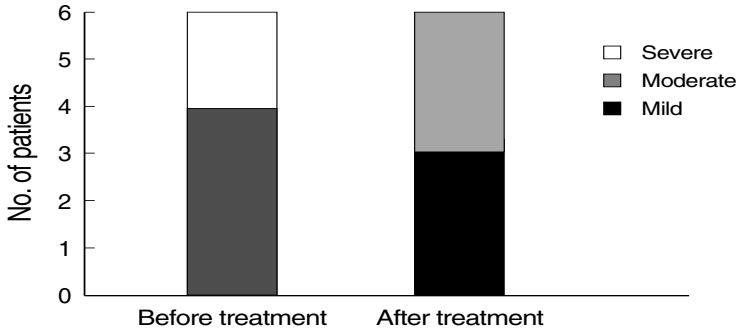


Fig. 2. Changes of painful voiding symptom in recurred patients (n=6).

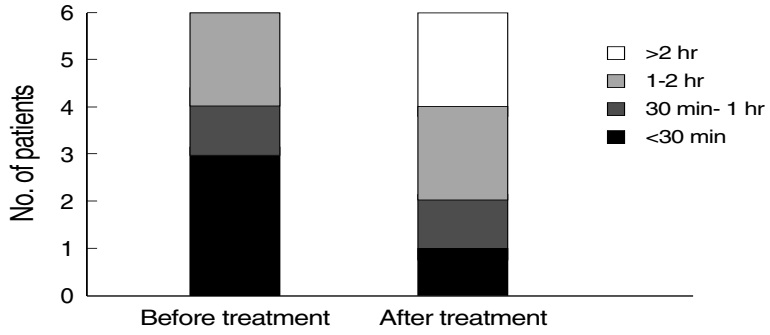


Fig. 3. Changes of frequency in recurred patients (n=6).

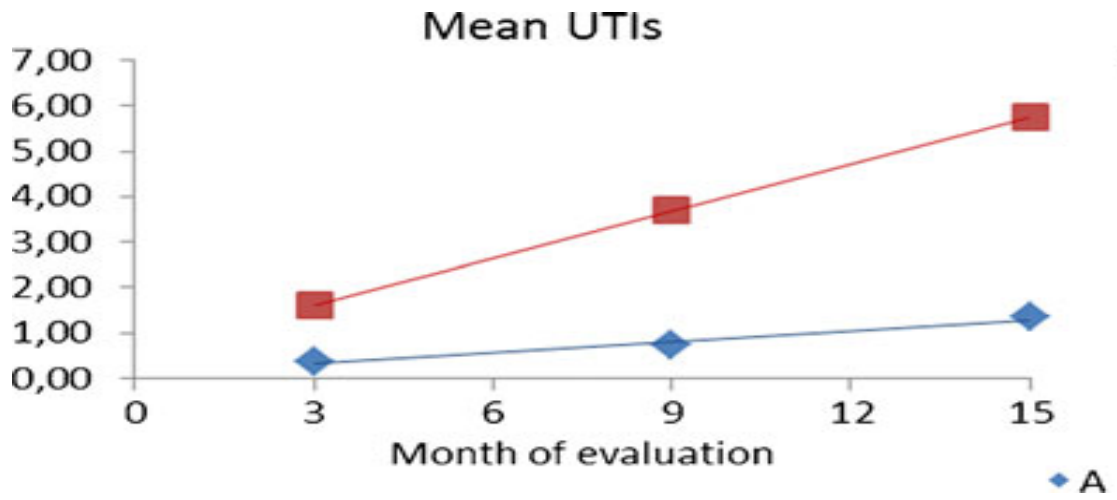
Int Urogynecol J (2013) 24:127–134
DOI 10.1007/s00192-012-1853-5

ORIGINAL ARTICLE

Evaluation of a therapeutic vaccine for the prevention of recurrent urinary tract infections versus prophylactic treatment with antibiotics

M. F. Lorenzo-Gómez · B. Padilla-Fernández · F. J. García-Criado · J. A. Mirón-Canelo · A. Gil-Vicente · A. Nieto-Huertos · J. M. Silva-Abuin

- Essai multicentrique
- 319 patientes >1 IU dans les 6 derniers mois
- Bras A : Uromune® (1/j pdt 3 mois)
- Bras B : sulfamethoxazole/trimethoprim 200/40 mg/j pdt 6 mois
- Résultats M3 : 0,36 IU vs 1,60 (P < 0,0001), respectivement
- Idem M9 et M15 (P < 0.0001)



