JN 25es Journées Nationales d'Infectiologie
DEAUVILLE et la région Normandie
du mercredi 12 au vendredi 14 juin 2024

Essai RETRAIN

OM-89 in patients with neurological bladder Investigateur Study

Lionel Piroth (Investigateur coordonateur)
Aurélien Dinh (Responsable scientifique)

Recurrent UTI

- Definition: 4≥ UTIs/year
- Management:
  - Antibiotics : treatment / prevention
- Model: neurogenic bladder
  - Main cause of morbi-mortality and healthcare consumption
  - Incidence
    - Europe: between 10.4 and 29.7 per million inhabitants per year
    - United States: 40 per million inhabitants (11,000 new cases per year)
  - Multi-drug resistant bacteria
- Most warrant: non antibiotic prophylaxis

In Which countries is OM-89 available?

Registered countries

- The first registration of OM-89 occurred in September 1987 in Switzerland
- OM-89 is:
  - Registered* in **62** countries
  - Marketed in more than **55** countries
- OM-89 can be purchased in countries where it is approved for use upon medical prescription

Reimbursed in

- OM-89 is currently **reimbursed** in:
  - Austria
  - Czech Republic
  - Slovakia
  - South-Korea

- Reimbursement options are being investigated in specific countries within the context of antibiotic sparing

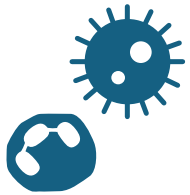
*Countries where OM-89 is registered but temporarily not marketed and distributed

What is the effect of OM-89 on innate and adaptive immunity?

OM-89 promotes immune-potentiating signals that activate both **innate** and **adaptive** immunity. This dual response increases the efficiency of the immune system, which leads to enhanced protection against infection in the urinary tract

At the intestinal level, OM-89 activates a large set of PRRs in a precise manner

Priming of immune system



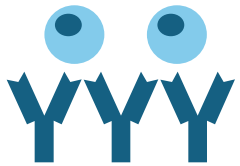
Phagocytosis (macrophages, neutrophils)[1,2]

Adhesion molecules at neutrophil surface[3]

Cytokine release[4,5]

DC maturation[6]

Innate immunity



Cellular (T and B cells)[4,6]

Humoral (IgG and IgA)[4,7]

Polyclonal adaptive immunity

CD, cluster of differentiation; GALT, gut-associated lymphoid tissue; IFN, interferon; Ig, immunoglobulin; IL, interleukin; MHC, major histocompatibility complex; NOD, nucleotide-binding oligomerization domain; TLR, Toll-like receptor; TNF, tumour necrosis factor

1. Pham TV *et al. J Biol Response Mod* 1990;9:231–40; 2. Bessler W *et al. Arzneimittelforschung* 2010;60:324–9; 3. Marchant A *et al. Respiration* 1992;59:24–7; 4. Huber M *et al. Int J Immunopharmacol* 2000;22:1103–11; 5. Bessler WG *et al. Arzneimittelforschung* 2009;59:571–7; 6. Schmidhammer S *et al. Urology* 2002;60:521–6; 7. Huber M *et al. Int J Immunopharmacol* 2000;22:57–68

Clinical evidences

Study, year	Dosing regimen	Patients enrolled	Study duration	Study design
Efficacy under conventional dosing scheme of 90 days				
Frey *et al.* 1986	90 days	n=64	6 months	DBPC*
Tammen *et al.* 1988	90 days	n=521	6 months	open
Schulman *et al.* 1993	90 days	n=166	6 months	DBPC
Magasi *et al.* 1994	90 days	n=122	6 months	DBPC
Loran *et al.* 2015	dosage used in routine clinical practice	n=52	6 months	observational
Long-term efficacy				
Tammen *et al.* 1990	90 days	n=150	6-11 months	DBPC
Efficacy under booster dosage				
Rugendorff *et al.* 1992	90 days, 3 month break, 10 days/ month for 3 months	n=89	Retrospective 24-month evaluation**	open
Bauer *et al.* 2005	90 days, 3 month break, 10 days/ month for 3 months	n=453	12 months	DBPC
Popa *et al.* 1996	90 days, 3 month break, 10 days/ month for 3 months	58 postmenopausal women	See Note***	open
Efficacy in special patient populations				
Hachen 1990	90 days	70 spinal cord injury patients	6 months	DBPC
Krebs *et al.* 2018	90 days, 3 month break, 10 days/ month for 3 months	136 patients with spinal cord injury	12 months	Retrospective cohort
Wade *et al.* 2020	90 days	49 patients with neurogenic bladder dysfunction (incl. spinal cord injury)	6 months	DBPC
Baertschi *et al.* 2003	6 mg/day until delivery	70 pregnant women	3-6 months + 6 weeks after delivery	open
Lettgen 1996	6 mg/day for 6 months	40 children	18 months	open
Czerwionka-Szaflarska *et al.* 1996	90 days	38 children	6 months	open
Systematic review and meta-analysis				
Bauer *et al.* 2002	90 days	n=601	6 months	5 DBPC
Naber *et al.* 2009	90 days	n=975	6-12 months	5 DBPC
Beerepoot *et al.* 2013[1]	90 days - 9 months	n=891	6-12 months	4 DBPC
Neho *et al.* 2016	90 days - 9 months	n=788	6-12 months	5 DBPC
Aziminia *et al.* 2019[1]	90 days - 9 months	n=1,148	6-12 months	6 DBPC

