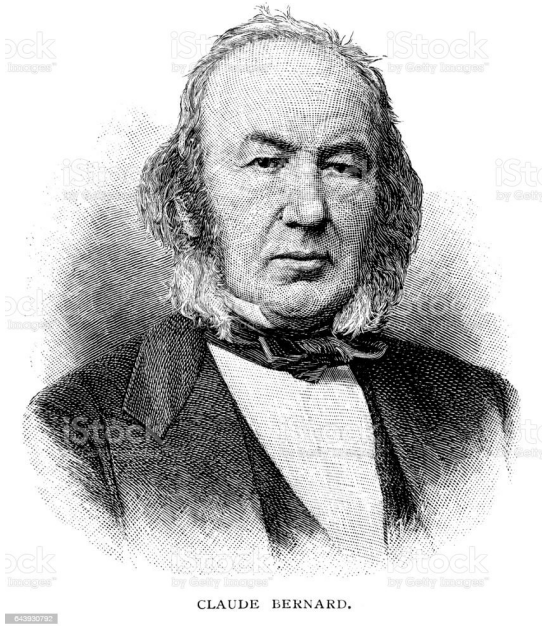
Traitement des infections urinaires : toujours plus court ?



17/11/2022

Journée Claude Bernard

Matthieu Lafaurie

Unité transversale d'infectiologie U2I

Hôpital Saint-Louis, Paris

Madame BRULL Laurine, 25 ans

- Pollakiurie, urgenturie, douleurs sus pubiennes depuis 10 heures.
- Aucun ATCD
- Vous diagnostiquez brillamment une cystite aiguë et la BU vous conforte.

Quelle durée d’antibiotique la plus courte vous parait raisonnable?

- 0 jour
- 1 jour
- 3 jours
- 5 jours
- 7 jours

Infection urinaire basse de la femme
Recommandations SPILF

Cystite à risque de complication

- Pivmécillinam 5 jours, 400 mg x2/j
- Furadantine 7 jours, 100 mg x 3/j

Cystite simple

- fosfomycine-trométamol, une dose unique de 3 g (1 jour)

MAIS…

Effect of 5-Day Nitrofurantoin vs Single-Dose Fosfomycin on Clinical Resolution of Uncomplicated Lower Urinary Tract Infection in Women

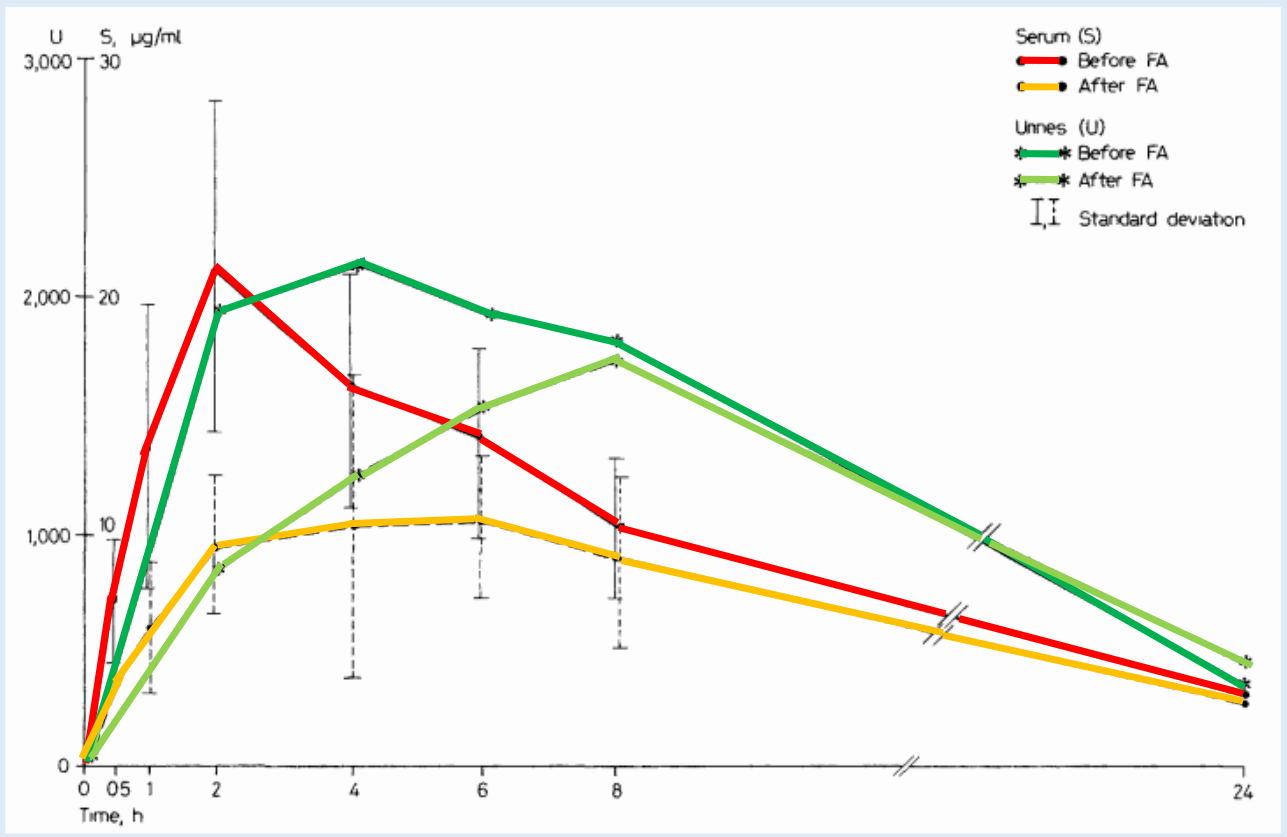
JAMA Huttner et al. 2018

Clinical and Bacteriologic Outcome	No./Total No. (%) Nitrofurantoin (n = 255)	Fosfomycin (n = 258)	Difference, % (95% CI)	*P* Value[a]
Primary Outcome				
Clinical response at 28 d[b]				
Clinical resolution	171/244 (70)	139/241 (58)	12 (4-21)	.004
Clinical failure	66/244 (27)	94/241 (39)		
Indeterminate	7/244 (3)	8/241 (3)		
Missing[c]	11 (4)	17 (7)		
Microbiologic response at 28 d[b]				
Culture obtained/baseline culture positive	175/194 (90)	163/183 (89)		
Bacteriologic success through 28 d	129/175 (74)	103/163 (63)	11 (1-20)	.04
Bacteriologic success failure by 28 d	46/175 (26)	60/163 (37)		

Trometamol-Fosfomycin (Monuril) Bioavailability and Food-Drug Interaction

E. Bergogne-Bérézin, C. Muller-Serieys, M.L. Joly-Guillou, N. Dronne

Eur. Urol. *13:* suppl. 1, pp. 64–68 (1987)



	Food absorption	
	before	after
Serum		
C_{max}, µg/ml	22.55 ± 6.03	12.74 ± 6.27
t_{max}, h	2.50 ± 1.08	3.98 ± 2.15
t1/2β, h	7.31 ± 1.74[1]	10.29 ± 3.47
AUC, µg/ml/h	227.86 ± 44.92	168.45 ± 57.11
Urine		
C highest, 0–8 h	2,187 ± 557	1,772 ± 897
t highest, h	4	8
Urinary recovery of the dose, %	25 (8 h)	16 (8 h)

Antibiotics versus placebo in the treatment of women with uncomplicated cystitis: A meta-analysis of randomized controlled trials

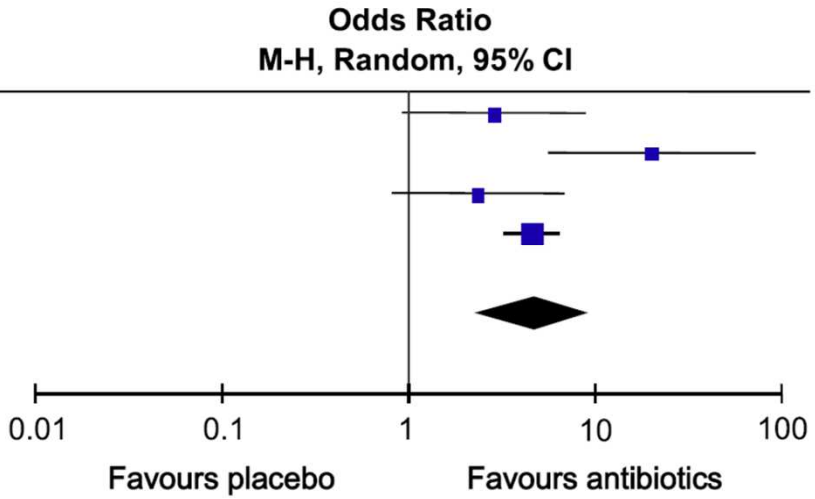
E. Falagas Journal of Infection (2009) **58**, 91—102

Guérison clinique

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
Dubi 1982	30	43	8	18	20.4%	2.88 [0.93, 8.97]
Asbach 1991	50	57	5	19	17.6%	20.00 [5.50, 72.77]
Christiaens 2002	13	35	7	35	21.6%	2.36 [0.81, 6.93]
Ferry 2007	388	643	53	212	40.4%	4.56 [3.22, 6.47]
Total (95% CI)		**778**		**284**	**100.0%**	**4.67 [2.34, 9.35]**
Total events	481		73			

Heterogeneity: Tau² = 0.28; Chi² = 7.09, df = 3 (P = 0.07); I² = 58%

Test for overall effect: Z = 4.36 (P < 0.0001)



Eradication bactérienne

Study or Subgroup	Antibiotics Events	Antibiotics Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Random, 95% CI
1.11.1 At the end of treatment						
Dubi 1982	30	43	8	18	16.1%	2.88 [0.93, 8.97]
Christiaens 2002	21	26	5	25	14.7%	16.80 [4.22, 66.95]
Ferry 2007	590	643	72	212	19.4%	21.65 [14.51, 32.28]
Subtotal (95% CI)		**712**		**255**	**50.3%**	**10.67 [2.96, 38.43]**
Total events	641		85			
Heterogeneity: Tau² = 1.02; Chi² = 10.85, df = 2 (P = 0.004); I² = 82%						
Test for overall effect: Z = 3.62 (P = 0.0003)						
1.11.2 At the first evaluation after the end of treatment						
Asbach 1991	50	57	5	19	15.3%	20.00 [5.50, 72.77]
Christiaens 2002	17	23	9	22	15.4%	4.09 [1.16, 14.43]
Ferry 2007	449	523	66	94	19.1%	2.57 [1.55, 4.27]
Subtotal (95% CI)		**603**		**135**	**49.7%**	**5.38 [1.63, 17.77]**
Total events	516		80			
Heterogeneity: Tau² = 0.84; Chi² = 8.50, df = 2 (P = 0.01); I² = 76%						
Test for overall effect: Z = 2.76 (P = 0.006)						