NEJM Evidence

Published January 21, 2022

DOI: 10.1056/EVIDoa2100018

ORIGINAL ARTICLE

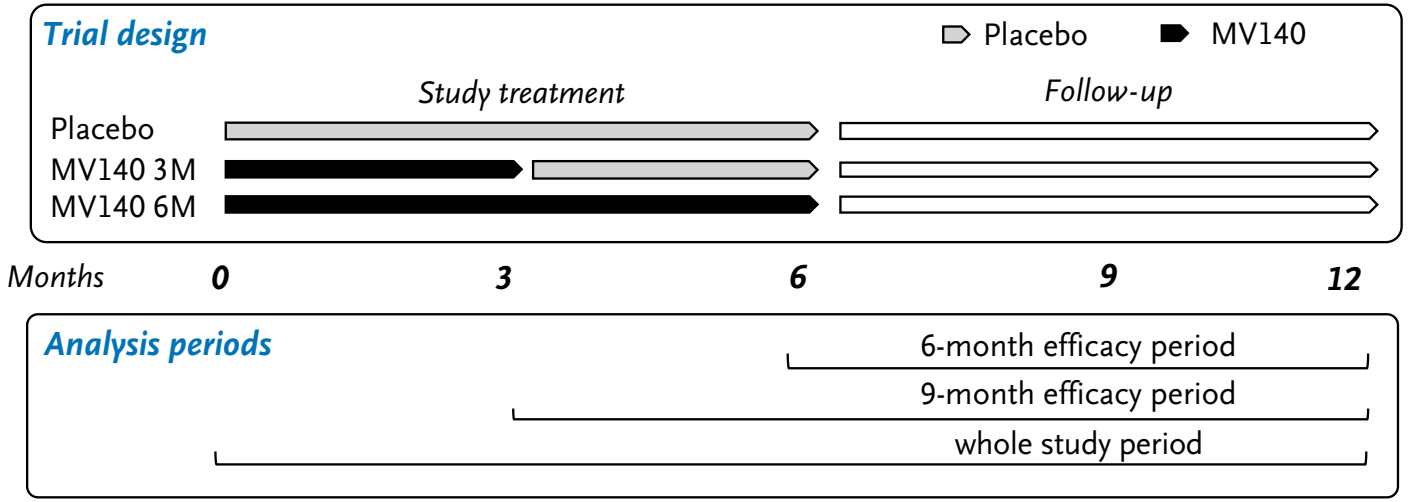
Sublingual MV140 for Prevention of Recurrent Urinary Tract Infections

María-Fernanda Lorenzo-Gómez, M.D., Ph.D.[1], Stephen Foley, M.B.B.S., F.R.C.S.[2], J. Curtis Nickel, M.D., F.R.C.S.C.[3], María-Begoña García-Cenador, Ph.D.[4], Barbara-Yolanda Padilla-Fernández, M.D., Ph.D.[5], Ignacio González-Casado, M.D.[6], Misericordia Martínez-Huélamo, M.D.[7], Bob Yang, M.B.B.S., M.R.C.S.[2], Christopher Blick, M.B.B.S., M.R.C.S., Ph.D.[2], Francini Ferreira, M.Sc.[8], Raquel Caballero, M.Sc.[9], Paula Saz-Leal, Ph.D.[9], and Miguel Casanovas, M.D., Ph.D.[9]

Heat-inactivated whole-cell bacterial preparation, administered sublingually,
The sublingual route was chosen for treatment delivery of MV140 because it has been shown to induce both systemic and mucosal immunity (including the genitourinary tract)
Similar results have been shown for other whole-cell bacterial formulations

RCT 1 an
240 femmes 18 à 75 ans
5 cystites (non compliquées)/an
2 sprays (100 ml) quotidiens

MV140 pdt 3 ou 6 mois ou placebo Pdt 6 mois (1:1:1)
Objectif principal n UTI durant les 9 mois suivant les 3 mois initiaux



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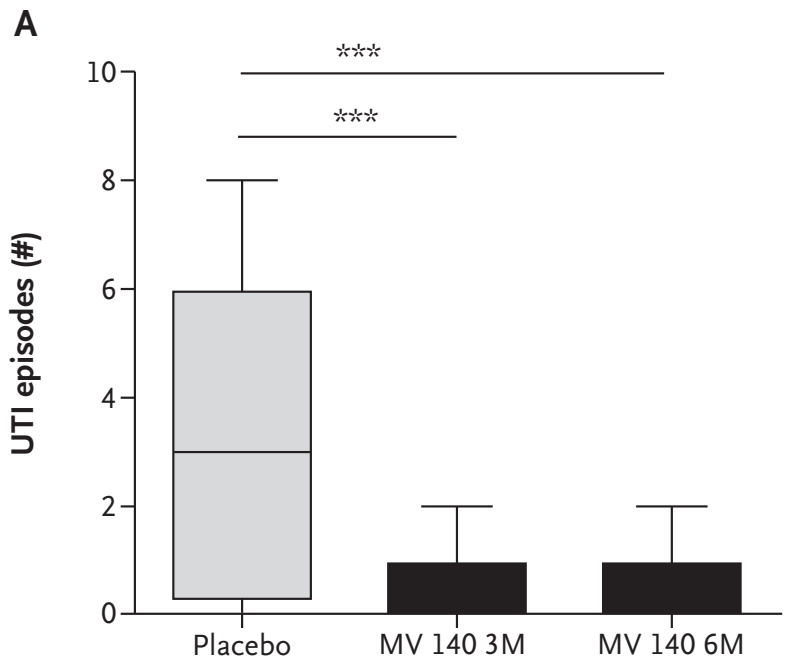