Proven efficacy to:

- Reduce recurrent bladder infections and their symptoms
- Spare antibiotic consumption, and associated collateral damage
- Improve overall quality of life and reduce the burden of disease

Méthode

- 110 participants (1:1) : OM-89 ou placebo
- Répartition par groupe : 55 patients par bras
- N cures d'antibiotiques pour la population éligible est estimé à (au moins) 4 par an dans la pratique courante actuelle avec une durée de 2 à 21 jours (médiane de 30 jours par an), soit un taux d'incidence estimé à 0,012 par personne-jour dans le groupe contrôle.
- Nous faisons l'hypothèse que l'OM-89 pourrait réduire ce taux d'incidence de 30%, soit un taux de 0,0084 traitement par per personne jour. En tenant compte d'une corrélation intra-individuelle de 0,2, un nombre de 110 patients est nécessaire (risque alpha fixé à 0.05 - formulation bilatérale, puissance 80 %, perdus de vue de 10 %).
- La randomisation sera stratifiée sur l'utilisation régulière d'une prophylaxie antibiotique

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

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 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 - 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

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)

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

Primary endpoint Analysis (interim)

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

Study design

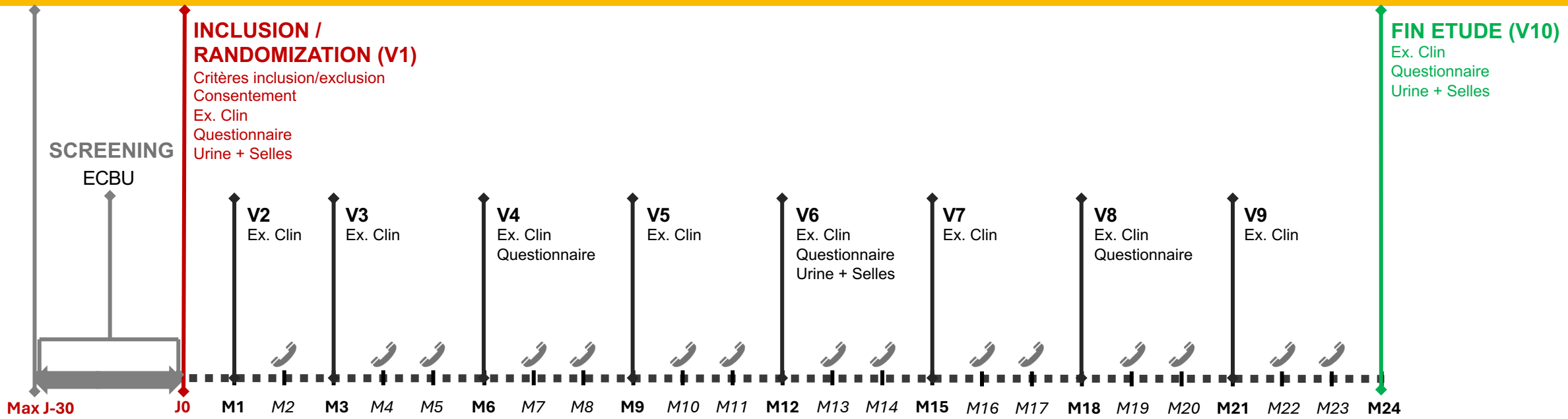


***Schéma posologique des bras expérimentaux et placebo:**

- **1 capsule par jour, le matin à jeun, pendant 90 jours consécutifs**
- **Arrêt du traitement pendant 90 jours**
- **1 capsule par jour, le matin à jeun, pendant 10 jours consécutifs, pendant trois mois consécutifs**

ECBU : Examen cytobactériologique des urines.
📞 : Appel téléphonique
V: Visites physiques
Ex. Clin: Examen Clinique incluant les paramètres vitaux
Questionnaire: Questionnaire de qualité de vie à compléter par le patient
Urines + Selles : Prélèvements non invasifs d'urine et de selles.