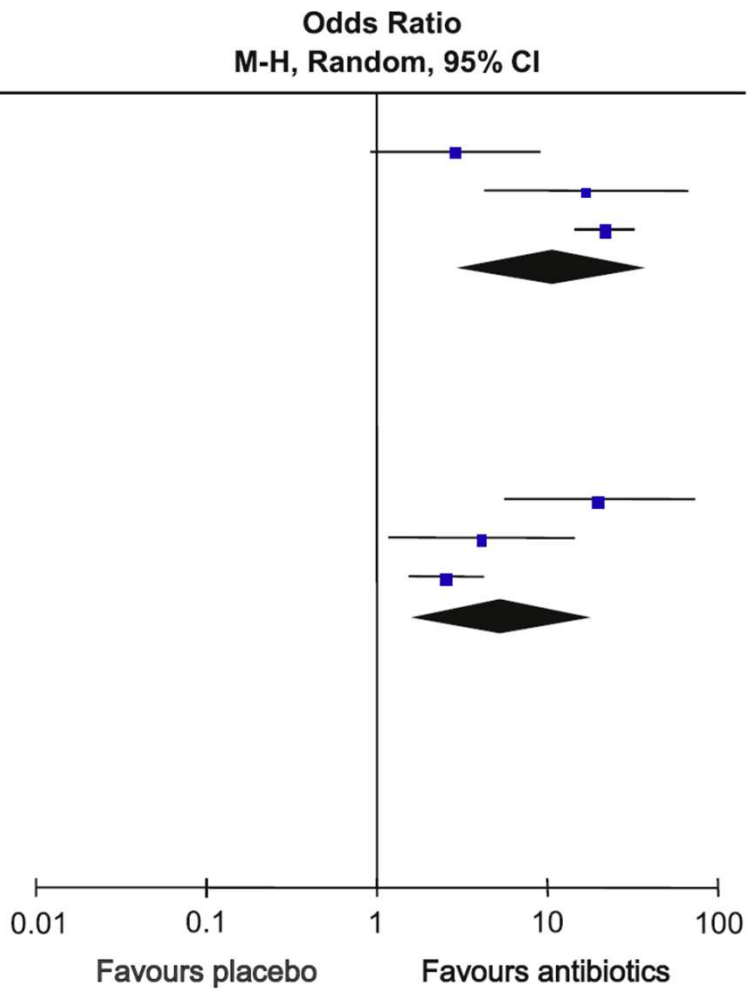


Table 2 Data from the included randomized controlled trials regarding the effectiveness outcomes of the meta-analysis.

First author, year[ref]	Therapeutic arm	ITT population (*n*)	Persistence of symptoms	Clinical success	Cure	Microbiological success at the end of treatment	Microbiological success at the 1st assessment after the end of treatment	Microbiological reinfection or relapse	Clinical relapse
Ferry, 2007[21]	Antibiotic group I *n/N* (%)	281	Total percentage: (56.0)	132/213 (61.9)	132/213 (61.9)	198/213 (92.9)	153/172 (88.9)	19/172 (11.0)	124/172 (72.0)
	Antibiotic group II *n/N* (%)	289		137/214 (64.0)	137/214 (64.0)	207/214 (96.7)	155/187 (82.8)	32/187 (17.1)	122/187 (65.2)
	Antibiotic group III *n/N* (%)	285		119/216 (55.0)	119/216 (55.0)	185/216 (85.6)	141/164 (85.9)	23/164 (14.0)	112/164 (68.2)
	Placebo group *n/N* (%)	288	(88.0)	53/212 (25.0)	53/212 (25.0)	72/212 (33.9)	66/94 (70.2)	28/94 (29.7)	48/94 (51.0)
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	Placebo group *n/N* (%)	38	NR	19/35 (54.2)	7/35 (20.0)	5/25 (20.0)	9/22 (40.9)	13/22(59.0)[b]	NR
Asbach, 1991[23]	Antibiotic group I *n/N* (%)	20	NR	17/19 (89.4)	17/19 (89.4)	NR	17/19 (89.4)	2/19 (10.5)	NR
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	Placebo group *n/N* (%)	20	NR	5/19 (26.3)	5/19 (26.3)	NR	5/19 (26.3)[a]	14/19 (73.6)	NR

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Dubi, 1982[24]	Antibiotic group I *n/N* (%)	21	NR	20/21 (95.2)	20/21 (95.2)	20/21 (95.2)	NR	1/21 (4.7)	NR
	Antibiotic group II *n/N* (%)	22	NR	10/22 (45.4)	10/22 (45.4)	10/22 (45.4)	NR	12/22 (54.5)	NR
	Placebo group *n/N* (%)	18	NR	8/18 (44.4)	8/18 (44.4)	8/18 (44.4)	NR	10/18 (55.5)	NR
Brooks, 1972[25]	Antibiotic group *n/N* (%)	25	6/24 (25.0)	NR	NR	NR	NR	6/24 (25.0)	NR
	Placebo group *n/N* (%)	20	8/20 (40.0)	NR	NR	NR	NR	7/20 (35.0)	NR

Abbreviations: ITT = intention to treat population; NR = not reported.

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Alternatives aux antibiotiques en thérapeutique: ibuprofène/diclofénac?

- Pour quelles patientes?

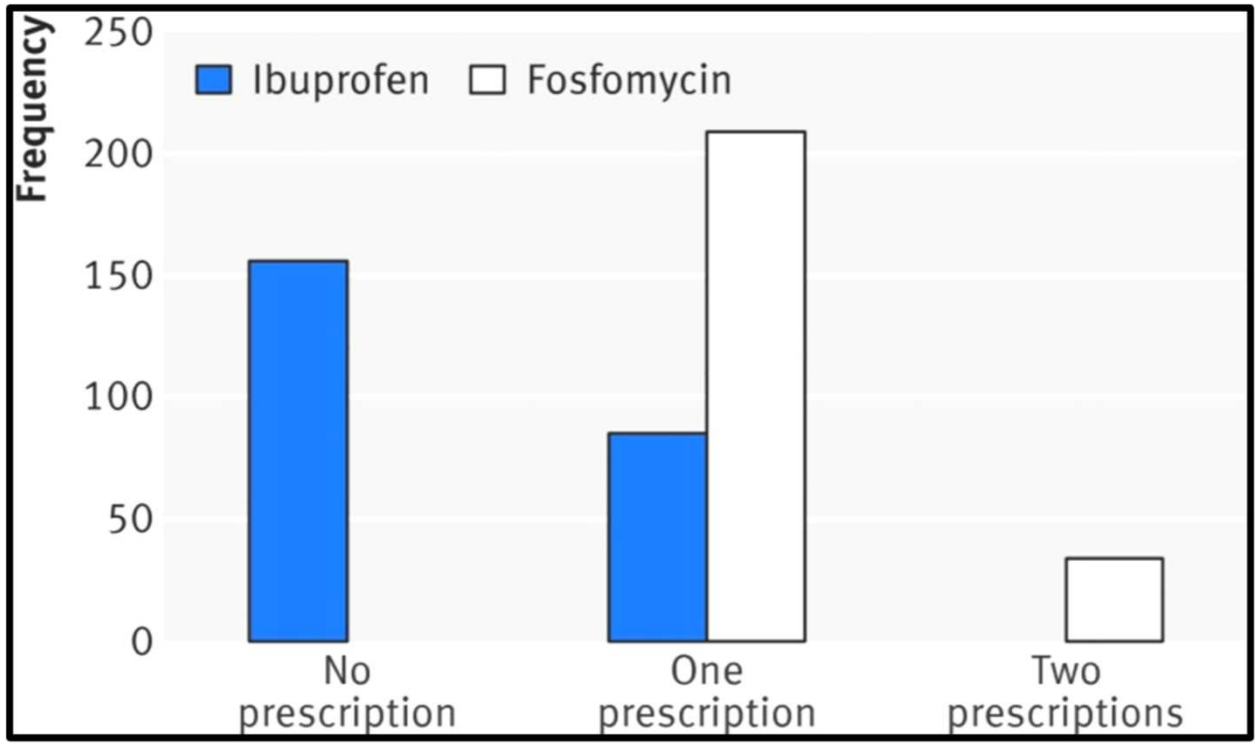
- cystite non compliquée (patientes non ménopausées, non enceintes et sans antécédent de pyélonéphrite= en bonne santé)
- Tolérance des symptômes de cystite acceptable…

- 3 études ibuprofène, 1 diclofénac

Ibuprofen versus fosfomycin for uncomplicated urinary tract infection in women: randomized controlled trial

Gágyor et al. BMJ 2015.

Ibuprofen (n=248) 3 jours vs fosfo (n=246) 1 dose



Guérison sans antibiotiques: 67% des femmes du groupe ibuprofen
Pyélonéphrite aiguë: ibuprofen 5, fosfo 1

Ibuprofen versus pivmecillinam for uncomplicated urinary tract infection in women—A double-blind, randomized non-inferiority trial

VIK et al. PLOS medicine 2018

Pivmécillinam vs ibuprofen pendant 3 jours

Table 2. Summary of primary and key secondary outcomes in women with uncomplicated UTI randomized to either ibuprofen or pivmecillinam: Intention to treat population.

Outcome	Ibuprofen (*n* = 181)	Pivmecillinam (*n* = 178)	Adjusted risk difference (95% CI)
Primary outcome			
Patients without symptoms by day 4	70 (39)	131 (74)	35% (27% to 43%)*
Secondary outcomes			
Patients without symptoms by day 7	114 (63)	162 (91)	28% (20% to 36%)
Patients without symptoms by day 14	141 (78)	167 (94)	16% (9% to 23%)
Median symptom duration after randomization (days)	6	3	
Urine cultures after 14 days **			
Urine culture positive	43 (28)	16 (10)	−16% (−26% to −7%)
Growth of primary pathogens	29 (19)	6 (4)	−14% (−23% to −6%)
Relapses/complications **			
Secondary treatment with antibiotics by day 14	73 (41)	14 (8)	−32% (−40% to −24%)
Secondary treatment with antibiotics by day 28	83 (46)	18 (10)	−36% (−44% to −27%)
Patients with febrile UTI†	5 (3)	0 (0)	−3% (−6% to 0.1%)
Patients with pyelonephritis†	7 (4)	0 (0)	−4% (−8% to −1%)
Serious adverse events	6 (3)	1 (1)	−3% (−6% to 0.1%)

A J 28: 53% guérison sans antibiotiques dans le groupe ibuprofène

Clinical Microbiology and Infection 2019 Moore et al.

Summary of use of antibiotics (ITT population A, $n = 382$)

Characteristic	Group 1[a] (uva-ursi + ibuprofen advice) ($n = 102$)	Group 2[a] (Placebo + Ibuprofen advice) ($n = 86$)	Group 3[a] (uva-ursi + No ibuprofen advice) ($n = 97$)	Group 4[a] (Placebo + No Ibuprofen advice) ($n = 97$)
Use of antibiotics at any time during Week 1, n (%)	17 (24.3)	21 (35.6)	33 (45.2)	41 (55.4)
Use of antibiotics at any time during Week 1 and Week 2, n (%)	24 (34.3)	21 (35.6)	33 (45.2)	42 (56.8)

- ANTIBIO Ibuprofen advice: 34.9% vs. no advice 51.0%; OR 0.27 (95% CI 0.10-0.72; p 0.009)
- Pas de PNA

Pyélonéphrite aigue

- Recommandation SPILF

- 7 jours si fluoroquinolones et/ou B-lactamine parentérale
- 5 jours si aminosides

- Possible avec Trimethoprim-Sulfamethoxazole?
- Peut on faire plus court?