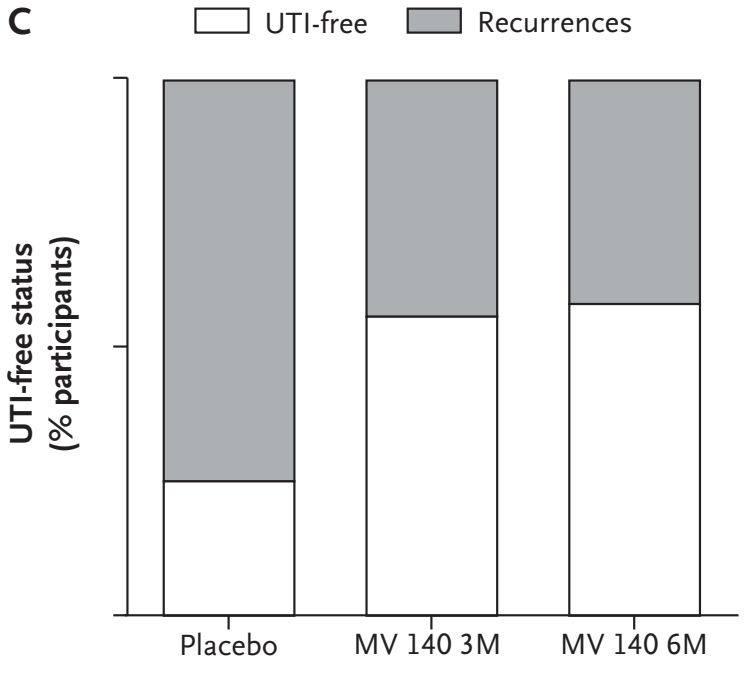

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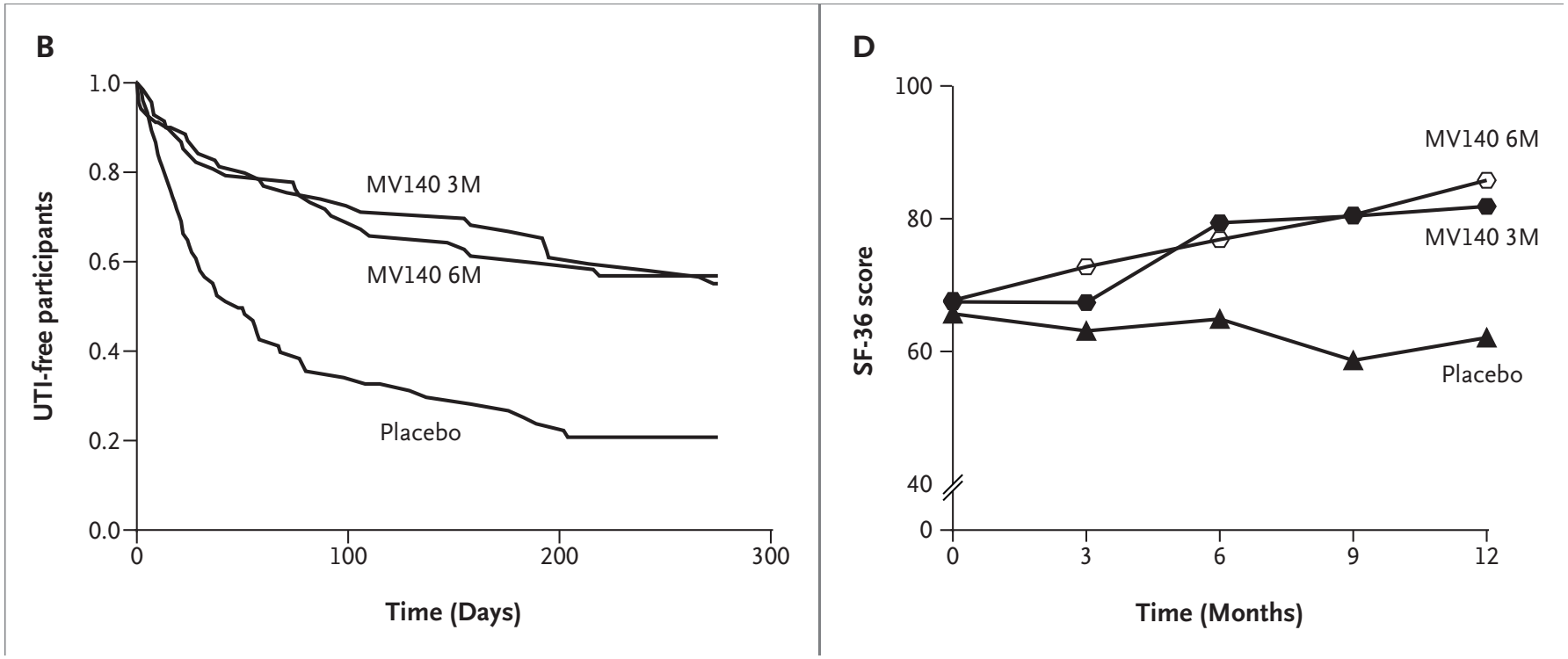