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

- Planned date first patient consented/enrolled/observed: JUL-2024
- Planned date last patient consented/ enrolled/observed: JUL-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

Retrain

- Contexte : IUVN IUR BMR >> Modèle pour IUR
- Question de recherche : prophylaxie non ATB
- Suivi long/roll over
- Critères inclusion : Pb définition cas
- Méthode : critères conso ATB
- Objectif critère objectif/facilement recueillable/bon usage ATB
- Réseau : centres experts (GENULF)

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 non-antibiotic alternatives for the treatment and prevention of UTI is of critical importance »

Nature 2018

Questions ?

OM-89 in patients with neurological bladder
(L. Piroth, France)

Title	**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 (RETRAIN study)**
Rationale / Background	**- Recurrent urinary tract infections** (**rUTIs**) **among patients using self-catheterization are a major concern**, especially in patients with spinal cord injury (SCI). - - **Prevalence of multidrug-resistant organisms in patients with SCI is high** (up to 50%) because of the frequent and prolonged antibiotic exposure. **- Prevention in this context is of great interest**, not only for preventing UTIs, but also for reducing the exposure to antibiotics. - Pilot studies using OM-89 in patients with spinal cord injury showed that it was able to reduce UTI frequency, regardless of patient age, duration of injury, catheter use, and bacterial species involved in UTI, highlighting the interest of undertaking a larger study (*Hachen 1990, Krebs 2018, Wade 2020*).
Study Design	Multicentre (10) study in **110 adult patients** (≥ 18 years old) **with neurogenic bladder due to spinal cord injury** who received 6 or more antibiotic treatment episodes in the preceding year and who are catheterized. Patients will be **randomly assigned (1:1) to OM-89 or placebo**. Randomization will be stratified on previous or concomitant use of prophylactic antibiotic therapy at enrolment. Two study phases (overall study length 24-months): - **Phase 1**: 12-month period on OM-89 or placebo according to randomization (according to boosting dosing scheme) - **Phase 2**: 12-month period on OM-89 for all patients (open-label)
Objectives	**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 number 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 design

Patient population (N=110)/10 centers in FR:

- Adult patients with stabilized neurogenic bladder due to spinal cord injury
- Using clean intermittent self-catheterization
- Received at least 6 AB treatments for UTIs in previous 12 months

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:

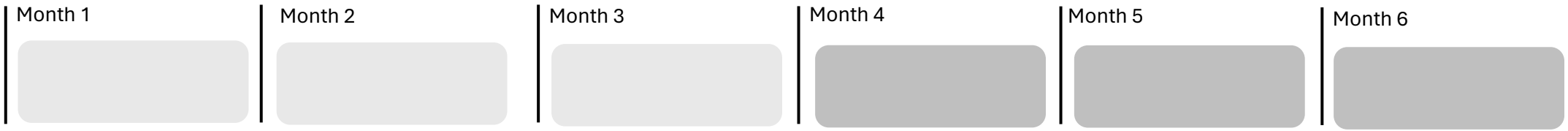
Compare the number of antibiotic treatments for UTIs at M12

Composition & Indications

Oral lyophilized bacterial lysate of 18 *E.coli* strains developed to stimulate host immune defenses against uro-pathogens

Use in adults and children as of 4 years of age:

- **Prevention of recurrent infections of the lower urinary tract***
  - 1 caps /day, empty stomach in the morning, for 90 consecutive days (3 months)



- **Co-medication for the treatment in acute episodes of Urinary Tract Infections**
  - 1 caps/day empty stomach in the morning for at least 10 days, until disappearance of the symptoms but for at least 10 consecutive days

Uro-Vaxom® Swiss SmPC

*treatment of recurrent and chronic urinary tract infections in some countries

What is the effect of OM-89 on innate and adaptive immunity?