A Seven-Day Course of Trimethoprim-Sulfamethoxazole May Be as Effective as a Seven-Day Course of Ciprofloxacin for the Treatment of Pyelonephritis. M. Fox *et al.* Am J Med. 2017

- Etude multicentrique, retrospective, femmes, Pyélonéphrite aiguë à *E. coli* CFU/mL sensible.

	TMP-SMX (n=81; 30%)	Ciprofloxacin (n=191; 70%)	p-value
Diabetes	12 (15%)	30 (16%)	1.00
Human immunodeficiency virus	2 (2%)	6 (3%)	1.00
Chemotherapy in past 6 months	1 (1%)	4 (2%)	1.00
Renal transplant	1 (1%)	4 (2%)	1.00
End-stage liver disease	1 (1%)	4 (2%)	1.00
Immunomodulators within the past 30 days	2 (2%)	11 (6%)	1.00
Indwelling or intermittent urinary catheterization	2 (2%)	6 (3%)	1.00
Serum creatinine on day of positive urine culture (median, IQR)	1 (0.7–1)	1 (0.8–1)	0.22
Escherichia coli bacteremia	7 (9%)	40 (21%)	<0.01
Hospitalized	18 (22%)	69 (36%)	0.01
Extended spectrum beta-lactamase producing *E. coli*	3 (4%)	4 (2%)	0.43

Antibiotic Prescribed on Day 1	Final Antibiotic: TMP-SMX (n=81)	Final Antibiotic: ciprofloxacin (n=191)
Ceftriaxone	19 (24%)	53 (28%)
Ciprofloxacin	0	105 (55%)
Trimethoprim-sulfamethoxazole	57 (70%)	0
Piperacillin-tazobactam	1 (1%)	4 (2%)
Cefepime	4 (5%)	19 (10%)
Aztreonam	0	10 (5%)

Critère principal: infection urinaire (signes cliniques et ≥ 10^5 E. coli/mL) dans les 30 jours suivant initiation ttt

TMP-SMX: 6 (7%) / Ciprofloxacine: 12 (6%)

OR 1,19 (95%CI 0,43-3,3)
ORa (hospitalisation, bactériémie): 2,3 (95% CI 0,72-7,42)

Plus court que 7 jours pour les pyélonéphrites aiguës?

A trial of levofloxacin 750 mg once daily for 5 days versus ciprofloxacin 400 mg and/or 500 mg twice daily for 10 days in the treatment of acute pyelonephritis

Klausner, Brown, Peterson, Kaul, Khashab, Fisher, Kahn Curr Med Res Opin. 2007

Treatment of complicated urinary tract infection and acute pyelonephritis by short-course intravenous levofloxacin (750 mg/day) or conventional intravenous/oral levofloxacin (500 mg/day): prospective, open-label, randomized, controlled, multicenter, non-inferiority clinical trial

Hong Ren et al. Int Urol Nephrol (2017)

Is 5 days of oral fluoroquinolone enough for acute uncomplicated

pyelonephritis? The DTP randomized trial.

Dinh et al. Eur J Clin Microbiol Infect Dis (2017)

Pas de données solides pour conseiller un traitement de 5 jours pour les pyélonéphrites aiguës…

- Effectifs peu importants
- Méthodologie « discutable »

En pratique, qui fait quoi?

Mr P. 83 ans, brulures urinaires, urgenturie depuis 5 jours. Pas de fièvre.

ECBU: *E. coli* 10^5 cfu/mL, sauvage, GB 95000/mL.

ATCD: IDM, hypercholestérolémie, PTH, **prostatectomie radicale pour ADK**,

Quel traitement, quelle durée?

- Nitrofurantoïne: 7 jours
- Ofloxacine: 14 jours
- Fosfomycine: J1-J3-J5
- Cotrimoxazole: 7 jours
- Cotrimoxazole: 10 jours
- Ciprofloxacine: 21 jours
- Pivmécillinam: 5 jours

En pratique, qui fait quoi?

Mr P. 79 ans, brulures urinaires, urgenturie depuis 5 jours. Pas de fièvre.

ECBU: *E. coli* 10^5 cfu/mL, sauvage, GB 95000/mL.

ATCD: IDM, hypercholestérolémie, PTH, **hypertrophie bénigne de la prostate**

Quel traitement, quelle durée?

- Nitrofurantoïne: 7 jours
- Ofloxacine: 14 jours
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- Pivmécillinam: 5 jours

En pratique, qui fait quoi?

Mr P. 83 ans, brulures urinaires, urgenturie depuis 5 jours. Pas de fièvre. ECBU: 10^5 E. coli, GB 125/mm3, sauvage.

ATCD: IDM, hypercholestérolémie, PTH, hypertrophie bénigne de la prostate

Quel traitement, quelle durée?

Avant de répondre: quelle infection traite t'on?

- Fosfomycine: J1-J3-J5
- Bactrim 7 jours
- Bactrim 10 jours
- Ciprofloxacine: 21 jours
- Pivmécillinam: 5 jours

TERMINOLOGIE

- **Cystite masculine**

SPILF: entité non individualisée dans les recommandations françaises

EAU (urologie Europe): « la cystite chez l'homme sans atteinte de la prostate est rare »

- **Infection urinaire de l'homme**

SPILF: infection urinaire masculine fébrile/non fébrile

EAU: classification du National Institute of Health (NIH) distinguant la prostatite aiguë de la prostatite chronique

Nombre	Catégorie	Caractéristiques	Signes présents dans l'urine	Prémassage	Post-massage
I	Prostatite bactérienne aiguë	Symptômes aigus d'infection urinaire	Globules blancs	+/−	+
			Bactéries	+/−	+
II	Prostatite bactérienne chronique	Infection urinaire récidivante par un même microrganisme	Globules blancs	+/−	+
			Bactéries	+/−	+
III	Prostatite chronique/syndrome de douleur pelvienne chronique	Principalement des douleurs, des troubles mictionnels et une dysfonction sexuelle			
IIIa	Inflammatoires		Globules blancs	−	+
			Bactéries	−	−
IIIb	Non inflammatoire*		Globules blancs	−	−
			Bactéries	−	−
IV	Prostatite inflammatoire asymptomatique	Découverte fortuite lors de l'évaluation urologique (p. ex., biopsie de la prostate, analyse du liquide séminal) pour d'autres pathologies	Globules blancs	−	+
			Bactéries	−	−

*Précédemment appelé prostatodynie.

+/− signifie éventuellement présents; + signifie présents; − signifie absent.

TRAITEMENT

SPILF

La notion de fièvre disparait pour le choix et la durée des antibiotiques

- *Si fièvre*: ttt probabiliste
- *Apyrexie et infection « bien » tolérée* : ttt différé selon documentation microbiologique si possible
- Durée :

  - 14 j si fluoroquinolone, triméthoprime-sulfaméthoxazole, β-lactamines injectables

  - 21 j pour les autres molécules **OU** si uropathie sous jacente non corrigée (= troubles mictionnels préexistants, lithiase…)

En pratique, selon SPILF

Mr P. 79 ans, brulures urinaires, urgenturie depuis 5 jours. Pas de fièvre.

ECBU: *E. coli* 10^5 cfu/mL, sauvage, GB 95000/mL.

ATCD: IDM, hypercholestérolémie, PTH, hypertrophie bénigne de la prostate
Quel traitement, quelle durée?

- Furandantine 7 jours
- Ofloxacine 14 jours
- Fosfomycine: J1-J3-J5
- Bactrim 7 jours
- Bactrim 10 jours
- Ciprofloxacine: 21 jours
- Pivmécillinam: 5 jours

En pratique, selon SPILF

Mr P. 83 ans, brulures urinaires, urgenturie depuis 5 jours. Pas de fièvre.

ECBU: *E. coli* 10^5 cfu/mL, sauvage, GB 95000/mL.

ATCD: IDM, hypercholestérolémie, PTH, prostatectomie radicale

Quel traitement, quelle durée?

- Furandantine 7 jours
- Ofloxacine 14 jours
- Fosfomycine: J1-J3-J5
- Bactrim 7 jours
- Bactrim 10 jours
- Ciprofloxacine: 21 jours
- Pivmécillinam: 5 jours

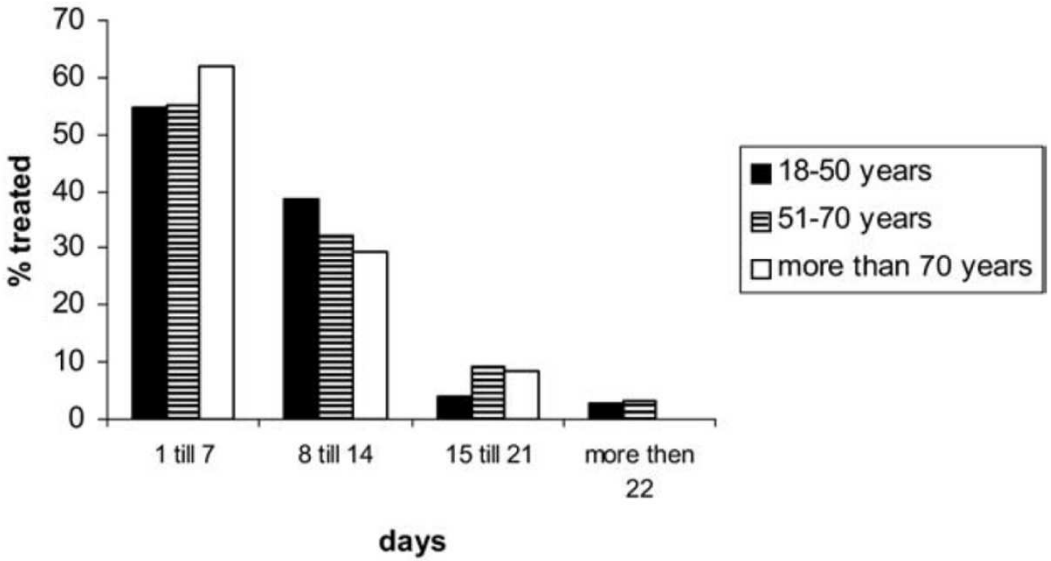
?

Infection urinaire non fébrile de l'homme

- Hommes souvent inclus dans les études de traitement des cystites compliquées, mais de façon variable et minoritaire (jusqu'à 10%).
- Quelques données spécifiques chez l'homme, essentiellement rétrospectives

Urinary Tract Infection in Male General Practice Patients: Uropathogens and Antibiotic Susceptibility. J. J. Koeijers, et al. UROLOGY 76 (2), 2010

- Cohorte de ville, 2013-2014.
- Hommes, >18 ans, infection urinaire non fébrile: dysurie aigue, pollakiurie et/ou urgenturie, <38°, pas de signes généraux, pas de matériel.
- 422 hommes, 18-104 ans.
- Traitement antibiotique prescrit dans 60% des cas.



Antibiotic Treatment	Age Category 18-50 y n = 86	51-70 y n = 99	>70 y n = 68	Total N = 253
Amoxicillin	1	3	0	2
Co-amoxicillin	10	12	10	11
TMP-SMX*	26	24	21	24
Trimethoprim	3	1	1	2
Nitrofurantoin	14	15	19	16
Quinolones	31	32	35	33
Other	14	12	13	13
Total %	100	100	100	100

Evolution? Rechutes?