NEJM 2022

RETRAIN STUDY

Multicentric randomized double blind controlled superiority trial with a roll-over phase to evaluate the efficacy of OM-89 vs placebo to REduce antibiotic consumption related to urinary TRact Infection treatment in patients with Neurological bladder

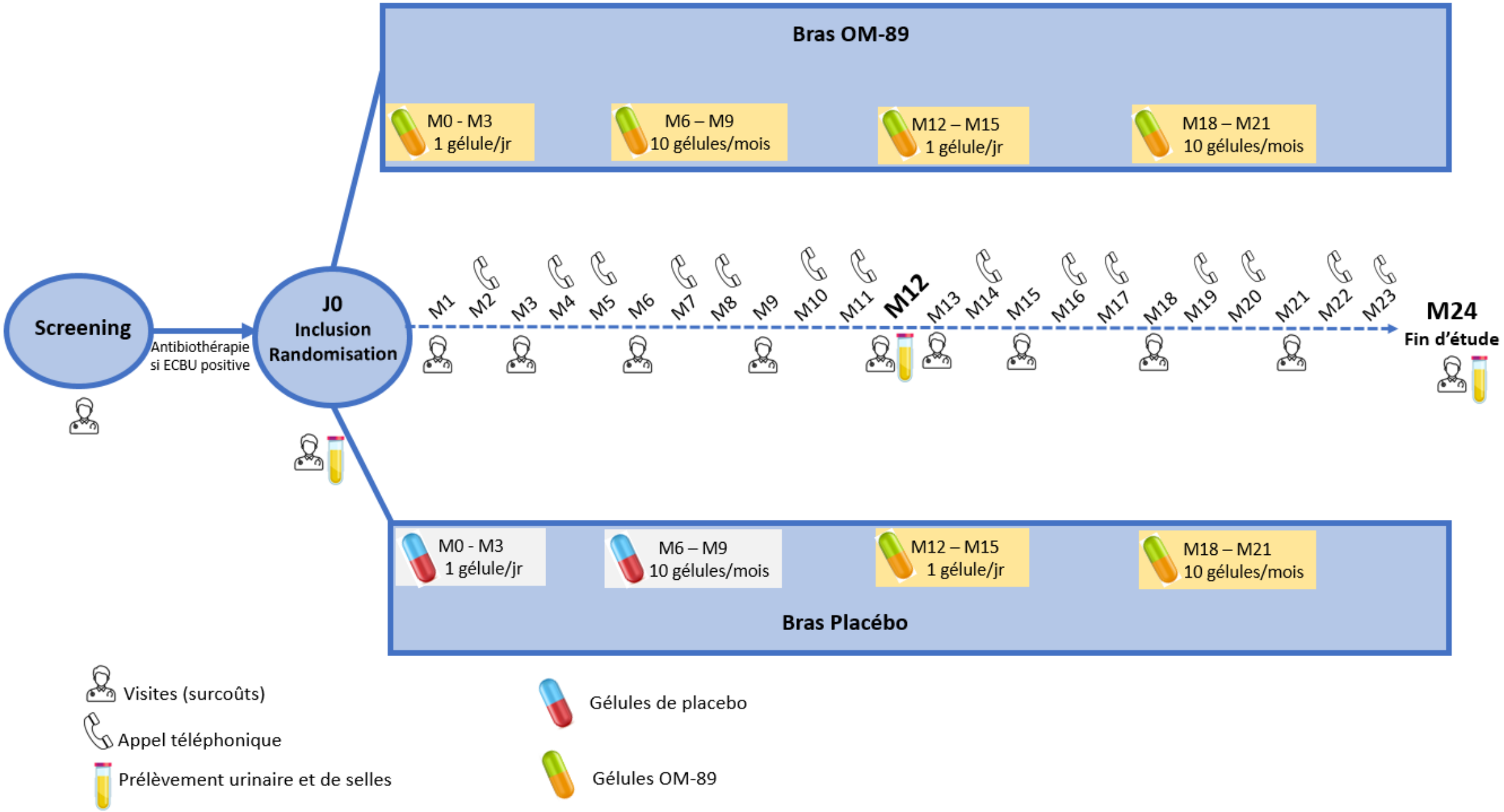
- Coordinating PI: Pr Lionel PIROTH - M.D PhD Infectious Diseases Specialist
- Scientific PI: Pr Aurélien DINH - M.D PhD Infectious Diseases Specialist
- Sponsor: CHU Dijon Bourgogne, France
- Investigator initiated Study fully supported by OM PHARMA

