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Efficacy of 7 versus 14 days of antibiotic therapy in male with febrile urinary tract infection due to fluoroquinolone susceptible organisms. PROSTASHORT: a randomized clinical trial.

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Conflits d’interêt

Pas encore

Antibiotic therapy duration for UTIs

SPILF practice guidelines (MMI 2018)

- **Cystitis**: 1 day for fosfomycine
- **Acute pyelonephritis**: 7 days (5 days?) for fluoroquinolones and/or parenteral ß-lactams; 5 days for aminoglycosides
- **Male UTI**: 14 days for FQ and/or parenteral ß-lactams and/or co-trimoxazole; 21 days for other antibiotics and/or uncontrolled underlying uropathy

No distinction between febrile UTI or afebrile UTI

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

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 α = .05 and with 2-sided 95% CIs.

Drenkonja, JAMA 07/2021

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.

Is it possible to make shorter than 14 days for male **febrile** UTI?

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%.

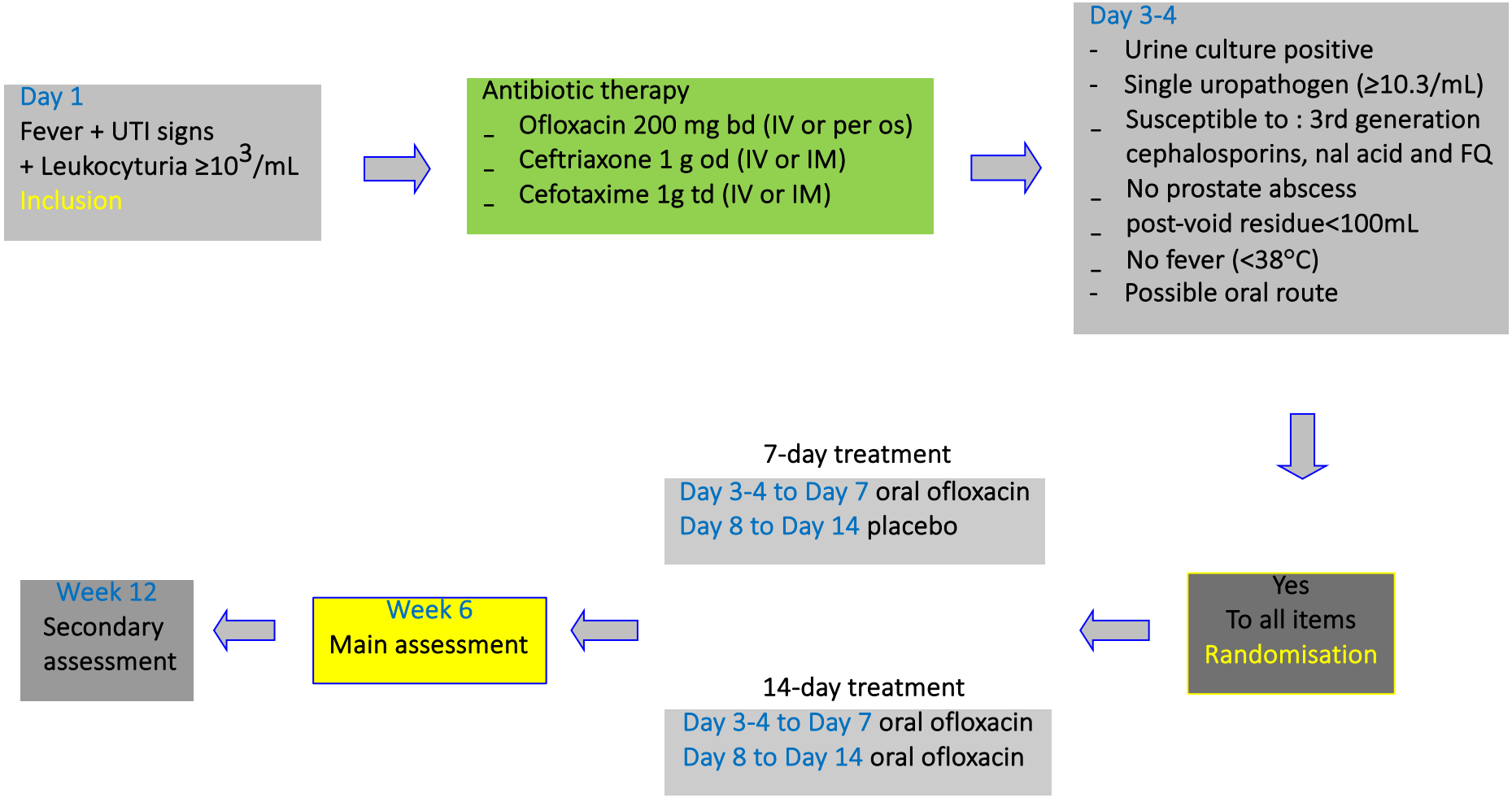
- **Missing data considered as failures**, pointwise and with 95% confidence interval calculated by the exact method.
- Sensitivity analysis for recoding missing data performed.