Retrospective evaluation of nitrofurantoin and pivmecillinam for the treatment of lower urinary tract infections in men. Hanna Montelin *et al.* PLOS one 2019

	Nitrofurantoïne (n=69)	Pivmécillinam (n=57)	Triméthoprime (n=45)
Durée ttt (médiane)	7 j	7 j	10 j
Echec	1 (1.4%)	4 (12%)	0
Rechutes (3 mois)	15%	17%	7%
Rechute si ttt ≤7 j	5/45 (11%)	9/35 (26%)	1/20 (5%)
Rechute si ttt >7 j	5/23 (22%)	0/18 (0)	2/25 (8%)
Doses	50 mg/8h (94%)	200 mg/8h (65%) 200 mg/12h (30%)	800 mg/12 h (98%)

Table 5. Univariate analysis for risk factors of new prescription and relapse.

	New prescription			Relapse		
	OR	95% CI	*P*	OR	95% CI	*P*
Antibiotics						
Trimethoprim	ref			ref		
Nitrofurantoin	1.75	0.74–4.15	0.204	2.37	0.62–9.15	0.209
Pivmecillinam	1.37	0.55–3.39	0.502	2.62	0.67–10.34	0.168
Recent UTI therapy	0.90	0.46–1.75	0.753	0.78	0.32–1.91	0.586
Gram-positive bacteria	0.54	0.26–1.12	0.089	0.80	0.31–2.08	0.640
Treatment duration > 7 d	1.10	0.56–2.16	0.780	0.87	0.34–2.21	0.771
Any risk factors	2.12	0.97–4.67	0.052	1.23	0.45–3.34	0.683
Urinary tract catheterization	2.34	1.14–4.80	0.022	1.73	0.67–4.45	0.265
Benign prostate hypertrophy	1.71	0.08–3.62	0.165	1.27	0.46–3.49	0.650
Prostate cancer	1.92	0.82–4.50	0.141	3.01	1.09–8.29	0.042
Diabetes mellitus	1.21	0.48–3.01	0.692	0.91	0.25–3.34	0.888
Neurogenic bladder disorder	1.04	0.35–3.13	0.942	0.40	0.05–3.14	0.322

Pas de différence significative

- échec selon antibiotique
- rechutes selon antibiotique
- rechutes selon ≤ 7 j vs > 7 j de façon globale
- Rechutes plus fréquentes avec pivmécillinam ≤ 7 j vs > 7 j

Effectiveness and safety of nitrofurantoin in outpatient male veterans.
Ingalsbe *et al.* Therapeutic advances in Urology, 2015

- Etude rétrospective, 2004-2013, EU.
- **Guérison clinique**: absence de signes urinaires 14 jours après fin du traitement par furadantine.

→ 485 patients pour analyse efficacité

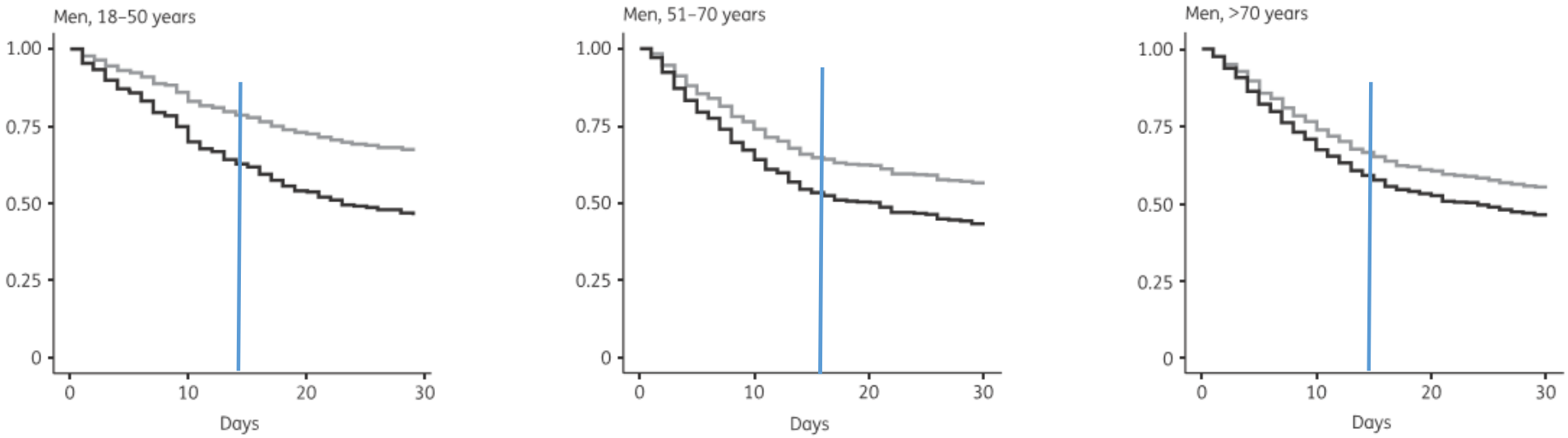
- Dose: 100 mg x2/jour dans 71% des cas
- **Guérison: 77%**
- Meilleure efficacité si clairance>60 ml/min et gram négatifs vs gram positifs
- **Durée traitement: succès clinique 8,6±3,6 versus échec 9,3±6,9 jours (p=0,28)**

Treatment duration of pivmecillinam in men, non-pregnant and pregnant women for community-acquired urinary tract infections caused by Escherichia coli: a retrospective Danish cohort study Boel *et al.* JAC 2019

- Cohorte rétrospective, 2010-2016.
- **Inclusion**: femmes et hommes, > 18 ans, traitement empirique par pivmécillinam pour bactériurie significative à *E. coli*. Infection urinaire basse.
- Pivmécillinam: 400mg x3/j

- 21864 inclusions dont 2524 hommes

- Succès clinique 5 jours > 3 jours chez les hommes



- **Pas de différence 5 jours versus 7 jours en termes de succès**

No clinical benefit to treating male urinary tract infection longer than seven days: an outpatient database study.

Germanos *et al.* Open forum infectious diseases, 2019.

- Cohorte rétrospective de ville (urologie, généraliste, médecine interne)
- Base de données, région de Houston
- 2011-2015
- Hommes, Infection urinaire basse et traitement antibiotique (FQ (69,7%), cotrimoxazole (21,2%), nitrofurantoïne (5,3%), triméthoprime, ß-lactamine, aminoside).
- 637 visites, 573 hommes.
- FDR rechute: durée du traitement > 7 jours; OR 2.62, 95% CI 1.04–6.61

(chez hommes sans HBP ni lithiases)

Fosfomycin in the treatment of extended spectrum beta-lactamase-producing *Escherichia coli*-related lower urinary tract infections

Pullukcu et al. International Journal of Antimicrobial Agents(2007)

- Cohorte rétrospective observationnelle
- 52 adultes, **<u>25 hommes</u>**

- SFU (dysurie, pollakiurie, urgenterie)
- Leucocyturie et *E. coli* >10^5, BLSE.
- Pas de fièvre, pas d'hyperleucocytose

- Fosfomycine trométamol: 3 g J1-J3-J5
- ECBU de contrôle à 7 à 9 jours

- Succès clinique et microbiologique: 94.3% (49/52) et 78.5% (41/52)

Pas de détails hommes/femmes

Matthews *et al.* Oral fosfomycin for treatment of urinary tract infection: a retrospective cohort study. *BMC Infect Dis*. 2016

- Cohorte rétrospective observationnelle
- 75 adultes, **18 hommes**

- SFU (dysurie, pollakiurie, urgenterie)
- Leucocyturie et uropathogène>10^5/mL (31/52 (59%) BLSE).
- Pas de fièvre, pas d'hyperleucocytose
- Fosfomycine trométamol 3 g, médiane J1-J3-J5

- ECBU stérile, 21/40 (53%), follow-up 13 jours
- Guérison clinique ou ECBU stérile: 42/61 (69%)
- FDR échec : infection à *K. pneumoniae*
- Infection chez l'homme: pas FDR d'échec

Effect of 7 vs 14 Days of Antibiotic Therapy on Resolution of Symptoms Among Afebrile Men With Urinary Tract Infection (Drenkonja et al. JAMA 07/2021)

- Etude **randomisée en double aveugle, contre placebo**
- 2 centres médicaux (Minnesota et Texas)
- **Patients**: hommes, > 18 ans, ttt prescrit pour 7 à 14 jours par Cipro ou cotrimoxazole pour infection urinaire non febrile, en ambulatoire, par leur médecin.
- Et au moins un signe parmi: dysuria, pollakiurie, urgenturie, hématurie, douleur angle costo-vertebral ou périnée ou flanc ou sus pubienne.
- **Non inclusion**: infection urinaire dans les 14 jours précédents, t°>38° C, germe urinaire resistant au ttt prescrit.
- **ECBU pas necessaire**
- Traitement prescrit pendant 7 jours
- Tirage au sort pour traitement à partir de J8
  - soit continuer le même ttt (mais cp différents), pdt 7 jours
  - soit prendre un placebo pdt 7 jours

Suivi téléphonique: J14, puis +7, +14 et +28.

Table 1. Baseline Demographics and Comorbid Conditions[a]

Variable	7-Day antimicrobial + 7-day placebo group (n = 136)[b,c]	14-Day antimicrobial group (n = 136)[c]
Age, median (IQR), y	70 (62-73)	70 (62-75)
Race[d,e]	(n = 135)	(n = 135)
White	107 (79)	105 (78)
Black	26 (19)	23 (17)
Native American	1 (1)	5 (4)
Multiple races	1 (1)	2 (1)
Hispanic/Latino ethnicity[d,f]	5/132 (4)	8/134 (6)
Charlson comorbidity index, median (IQR)[g]	1 (0-2)	1 (0-2)
Urinary tract-related comorbidities	(n = 136)	(n = 136)
Any prior UTI	84 (62)	78 (57)
Prostatic hypertrophy	56 (41)	47 (35)
Urinary incontinence	44 (32)	52 (38)
Intermittent catheter use	24 (18)	23 (17)
Prostate cancer	21 (15)	23 (17)
Urethral stricture	17 (13)	16 (12)
Prior prostatitis	16 (12)	18 (13)
Indwelling catheter use	8 (6)	8 (6)
Nonurinary comorbidities	(n = 136)	(n = 136)
Diabetes	46 (34)	60 (44)
Cerebrovascular accident	13 (10)	5 (4)
Chronic kidney disease	8 (6)	14 (10)
Spinal cord injury	5 (4)	6 (4)
HIV	2 (1)	2 (1)
Most common symptoms associated with UTI diagnosis	(n = 136)	(n = 136)
Dysuria	93 (68)	88 (65)
Frequency	80 (59)	70 (51)
Urgency	52 (39)	39 (29)

Table 2. Distribution of Organisms Isolated From 145 Urine Cultures With Growth at Greater Than 100 000 Colony-Forming Units/mL[a]

Organism isolated	No. (%)	
	7-Day antimicrobial + 7-day placebo group (n=70)	14-Day antimicrobial group (n-75)
Escherichia coli	30 (43)	29 (39)
Klebsiella species	11 (16)	12 (16)
Enterococcus species	7 (10)	6 (8)
Coagulase-negative staphylococci	6 (9)	8 (11)
Citrobacter species	3 (4)	3 (4)
Morganella morganii	3 (4)	1 (1)
Streptococcus species	3 (4)	2 (3)
Enterobacter species	2 (3)	2 (3)
Proteus mirabilis	2 (3)	2 (3)
Serratia marcescens	2 (3)	1 (1)
Staphylococcus aureus	1 (1)	2 (3)
Aerococcus urinae	1 (1)	1 (1)
Gram-positive bacilli, not further identified	1 (1)	1 (1)
Pseudomonas aeruginosa	0	2 (3)
Salmonella species	0	1 (1)

ECBU positif: n=145, 53%; dont 14 à SCN…

Table 3. Primary and Secondary Outcomes

Characteristic	No./total No. (%)		
Resolution of UTI symptoms 14 days after stopping active antimicrobials	7-Day antimicrobial + 7-day placebo group	14-Day antimicrobial group	Absolute difference, % (1-sided 97.5% CI)[a]
As-treated population (primary analysis)	122/131 (93.1)	111/123 (90.2)	2.9 (-5.2 to ∞)
As-randomized population	125/136 (91.9)	123/136 (90.4)	1.5 (-5.8 to ∞)
Recurrence of UTI symptoms within 28 days of stopping study medication (secondary outcome)	7-Day antimicrobial + 7-day placebo group	14-Day antimicrobial group	Absolute difference, % (2-sided 95% CI)[b]
As-treated population	13/131 (9.9)	15/123 (12.9)	-3.0 (-10.8 to 6.2)
As-randomized population	14/136 (10.3)	23/136 (16.9)	-6.6 (-15.5 to 2.2)

Abbreviation: UTI, urinary tract infection.