RETRAIN STUDY

Design & Methods

- **Design:** Multicentric randomized double blind controlled vs placebo superiority trial
  - **Phase 1.** 12-month period on OM-89 or placebo according to the randomization
  - **Phase 2.** 12-month period on OM-89 for all patients (unblinded)
- **Number of randomized patients:** 110 patients over 10 sites in France
- **Primary objective:** Reduction of antibiotics treatment for urinary tracts infection - any antibiotic given to cure or prevent UTIs, whatever the type, dose or duration (if given continuously for less than 21 days) – at M12

SCHÉMA DE L'ETUDE



RETRAIN STUDY

Design & Methods

PHASE 1				PHASE 2			
M1-M3	M4-M6	M7-M9	M10-M12	M13-M15	M16-M18	M19-M21	M22-M24
OM-89 (daily for 90 days)		OM-89 (10 days/month for 3 months)		OM-89 (daily for 90 days)		OM-89 (10 days/month)	
Placebo (daily for 90 days)		Placebo (10 days/month for 3 months)		OM-89 (daily for 90 days)		OM-89 (10 days/month)	

1st Year (randomized 1:1 OM-89 vs placebo)

Primary endpoint Analysis (interim)

2nd Year (open-label, all on OM-89)

Primary objective:
Compare the number of antibiotic treatments for UTIs at M12

Secondary objectives: to compare
- the number of UTIs at M12 and M24
- The hospitalization rates for UTIs at M12 and M24
- the nb of days on AB over the 1st and 2nd year
- The patient's QoL at M6, M12, M18 and M24
- The safety of the long-term treatment with OM-89

RETRAIN STUDY

Patients

- Inclusion criteria
  - adult patients (≥18 years old)
  - with stabilized neurogenic bladder due to spinal cord injury since more than 2 years and which has benefited from a urodynamics examination
  - using clean intermittent self-catheterization (CISC) (5 to 6 per day)
  - who received 6 or more antibiotic treatment episodes for UTIs in the preceding year (for curative or prophylactic reason)
  - with negative urinary culture at the screening visit or who have been treated by antibiotics for urinary decontamination before study enrollment
  - affiliated to a social security scheme
  - who has given written informed consent for participation to this trial

RETRAIN STUDY

Secondary objectives

To compare between the experimental group and the control group:

- the incidence of UTIs – febrile and non-febrile - at M12 and M24 (as compared with M12)
- the evolutional trend of incidence of UTIs during the 2-year follow-up
- the hospitalization rates for UTIs at M12 and M24 (as compared with M12), as well as the evolution of hospitalization rate during the two years of follow-up
- the hospitalization rates for sepsis at M12 and M24 (as compared with M12), as well as the evolution of hospitalization rate during the two years of follow-up
- the number of days on antibiotics over the first and the second year of follow-up and its evolution over time
- the antibiotic cures rate for UTIs over the first and the second year of follow-up
- patients' health-related quality of life
- the safety on long-term treatment with OM-89

RETRAIN STUDY

Patients

Exclusion criteria

- Urinary drainage method other than CISC
- Urinary stones (assessed by echography during the preceding year, standard of care)
- Presence of any endo-urinary device (urinary prosthesis, ureteral stent)
- Enterocystoplasty or irradiated bladder (past or currently)
- Known allergy or previous intolerance to OM-89
- Previous use within the last 6 months of enrollment or ongoing use of bacterial lysates (incl. OM-89)
- Any known malignancy or neoplasia
- Any auto-immune disease
- Previous and/or concomitant use immunosuppressants within 6 months prior to study enrollment
- Currently enrolled in or has completed any other investigational device or drug study within <30days prior to screening.
- Women who are pregnant, breastfeeding, or without contraceptive measures and who could become pregnant