OM-89 promotes immune-potentiating signals that activate both **innate** and **adaptive** immunity. This dual response increases the efficiency of the immune system, which leads to enhanced protection against infection in the urinary tract

At the intestinal level, OM-89 activates a large set of PRRs in a precise manner

Priming of immune system

- Phagocytosis (macrophages, neutrophils)[1,2]
- ↑ Adhesion molecules at neutrophil surface[3]
- Cytokine release[4,5]
- DC maturation[6]

Innate immunity

- Cellular (T and B cells)[4,6]
- Humoral (IgG and IgA)[4,7]

Polyclonal adaptive immunity

CD, cluster of differentiation; GALT, gut-associated lymphoid tissue; IFN, interferon; Ig, immunoglobulin; IL, interleukin; MHC, major histocompatibility complex; NOD, nucleotide-binding oligomerization domain; TLR, Toll-like receptor; TNF, tumour necrosis factor

1. Pham TV et al. J Biol Response Mod 1990;9:231–40; 2. Bessler WG et al. Arzneimittelforschung 2010;60:324–9; 3. Marchant A et al. Respiration 1992;59:24–7; 4. Huber M et al. Int J Immunopharmacol 2000;22:1103–11; 5. Bessler WG et al. Arzneimittelforschung 2009;59:571–7; 6. Schmidhammer S et al. Urology 2002;60:521–6; 7. Huber M et al. Int J Immunopharmacol 2000;22:57–68

A unique position in the guidelines

Leitlinien, AWMF-Register-Nr. 043/044, 2017. http://www.awmf.org/leitlinien/detail/ll/043-044.html. Accessed November 2022; 2. Apolikhin, Consensus conference of the Commission "Kidney, urinary and male genital tract infections" of the Scientific Council for "Uronephrology" of the Russian Academy of Medical Sciences, with international participation, Moscow, February 10, 2012; 3. Perepanova TS *et al.* Russian national guidelines "Antimicrobial therapy and prevention of kidney-,urinary tract- and male genital tract Infections" 2012; 4. Lee SJ *et al. Urogenit Tract Infect* 2017;12:7–14; 5. Colegio Mexicano de Especialistas em Ginecologia y Obstetricia. *Ginecol Obstet Mex* 2010;78:S437–59; 6. Brazilian Uro Society. http://portaldaurologia.org.br/medicos/wp-content/uploads/2015/09/infeccao_urinaria_de_repeticao.pdf. Accessed November 2022; 7. Betschart C *et al.* Swiss Society of Gynecology and Obstetrics. Expertenbrief 58. https://www.sggg.ch/fileadmin/user_upload/58_Akute_und_rezidivierende_Harnwegsinfekt.pdf. Accessed November 2022; 8. Haddad JM *et al.* [illegible]