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


Day 1
Fever + UTI signs
+ Leukocyturia ≥10^3/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 (≥10.3/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
Randomisation
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

Randomization

- Randomization criteria: Day 3-4
  - positive urine culture with a single uropathogen ($\geq 10^3$ UFC/ml)
  - uropathogen susceptible to nalidixic acid, FQ and 3rd generation cephalosporins
  - possibility of oral treatment
  - temperature <38° C on ceftriaxone, cefotaxime or ofloxacin initiated empirically at diagnosis
  - No prostatic abscess and post-void residue > 100 ml on ultrasound

- Stratification by:
  - study site
  - urinary tract-related comorbidities
  - age (<50 years/≥50 years)

Primary end-point

Cure of the UTI 6 weeks after initiation of active antibiotic therapy and defined as follows:

- **Negative urine culture** (except contaminants *i.e.* alpha-hemolytic streptococci, *Lactobacillus*, *Corynebacteria*, *Gardnerella* or coagulase negative Staphylococci)
- **No fever** (T<38° or T ≥38° not related to UTI)
- **No antibiotic treatment** whose spectrum includes the causative uropathogen

Secondary end-points

- Adverse events related to antibiotic treatment
- Intestinal carriage of antimicrobial-resistant gram-negative bacilli
- Infectious and urological complications during treatment and follow-up

Failure criteria

Bacteriological failure

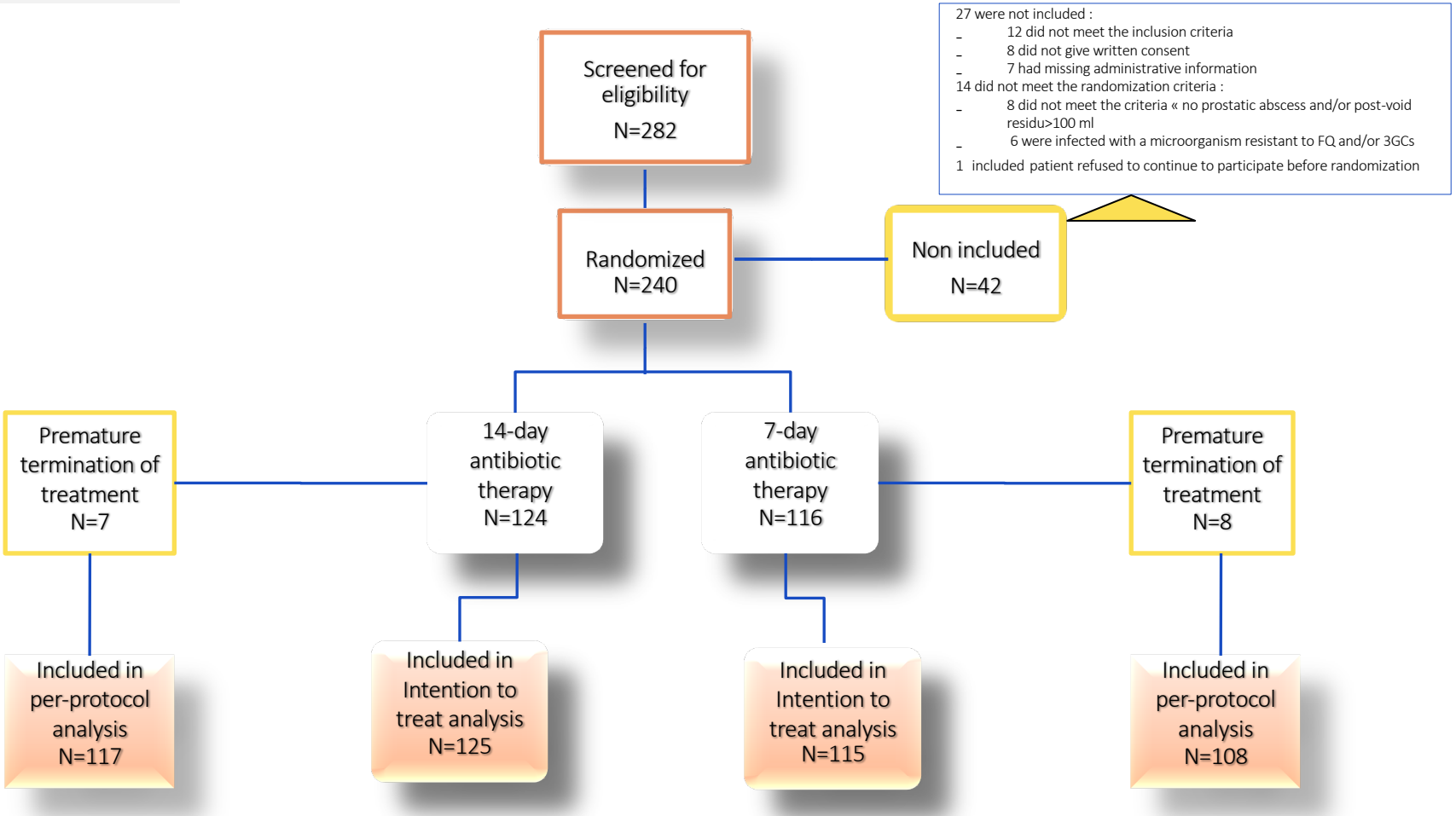
- Bacteriuria (presence of uropathogen) in the following weeks until week 6
  - *Relapse*: bacteriuria due to the same uropathogen
  - *Re-infection*: bacteriuria with bacteria different from the initial bacteria.