[a] The primary analysis used a 1-sided 97.5% CI for noninferiority, which was established if the lower bound of the 1-sided 97.5% CI did not cross the noninferiority margin of −10% difference in symptom resolution.

[b] The secondary outcome was analyzed using a 2-tailed superiority hypothesis test of differences in proportions (2-sample test for equality of proportions with continuity correction) with $\alpha = .05$ and with 2-sided 95% CIs.

Among afebrile men with suspected UTI, treatment with ciprofloxacin or trimethoprim/sulfamethoxazole for 7 days was non inferior to 14 days of treatment with regard to resolution of UTI symptoms by 14 days after antibiotic therapy.

DONC…

Durée de traitement infection urinaire masculine non fébrile

- Eléments de preuve…pas tout à fait irréfutables, mais qui s'accumulent

Antibiotique par voie orale	Dose journalière	durée
Pivmécillinam	400 mg x2 (ou x3)	(5-) 7 jours
Nitrofurantoïne	100 mg x3	7 jours
Fosfomycine trométamol	3 g	J1, J3 +/- J5
TMP-SMZ	800 mg x2	7 jours
Fluoroquinolone		7 jours
- **ofloxacine**	200 mg x2	
- **lévofloxacine**	500 mg x1	
- **ciprofloxacine**	500 mg x2	

Infection urinaire masculine fébrile?

Ciprofloxacin for 2 or 4 Weeks in the Treatment of Febrile Urinary Tract Infection in Men A Randomized Trial with a 1 Year Follow-up. Ulleryd et Sandber, Scand J Infect Dis, 2003.

- Etude prospective, randomisée, en ouvert, monocentrique (1993-1996)
- Objectif:

- non infériorité
- éradication bactérienne, 2 semaines post traitement (hypothèse de 95% de guérison microbiologique)
- marge infériorité: 20% de différence
- effectif 100 patients

- Adultes, ≥ 38°C, au moins un signe: pollakiurie, dysurie, douleur flanc ou costo vertébrale, ECBU positif avec uropathogène sensible à la cipro.
- Patients hospitalisés, randomisation ciprofloxacine 500 mg x2/j; 2 vs 4 semaines

Table I. *Characteristics of study patients*

	Ciprofloxacin 500 mg b.i.d.	
	2 weeks	4 weeks
Patients randomized	57	57
Patients valid for efficacy analysis	38	34
Median age (y)	61 (18–85)	62 (30–77)
History of UTI	20 (53)	14 (41)
Median initial temperature (°C)[a]	39.3 (38.0–40.7)	39.6 (38.0–41.4)
Median initial CRP (mg/l)	135 (15–420)	130 (9–370)
Median initial WBC ($\times 10^9$/l)	13.2 (4.0–25.6)	13.6 (5.1–29.8)
Pyuria	28/35 (80)	28/33 (85)
Positive blood culture	7 (18)	3 (9)
Flank pain and/or costovertebral angle tenderness	12 (32)	15 (44)
Prostatic tenderness	5/32 (16)	4/34 (12)
Signs of prostatic involvement[b]	34 (89)	31 (91)

Table III. *Bacteria isolated from pretreatment urine cultures*

	Ciprofloxacin 500 mg b.i.d.	
Organism	2 weeks ($n = 38$)	4 weeks ($n = 34$)
Escherichia coli[a]	32 (5)	27 (3)
Klebsiella spp.	1	3
Enterobacter spp.[a]	2 (2)	0
Enterococci	0	3
Group B streptococci	2	0
Staphylococcus epidermidis	1	1

Table V. *Cumulative clinical cure rate (%) and type of recurrent urinary tract infection (UTI)*

	Ciprofloxacin 500 mg b.i.d.	
	2 weeks ($n = 38$)	4 weeks ($n = 34$)
2 weeks post-treatment	$n = 38$	$n = 34$
Cure	35 (92)	33 (97)
Lower urinary tract symptoms with bacteriuria	2	0
Febrile UTI	1	0
Lower urinary tract symptoms without bacteriuria	0	1
After 3 months	$n = 36$	$n = 34$
Cure	30 (83)	30 (88)
Lower urinary tract symptoms with bacteriuria	3	2
Febrile UTI	2	0
Lower urinary tract symptoms without bacteriuria	1	2
After 6 months	$n = 33$	$n = 33$
Cure	25 (76)	29 (88)
Lower urinary tract symptoms with bacteriuria	3	2
Febrile UTI	4	0
Lower urinary tract symptoms without bacteriuria	1	2
After 12 months	$n = 32$	$n = 33$
Cure	23 (72)	27 (82)
Lower urinary tract symptoms with bacteriuria	3	2
Febrile UTI	5	1
Lower urinary tract symptoms without bacteriuria	1	3

Table IV. *Cumulative bacteriological cure rate (%)*

	Ciprofloxacin 500 mg b.i.d.	
	2 weeks ($n = 38$)	4 weeks ($n = 34$)
2 weeks post-treatment	$n = 38$	$n = 34$
Bacteriological cure	34 (89)	33 (97)
Relapse	2	1
Reinfection	2	0
After 3 months	$n = 36$	$n = 34$
Bacteriological cure	27 (75)	29 (85)
Relapse	3	4
Reinfection	6	1
After 6 months	$n = 33$	$n = 33$
Bacteriological cure	21 (64)	27 (82)
Relapse	4	4
Reinfection	7	2
Unspecified recurrence	1	0
After 12 months	$n = 32$	$n = 33$
Bacteriological cure	19 (59)	25 (76)
Relapse	4	4
Reinfection	8	4
Unspecified recurrence	1	0

Pas de différence significative guérison clinique ni guérison microbiologique 2 semaines ou 12 mois post ttt

Treatment duration of febrile urinary tract infection: a pragmatic randomized, double-blind placebo-controlled non inferiority trial in men and women NieuwKoop et al. BMC medicine 2017.

- Etude randomisée, double aveugle contre placebo, non infériorité
- Adultes, hommes et femmes, infection urinaire fébrile
- 7 jours vs 14 jours
- Ciprofloxacine 500 mg ou placebo 2 fois/jour la 2ème semaine.

- *Critère de jugement principal*:

guérison clinique 10-18 jours après traitement

- *Critères secondaires*:

guérison bactériologique, 10-18 jours après traitement et guérison clinique 70–84 jours post-traitement.

- Effectif nécessaire: 200/bras, marge non infériorité de 10%

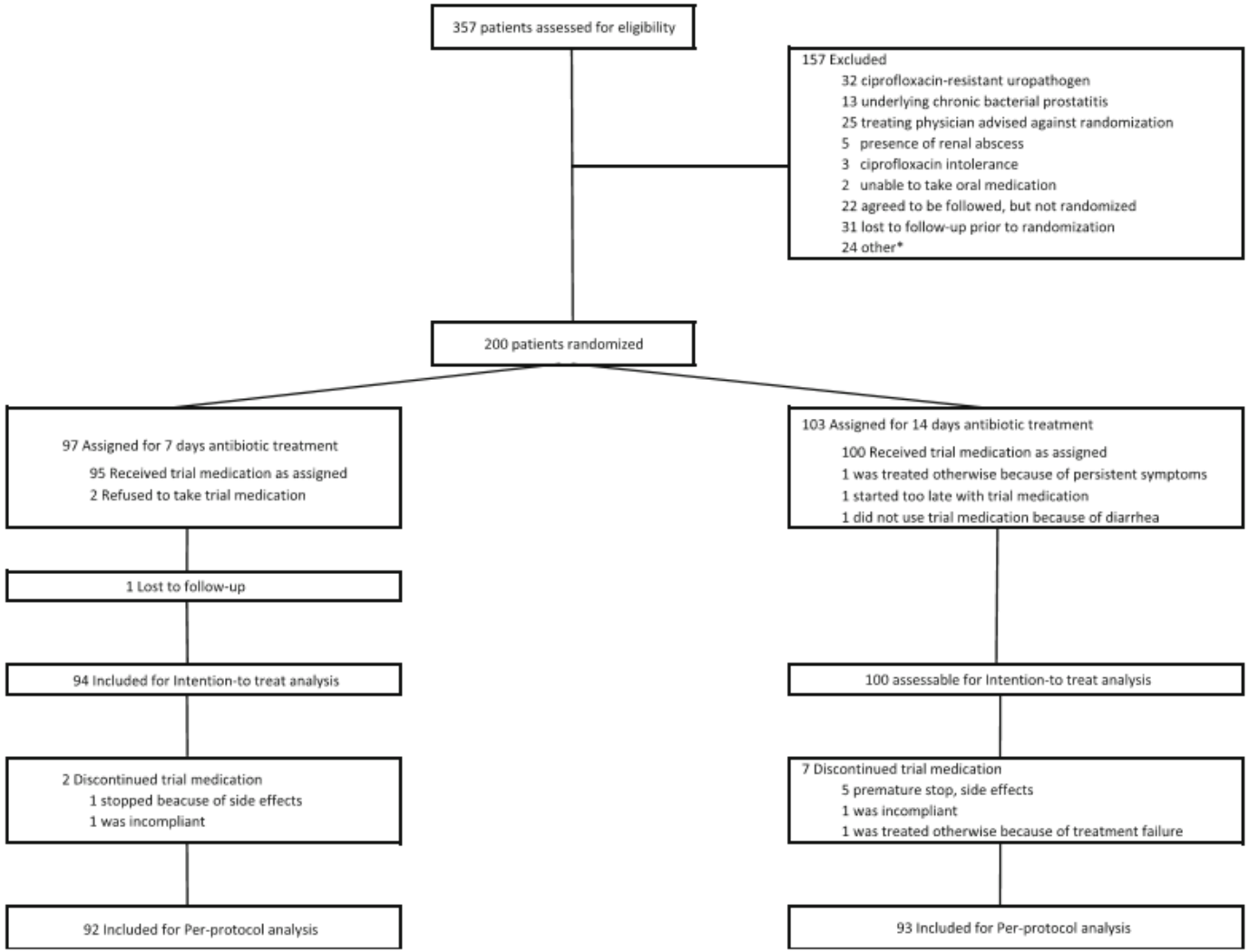


Fig. 1 Trial profile. * concurrent medical conditions (n = 16), logistic reasons (n = 5), abroad during treatment with study medication (n = 3)