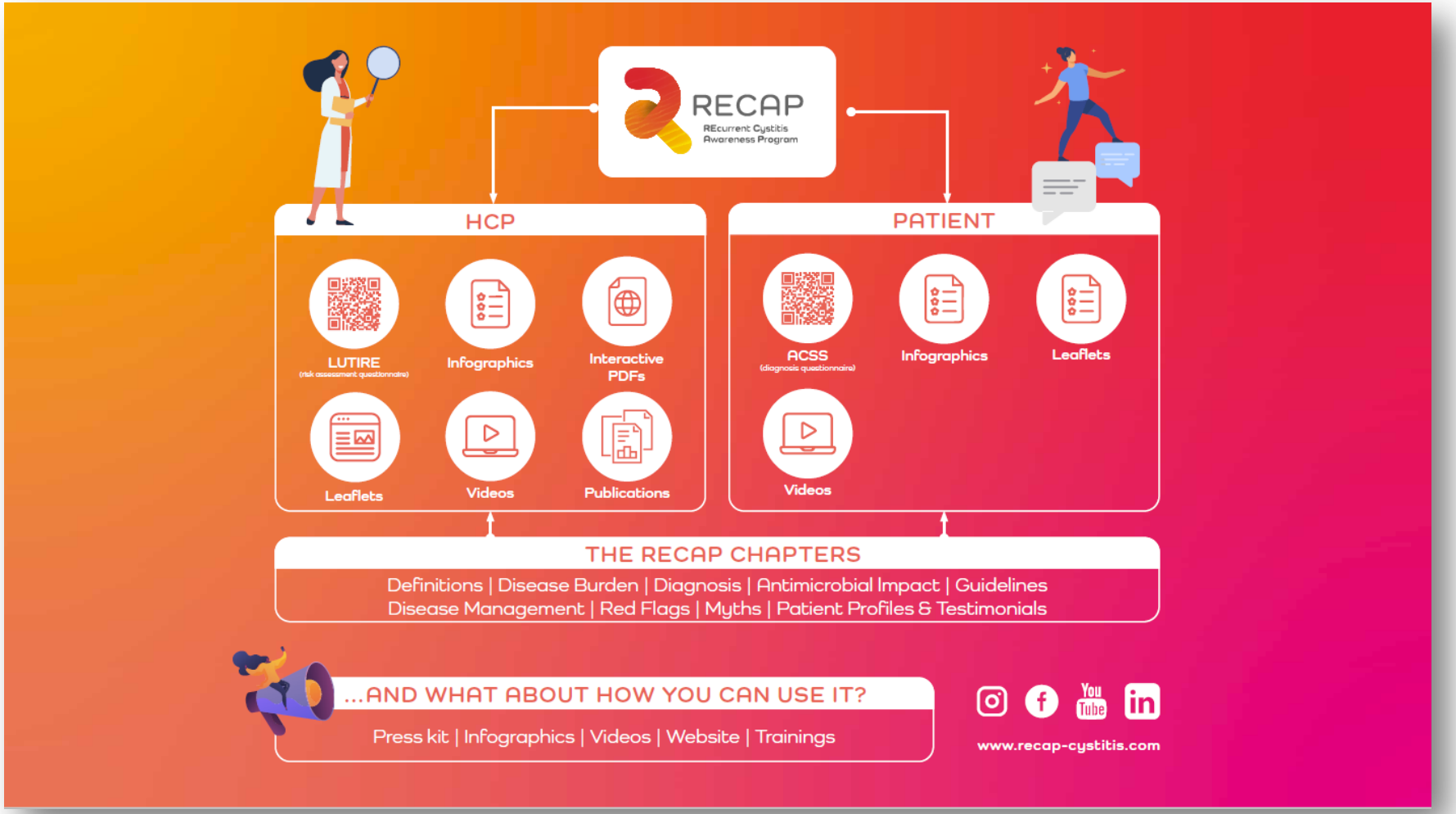
EAU recommendations at a glance[1]

Select a treatment for more information

Disease management	Treatment	LE, SR	Recommendation
Behavioural modifications Before initiation of long-term prophylactic drug treatment, women with rUTI should be counselled on avoidance of risks (eg, insufficient hydration, habitual and post-coital delayed urination, wiping from back to front after defecation, douching and wearing occlusive underwear)	Avoidance of risks	LE = 3, SR = weak	There is limited evidence available regarding these approaches.
Non-antimicrobial prophylaxis	Immunoactive prophylaxis	LE = 1a, SR = strong	OM-89 is well documented and can be recommended in female patients with rUTI.
	Hormone replacement	LE = 1b, SR = strong	A strong recommendation is given for vaginal oestrogen replacement in post-menopausal women.
	Probiotics	LE = 1b, SR = weak	A weak recommendation is given for local or oral probiotics containing strains of proven efficacy for vaginal flora regeneration to prevent UTIs.
	Cranberry	LE = 1a, SR = weak	A weak recommendation is given for the use of cranberry products, but patients should be informed that the evidence for this is low quality and contradictory.
	D-mannose	LE = 2, SR = weak	A weak recommendation is given for D-mannose, but patients should be informed that further studies are needed.
	Hyaluronic acid and its derivatives	LE = 2, SR = weak	A weak recommendation is given for endovesical instillations of hyaluronic acid and its derivatives, but patients should be informed that further studies are needed to confirm the results of initial trials.
	Methenamine salts	No reccomendation	No recommendation on the use of methenamine hippurate can be made, due to these contradictory results.
Antimicrobial prophylaxis Antimicrobials should only be offered to patients after behavioural modifications and non-antimicrobial measures have been unsuccessful	Continuous low-dose antimicrobial prophylaxis and post-coital antimicrobial prophylaxis	LE = 1b, SR = strong	Use to prevent recurrent UTI when non-antimicrobial interventions have failed. Counsel patients regarding possible side effects.
	Intermittent self-start therapy	LE = 2b, SR = strong	For patients with good compliance self-administered short-term antimicrobial therapy should be considered.

Bonkat G, et al. Available from: https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-Guidelines-on-Urological-Infections-2022.pdf. Last accessed November 2022

RECAP: REcurrent Cystitis Awareness Program



A variety of materials for HCPs & patients

Urinary tract infections