RETRAIN STUDY

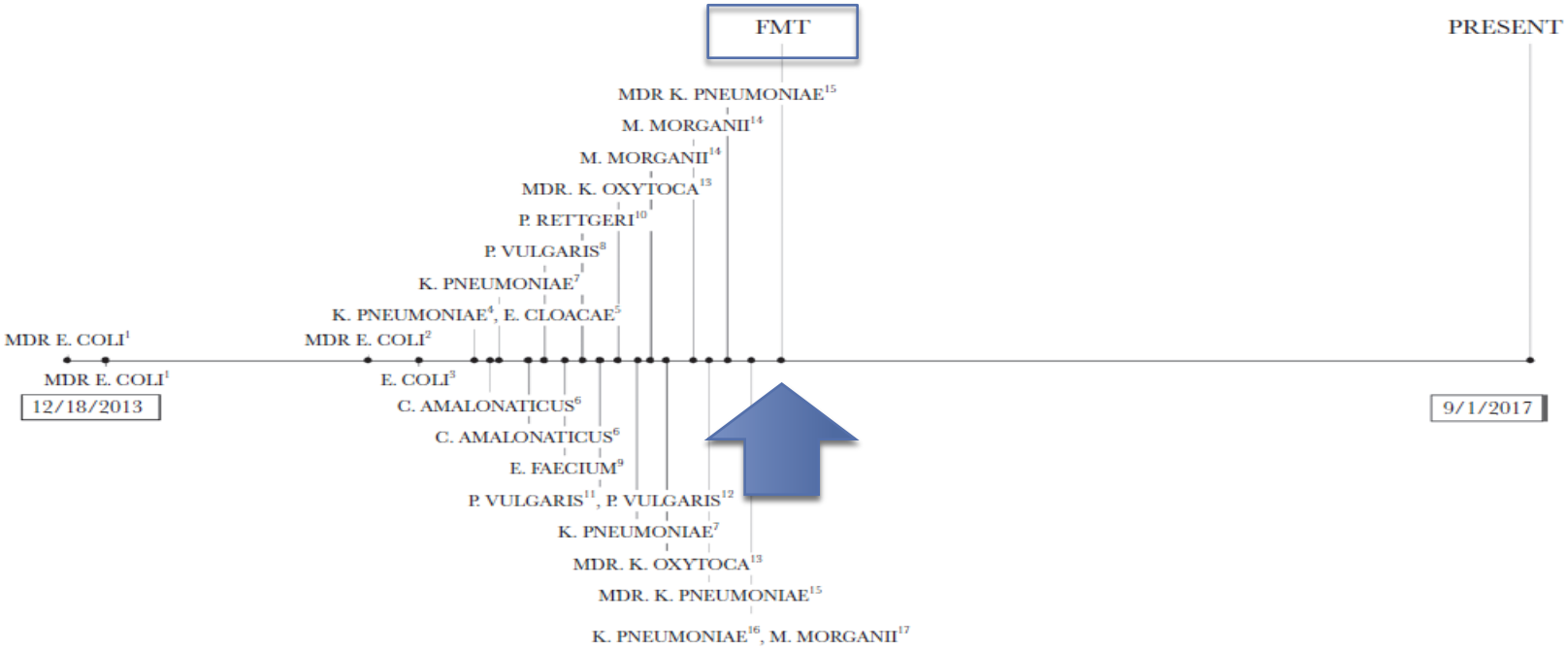
- Planned date first patient consented/enrolled/observed: JUN-2024
- Planned date last patient consented/ enrolled/observed: JUN-2025
- Planned date of first analysis (end of phase 1) OCT 2026
- Planned date last patient finishes observation/ treatment: JUN-2027
- Planned date CSR / published manuscript available: OCT-2027

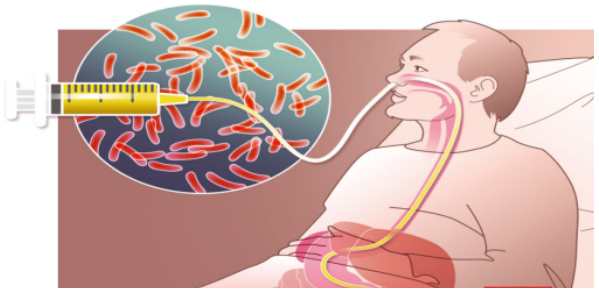
TRANSPLANTATION MICROBIOTE FÉCALE

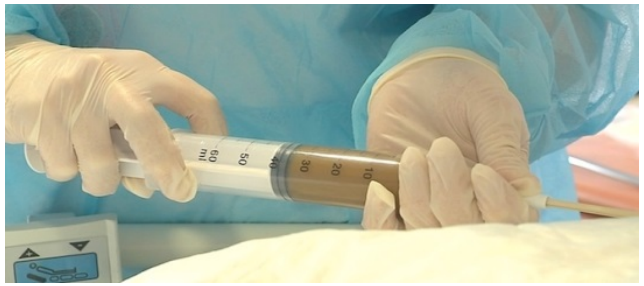
Fecal Microbiota Transplant for Refractory *Clostridium difficile* Infection Interrupts 25-Year History of Recurrent Urinary Tract Infections

Tiffany Wang,[1] Colleen S. Kraft,[2,3] Michael H. Woodworth,[2] Tanvi Dhere,[4] and Molly E. Eaton[2]