Table 1 Baseline characteristics of 357 patients with febrile urinary tract infection

	Randomized (n = 200)		Not randomized (n = 157)	*P* value[c]
	Antibiotic treatment for 7 days (n = 97)	Antibiotic treatment for 14 days (n = 103)		
Age (years)	60 (48–72)	61 (40–73)	63 (49–75)	0.277
Male sex	44 (45%)	42 (41%)	58 (37%)	0.247
Urologic history				
Indwelling urinary catheter	3 (3%)	2 (2%)	12 (8%)	0.024
Urinary tract disorder[a]	28 (29%)	28 (27%)	52 (33%)	0.296
Recurrent UTI[b]	19 (20%)	19/100 (19%)	47/147 (32%)	0.007
Comorbidity				
Diabetes mellitus	12 (12%)	17 (17%)	25 (16%)	0.709
Malignancy	3 (3%)	5 (5%)	17 (11%)	0.012
Heart failure	12 (12%)	6 (6%)	19 (12%)	0.340
Cerebrovascular disease	5 (5%)	5 (5%)	13 (8%)	0.210
Chronic renal insufficiency	3 (3%)	2 (2%)	10 (6%)	0.070
COPD	10 (10%)	11 (11%)	23 (15%)	0.236
Immunocompromised	3 (3%)	8 (8%)	14 (9%)	0.209
Signs and symptoms at presentation				
Presentation at emergency department	59 (61%)	68 (66%)	145 (92%)	<0.001
Antibiotic pretreatment	23 (24%)	29 (28%)	56 (36%)	0.048
Fever duration, hours	30 (15–48)	36 (20–60)	48 (19–96)	0.081
Dysuria	82/95 (86%)	78/102 (77%)	102/145 (70%)	0.019
Flank pain	57/96 (59%)	67/102 (66%)	91/144 (63%)	0.914
Suprapubic pain	51/96 (53%)	48/100 (48%)	72/145 (50%)	0.876
Perineal pain	4/96 (4%)	7/98 (7%)	8/140 (6%)	0.986
Shaking chills within previous 24 hours	63/97 (65%)	60/101 (59%)	102/149 (70%)	0.256
Temperature > 38 °C	66 (68%)	76 (74%)	121 (77%)	0.226
Systolic blood pressure (mm Hg, mean, SD)	132 (19)	132 (22)	129 (20)	0.324
Pulse rate (beats/minute)	93 (17)	94 (19)	97 (19)	0.360
Outpatient treatment	45 (46%)	45 (44%)	23 (15%)	<0.001
Positive urine culture	69 (71%)	68 (66%)	107 (68%)	0.944
Positive blood culture	20/88 (23%)	15/98 (15%)	45/153 (29%)	0.012
Positive urine and/or blood culture	75 (77%)	70 (68%)	118 (75%)	0.571
Initial intravenous dose(s) of antibiotics	48 (50%)	55 (53%)	133 (85%)	< 0.001

Table 3 Clinical and bacteriologic outcomes in the intention-to-treat and per-protocol population

	Randomized		Difference (90% CI)	Non-inferiority test *P* value	Not randomized population
	Antibiotic treatment for 7 days	Antibiotic treatment for 14 days			
Intention-to-treat population	(n = 94)	(n = 99)			
Short-term efficacy[a]	(n = 94)	(n = 99)			(n = 119)
Clinical cure[b]	85 (90.4%)	94 (94.9%)	−4.5% (−10.7 to 1.7)	0.072	101 (84.9%)
Bacteriologic cure[c]	86/93 (92.5%)	89/92 (96.7%)	−4.3% (−9.7 to 1.2)	0.041	94/109 (86.2%)
Cumulative efficacy[d]	(n = 94)	(n = 94)			(n = 116)
Clinical cure[b]	87 (92.6%)	86 (91.5%)	1.1% (−5.5 to 7.6)	0.005	88 (75.9%)
Per-protocol population	(n = 92)	(n = 92)			
Short-term efficacy[a]	(n = 92)	(n = 92)			NA
Clinical cure[b]	83 (90.2%)	87 (94.6%)	−4.3% (−10.8 to 2.1)	0.073	
Bacteriologic cure[c]	84/91 (92.3%)	83/86 (96.5%)	−4.2% (−9.9 to 1.4)	0.045	
Cumulative efficacy[d]	(n = 92)	(n = 87)			
Clinical cure[b]	85 (92.4%)	79 (90.8%)	1.6% (−5.3 to 8.4)	0.005	

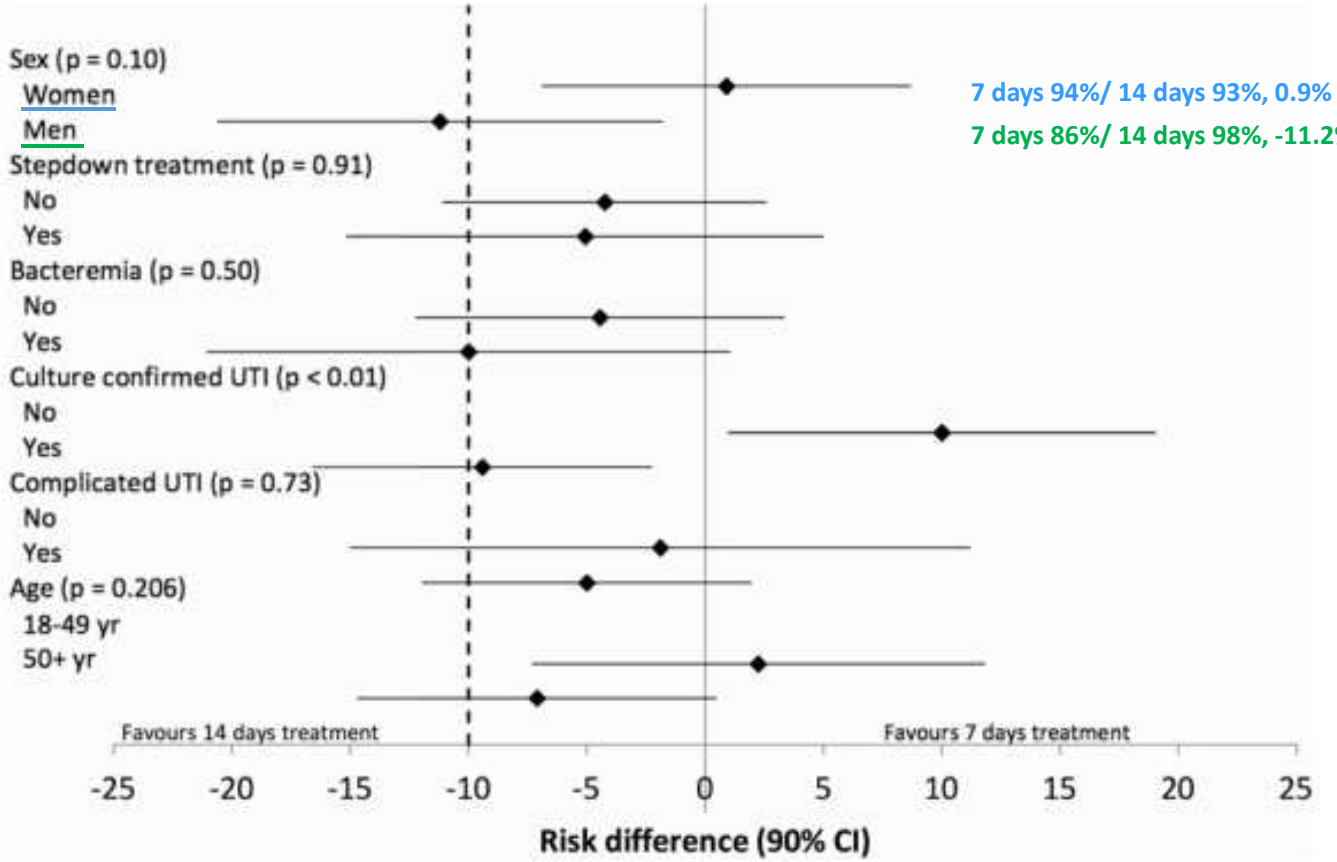
Data presented as number (%), unless otherwise indicated. NA: not applicable

[a]Short-term efficacy: endpoints assessed at 10- to 18-days post-treatment visit

[b]Clinical cure: being alive with absence of fever and resolution of UTI symptoms through post-treatment visit with no additional antimicrobial therapy for a relapse of UTI prescribed

[c]Bacteriologic cure: elimination of study entry uropathogen or pathogen growth < 10^4 CFU/mL (women) or <10^3 CFU/mL (men) combined with disappearance of leucocyturia

[d]Cumulative efficacy: endpoint assessed at 70- to 84-days post-treatment visit



7 days 94%/ 14 days 93%, 0.9% (90% CI, -6.9 to 8.7, p=0.011)

7 days 86%/ 14 days 98%, -11.2% (90% CI, -20.6 to -1.8, p=0.42)

Fig. 2 Difference in clinical cure rates (10- to 18-days post-treatment) of febrile UTI treated for 7 days versus 14 days in specific subgroups. Stepdown treatment implies initial empiric intravenous antibiotic treatment. *UTI* urinary tract infection; *CI* confidence interval. *P* values represent test for interaction. Data presented from intention to treat analysis

Antimicrobial for 7 or 14 days for febrile urinary tract infection in men: a multicenter noninferiority double blind placebo-controlled, randomized clinical trial.

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Soumis

Study design, methods

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

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

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

Eligibility criteria

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

Exclusion criteria

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

Endpoints

- The primary endpoint was treatment success, defined as a negative urine culture, the absence of fever and of subsequent antibiotic treatment between the end of treatment and 6 weeks after day 1.

- Secondary endpoints included recurrent urinary tract infection within weeks 6 and 12 after day 1, rectal carriage of antimicrobial-resistant *Enterobacterales* and drug-related events.

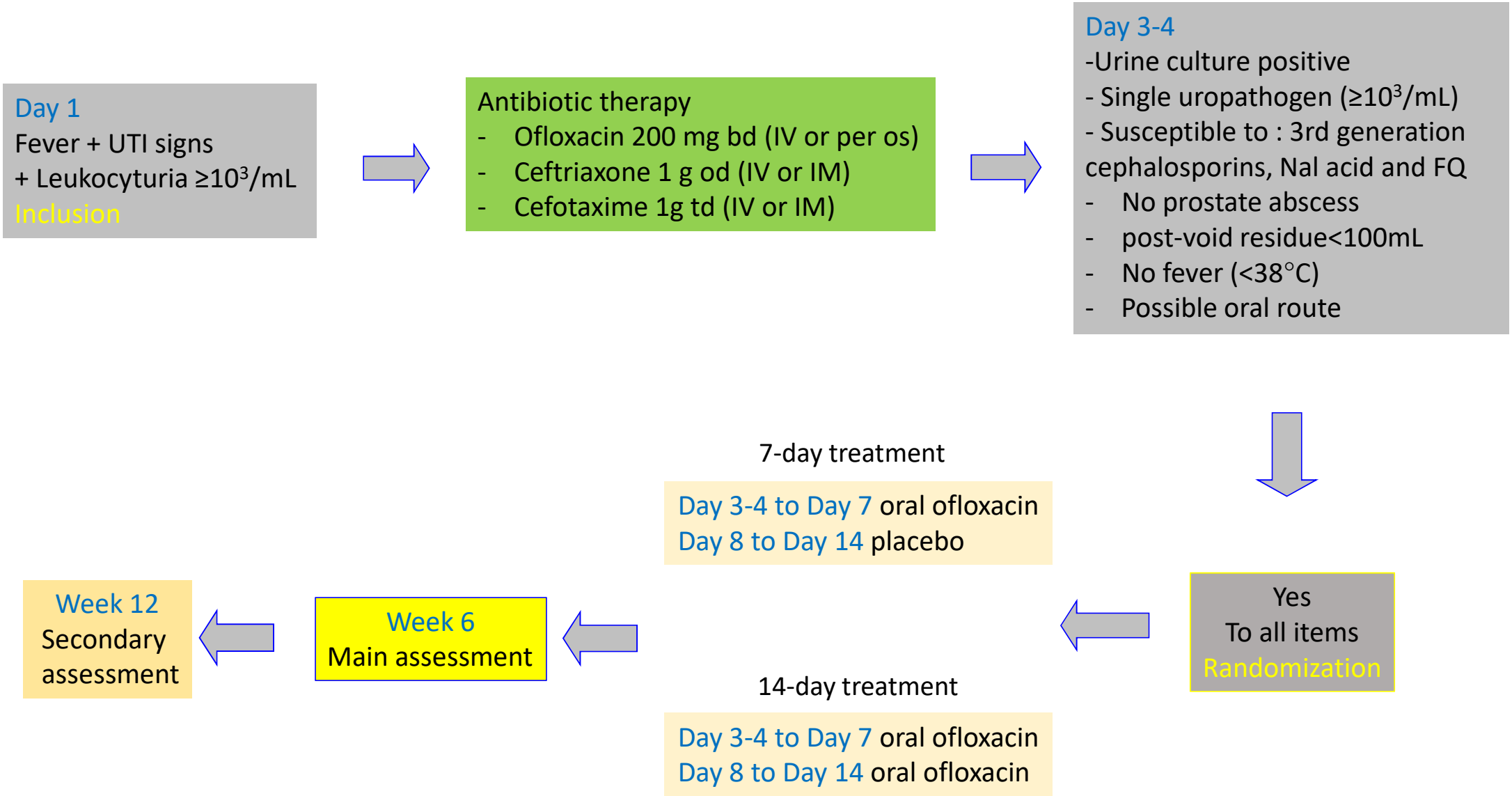
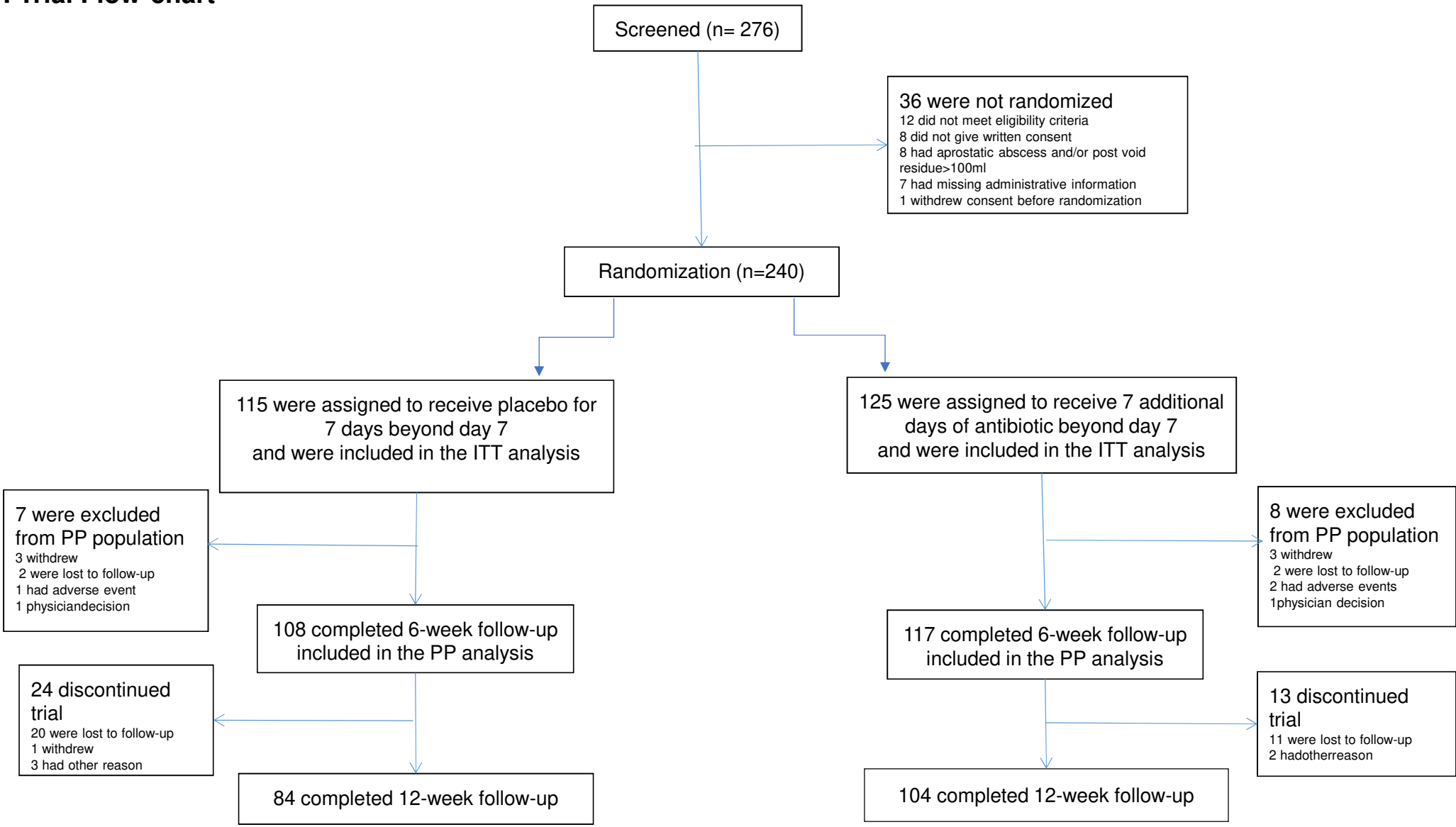

Day 1
Fever + UTI signs
+ Leukocyturia ≥10³/mL
Inclusion
Antibiotic therapy
- Ofloxacin 200 mg bd (IV or per os)
- Ceftriaxone 1 g od (IV or IM)
- Cefotaxime 1g td (IV or IM)
Day 3-4
-Urine culture positive
- Single uropathogen (≥10³/mL)
- Susceptible to : 3rd generation cephalosporins, Nal acid and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

Figure 1: Trial Flow-chart



	7-Day Therapy (N=115)	**14-Day Therapy (N=125)**
Median age (IQR)-yr	62.3 (49.9-73.2)	58.9 (49.3-72.5)
>50	86 (74.8)	91 (72.8)
Median BMI (IQR)- m/kg^2	24.8 (22.7-27.2)	25 (22.7-27.2)
Coexisting medical condition- no./total no. (%)		
Obesity (BMI 30 or higher)	20 (17.4)	10 (8.0)
Immunodepression	12 (10.4)	8 (6.4)
Diabetes	28 (24.3)	20 (16.0)
Chronic kidney disease	13 (11.3)	6 (4.8)
Median Charlson comorbidity index (IQR)	0 (0-1)	0 (0-1)
Urinary-tract-related comorbidities		
Any prior urologic history	38 (33.0)	38 (30.4)
Benign prostatic hypertrophy	28 (24.3)	23 (18.4)
Prostate resection	12 (10.4)	8 (6.4)
Prostate cancer	2 (1.7)	4 (3.2)
Prior urinary tract infection	11 (9.6)	15 (12.0)
Prostate calcifications- no./total no. (%)	23 (20.0)	24 (19.4)
Median prostate size volume(IQR) - cc	35 (25-57)	33 (25-45)
< 30 cc - no./total no. (%)	35 (33.7)	42 (38.5)
Clinical presentation - no./total no. (%)		
Median body temperature (IQR) - °C	38.3 (37.7-38.9)	38.2 (37.3-38.8)
Urinary burning	92 (80.0)	104 (83.2)
Dysuria	75 (65.2)	86 (68.8)
Frequency of urination	77 (66.9)	89 (71.2)
Urgencyof urination	48 (41.7)	54 (43.2)
Median blood WBC at diagnosis (IQR) – Giga/liter	13.4 (10.4-17.0)	12.7 (9.6-17.4)
N° of patients with positive blood cultures - no./total patients with blood cultures performed. (%)	15/96 (15.6)	18/100 (18)
Pathogen identified - no (%)		
Escherichia coli	105 (91.3)	97 (77.6)
Klebsiella spp.	5 (4.3)	14 (11.2)
Other pathogens:	5 (4.3)	14 (11.2)
Median WBC in urines (IQR), Giga/liter	1.0 (0.3-1.0)	1.0 (0.5-1.0)
Initial antibiotic treatment		
3rdGC	105 (91.3)	110 (88.0)
Ofloxacin	10 (8.7)	15 (12.0)
Median duration of 3rdGC treatment (IQR), days	2 (2-3)	2 (2-3)

Table 2. Difference in Risk of treatment success 6 weeks after the first day of Antibiotic Therapy (Primary Outcome) in the Intention-to-Treat and Per-Protocol Analyses.