- Patiente de 83 ans
- Méningome cérébral, hémangiomes cérébraux
- 25 ans d'IU récidivantes
- 20 IU de novembre 2013 à octobre 2015
- Allergie : FQ, Fura, CTX
- Multiples preventions, Multiples cures ATB
- ICD >> TMF







OFID 2018

Fecal Microbiota Transplantation for Recurrent *Clostridium difficile* Infection Reduces Recurrent Urinary Tract Infection Frequency

Raseen Tariq,[1] Darrell S. Pardi,[1] Pritish K. Tosh,[2] Randall C. Walker,[2] Raymund R. Razonable,[2] and Sahil Khanna[1]

- **8 patients (6 femmes)**
- **Âge médian 78,5 ans**
- **⩾3 IU/an**
- **n UTI avant vs après FMT : 4 vs 1**

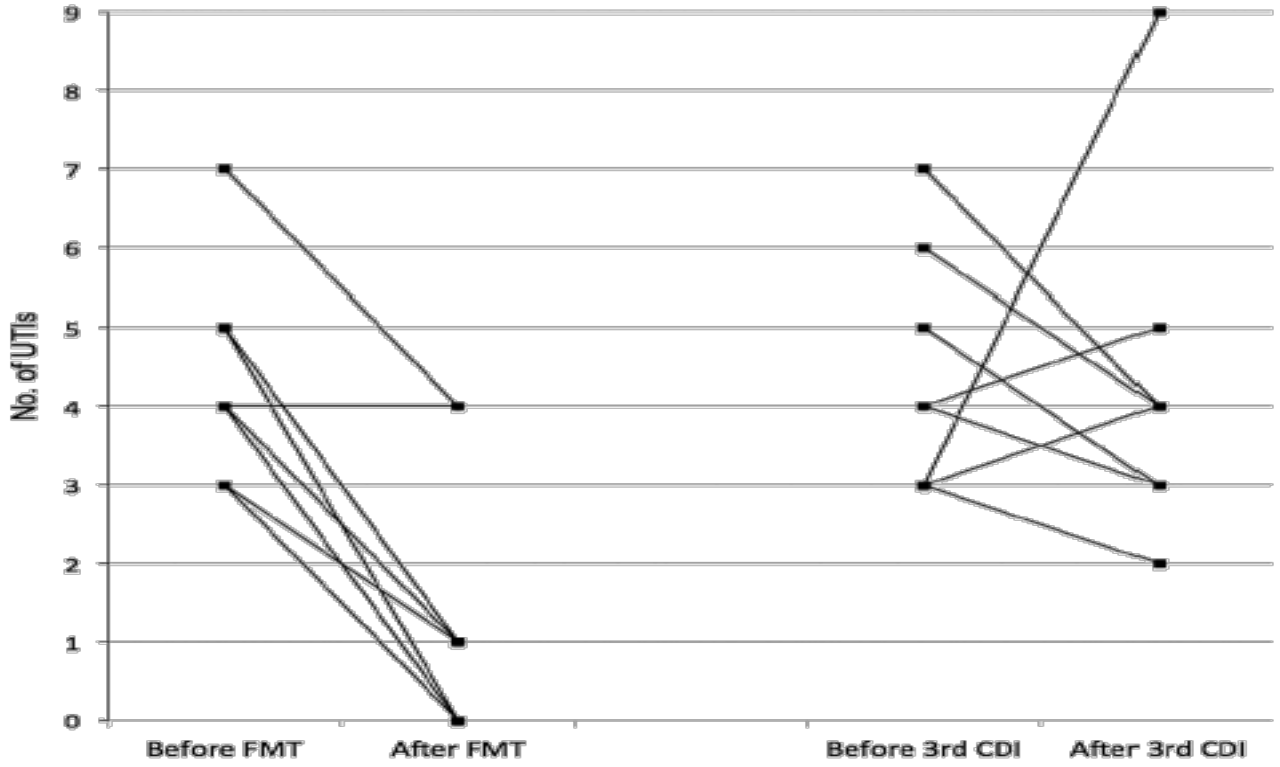


Figure 1. Frequency of urinary tract infections. Graph shows the number of infections 1 year before and 1 year after fecal microbiota transplantation and 1 year before and 1 year after the third *Clostridium difficile* infection episode in the control group. Each square and line represent 1 patient.