Analysis	7-Day Therapy	14-Day Therapy	p	Risk Difference 95%CI
	No. of patients with event/total no.(%)			
Intention-to-treat	(N=115)	(N=125)		
Main analysis*	**64/115 (55.7)**	**97/125 (77.6)**		**-21.9 (-33.3 to -10.1)**
Microbiological success	91 (79.1)	117 (93.6)	0.001	
Clinical success	110 (95.6)	125 (100)	0.02	
No new antibiotic after the end of treatment	93 (82.6)	116 (92.8)	0.007	
No missing data	99 (86.1)	111 (88.8)	0.56	
Per-Protocol	(N=108)	(N=117)		
Main analysis*	**64/108 (59.3)**	**96/117 (82.1)**		**-22.8 (-34.2 to -11.0)**

* Missing outcomes for patients who were lost to follow-up were considered as failures

Table 3. Predictive factors of treatment success

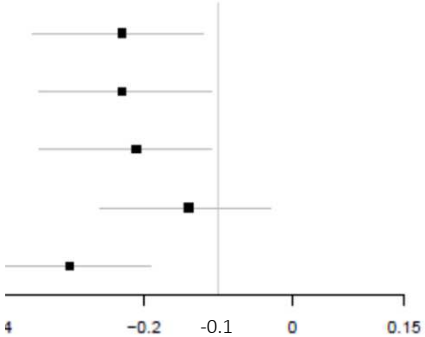
	No. treatment success/ TOTAL	Univariate analysis OR treatment success (95%CI)	Multivariate analysis OR treatment success (95%CI)	Multivariate analysis p-value
	161/240 (67.1)			
Randomization group				
14-Day Therapy	97/125 (77.6)	1.0 (reference)		
7-Day Therapy	64/115 (55.6)	0.4 (0.2-0.6)	0.4 (0.2-0.7)	0.002
Age > 50 yr	109/177 (61.6)	0.3 (0.2-0.7)	0.4 (0.2-0.9)	0.023
Coexisting medical condition- no./total no. (%)				
Diabetes	25/48(52.1)	0.5 (0.2-0.9)	0.9 (0.3-2.2)	0.78
Obesity (BMI 30 or higher)	15/30 (50.0)	0.4 (0.2-0.9)	0.7 (0.3-1.6)	0.35
Charlson comorbidity index >0	50/89 (56.2)	0.5 (0.2-0.8)	0.8 (0.3-1.7)	0.49
Urinary-tract-related comorbidities				
Any urologic history	45/76 (59.2)	0.6 (0.3-1.1)	1.3 (0.4-3.8)	0.67
Prostatic hypertrophy	26/51 (51.0)	0.4 (0.2-0.8)	0.5 (0.2-1.7)	0.27
Prostate calcifications	30/47 (63.8)	0.8 (0.4-1.6)		
Prostate size >30g	90/136 (66.2)	0.9 (0.5-1.6)		
Clinical presentation				
Fever	98/145 (67.6)	1.1 (0.6-1.8)		
Urinary burning	134/196 (68.4)	1.4 (0.7-2.8)		
Dysuria	109/161 (67.7)	1.1 (0.6-1.9)		
Frequencyof urination	119/166 (71.7)	1.9 (1.1-3.4)		
Urgencyof urination	74/102 (72.5)	1.5 (0.9-2.7)		
WBC at diagnosis > 1 Giga/L	122/181 (67.4)	1.1 (0.6-2.0)		
Patients with positive blood culture	20/33 (60.6)	0.7 (0.3-1.6)		
Pathogen identified - no./total no. (%)				
Escherichia coli	135/202 (66.8)	0.9 (0.4-2.0)		
Other pathogens	26/38 (68.4)	1.0 (reference)		
WBC in urines >1 Giga/L	83/131 (63.3)	0.7 (0.4-1.2)		
Initial antibiotic treatment				
3rdGC	143/215 (66.5)	0.8 (0.3-1.9)		

Table S1. Sensitivity analysis, according to data from lost to follow-up patients status

Analysis	7-Day Therapy	14-Day Therapy	Risk Difference, 95%CI
	No. of patients with event/total no. (%)		
Intention-to-treat	(N=115)	(N=125)	
Data from patients who were lost to follow-up were removed	64/99 (64.6)	97/111 (87.4)	-22.7 (-34.0 to -11.4)
Data from patients who were lost to follow-up were considered as successes	80/115 (69.6)	111/125 (88.8)	-19.2 (-29.4 to -09.2)
Data from patients who were lost to follow-up were considered as successes if 7-Day treatment and failures if 14-Day treatment	80/115 (69.6)	97/125 (77.6)	-8.0 (-19.2 to +03.1)
Data from patients who were lost to follow-up were considered as successes if 14-Day treatment and failures if 7-Day treatment	64/115 (55.7)	111/125 (88.8)	-33.1 (-43.6 to -22.3)
Per-Protocol	(N=108)	(N=117)	
Data from patients who were lost to follow-up were removed	64/97 (66.0)	94/108 (87.0)	-21.0 (-32.4 to -9.6)
Data from patients who were lost to follow-up were considered as successes	79/112 (70.5)	108/122 (88.5)	-18.0 (-28.3 to -7.8)
Data from patients who were lost to follow-up were considered as successes if 7-Day treatment and failures if 14-Day treatment	79/112 (70.5)	94/122 (77.0)	-6.5 (-17.8 to 4.8)
Data from patients who were lost to follow-up were considered as successes if 14-Day treatment and failures if 7-Day treatment	64/112 (57.1)	108/122	-31.4 (-42.0 to -20.4)

Sensitivity analysis

Subset	Pts	Cure W6 (14 days)	Cure W6 (7 days)	Diff. In the percentage of cure (7 day – 14 day)
Pts evaluated	208	96	64	−0.23[−0.35;−0.12]
A	225	96	64	−0.23[−0.34;−0.11]
B	225	104	73	−0.21[−0.34;−0.11]
C	225	96	73	−0.14[−0.26;−0.03]
D	225	104	64	−0.3[−0.4;−0.19]



A: Missing data= failure
B: Missing data= cure
C: Missing data= 14-day arm/failure and 7-day arm/cure
D: Missing data= 14-day arm/cure and 7-day arm/failure

Missing data 14 day-arm 14.4% 7 day-arm 25%

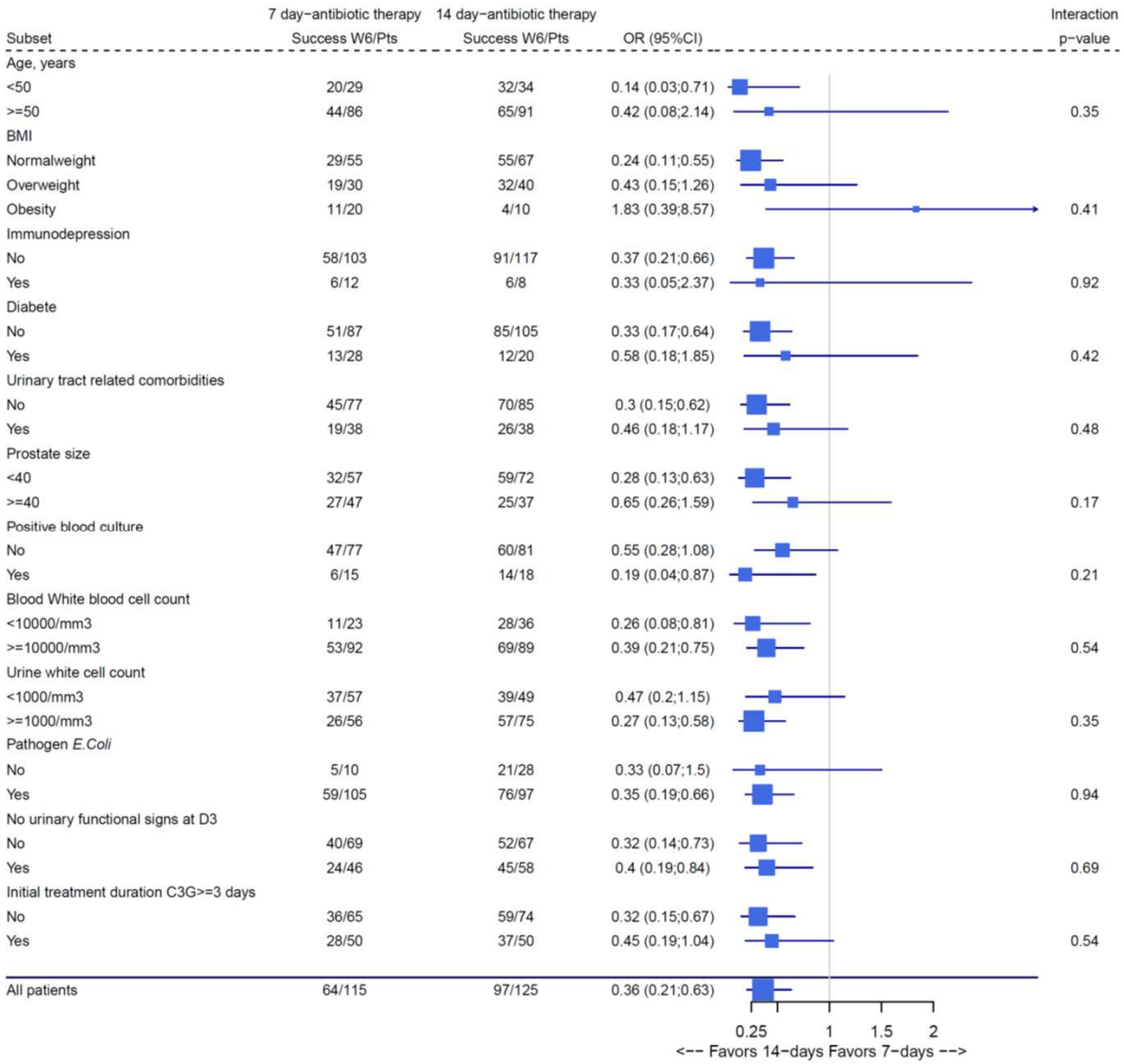
Table S2. Adverse events (AE)reported during antibiotic therapy

Patient	AE	Grade	Treatment related	Discontinuation
7-Day Therapy (N=115)				
Number 1	Osteoarticular pain	3	Probable	Yes
Number 2	Skin rash	1	Not related	No
Number 3	Diarrhea	2	Certain	No
Number 4	Osteoarticular pain	1	Unknown	No
14-Day Therapy (N=125)				
Number 5	Diarrhea	1	Probable	No
Number 6	Diarrhea	1	Possible	No
Number 7	Skin rash	1	Not related	No
Number 8	Skin rash	1	Not related	No
Number 9	Skin rash	2	Possible	No
Number 10	Headache	1	Not related	No
Number 11	Osteoarticular pain	1	Not related	No
Number 12	Osteoarticular pain	3	Certain	Yes
Number 13	Osteoarticular pain	1	Unknown	No

Table S3. Fecal carriage of ofloxacin-resistant *Enterobacterales* (OFX-R-E) and extended spectrum beta lactamase-producing *Enterobacterales* (ESBL-E) at baseline and at week 6 and 12.

		7-DayTherapy (N=115)	14-Day-Therapy (N=125)	p-value
Baseline				
	OFX-R-E, no./total no. (%)	19/57 (33%)	11/63 (17%)	
	ESBL-E, no./total no. (%)	10/57 (18%)	4/63 (6%)	
Week 6				
	OFX-R-E, no./total no. (%)	28/57 (49%)	20/63 (32%)	0.063
	Persisting carriage, no	12	8	
	Acquisition, no	16	12	
	ESBL-E, no./total no. (%)	8/57 (14%)	5/63 (8%)	0.38
	Persisting carriage, no	4	2	
	Acquisition, no	4	3	
Week 12				
	OFX-R-E, no./total no. (%)	15/57 (26%)	22/63 (35%)	0.33
	Persisting carriage, no	10	7	
	Acquisition, no	5	15	
	ESBL-E, no./total no. (%)	6/57 (11%)	2/63 (3 %)	0.15
	Persisting carriage, no	4	1	
	Acquisition, no	2	1	

Figure 2.Forest Plot looking for treatment success by subset interactions



Au total

- Cystite non compliquée: 1 jour (voire moins…)
- Pyélonéphrite non compliquée: 7 jours (voire 5)
- Infection urinaire de l’homme non fébrile: 7 jours (voire 5)
- Infection urinaire de l’homme fébrile: pas 7 jours…