CID 2017

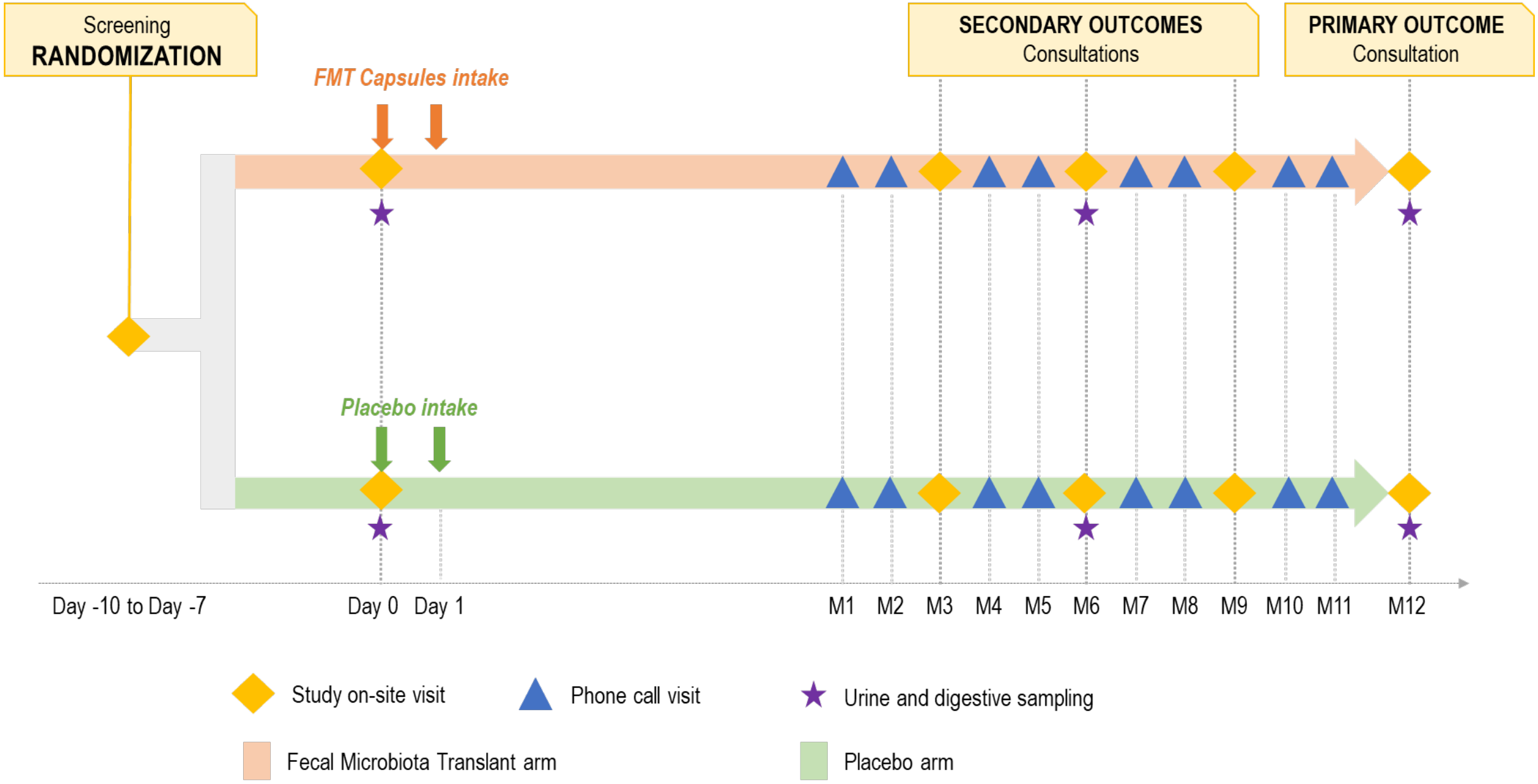
“PROPHYLAXIS FOR RECURRENT URINARY TRACT INFECTIONS AMONG PATIENTS USING CLEAN INTERMITTENT SELF-CATHETERIZATION”

PIUR

CLINICAL TRIAL ON MEDICINAL PRODUCT FOR HUMAN USE

Version N°1-0 dated 18/03/2023
Project Code: / EU CT number:

Coordinating investigator	Prof Aurélien DINH Department of Infectious and Tropical Diseases Hospitals Raymond-Poincaré and Ambroise-Paré, AP-HP Tél 01 47 10 77 60 / Email aurelien.dinh@aphp.fr


Screening
RANDOMIZATION
FMT Capsules intake
SECONDARY OUTCOMES
Consultations
PRIMARY OUTCOME
Consultation
Placebo intake
Day -10 to Day -7
Day 0
Day 1
M1
M2
M3
M4
M5
M6
M7
M8
M9
M10
M11
M12
Study on-site visit
Phone call visit
Urine and digestive sampling
Fecal Microbiota Translant arm
Placebo arm

Nonantibiotic prevention and management of recurrent urinary tract infection

*Néha Sihra[1], Anna Goodman[2], Rhana Zakri[1], Arun Sahai[1] and Sachin Malde[1] **

« The growing problem of antimicrobial resistance means that the search for nonantibiotic alternatives for the treatment and prevention of UTI is of critical importance »

Nature 2018