- Taking antimicrobials active against the germ responsible for the acute prostatitis, between the end of treatment and week 6 (even if the indication for the antibiotic therapy is not uro-nephrological).

Clinical failure

- Fever (T≥ 38° C) with or without clinical signs of UTI and no obvious cause other than urological

Flow-chart


Screened for eligibility
N=282
27 were not included :
- 12 did not meet the inclusion criteria
- 8 did not give written consent
- 7 had missing administrative information
14 did not meet the randomization criteria :
- 8 did not meet the criteria « no prostatic abscess and/or post-void residu>100 ml
- 6 were infected with a microorganism resistant to FQ and/or 3GCs
1 included patient refused to continue to participate before randomization
Randomized
N=240
Non included
N=42
Premature termination of treatment
N=7
14-day antibiotic therapy
N=124
7-day antibiotic therapy
N=116
Premature termination of treatment
N=8
Included in per-protocol analysis
N=117
Included in Intention to treat analysis
N=125
Included in Intention to treat analysis
N=115
Included in per-protocol analysis
N=108

Baseline characteristics of the study population

	14-day antibiotic therapy N=125	7-day antibiotic therapy N=115	Total N=240
Age, y	58.9 [49.3;72.5]	62.3 |49.9;73.2]	60.4 [49.4;72.9]
Age≥50 y	91 (72.8)	86 (74.8)	177 (73.8)
Body Mass Index	25 [22.7;27.2]	24.8 [22.7;27.2]	24.8 [22.6;27.8]
Obesity (BMI>30)	10 (8.5)	20 (19)	30 (13.5)
Comorbidities			
Immunodepression	8 (6.4)	12 (10.4)	20 (8.3)
Diabetes mellitus	20 (16)	28 (24.3)	48 (20)
Charlson score	0 [0;1]	0 [0;1.5]	0 [0;1]
Urologic history			
Any prior urinary tract infection	9 (7.2)	1 (0.9)	10 (4.2)
Benign prostate hypertrophy	23 (18.4)	28 (24.3)	51 (21.3)
Prostate resection	8 (6.4)	12 (10.4)	20 (8.3)
Other	8 (6.5)	7 (6.1)	15 (6.3)
Prostate calcifications	24 (19.4)	23 (20)	47 (19.7)
Prostate size, g	33 [25;45]	35 [25;57]	35 [25;52]
Prostate size <30 g	42 (38.5)	35 (33.7)	77 (36.2)

Baseline urinary tract infection characterisics

	14-day antibiotic therapy N=125	7-day antibiotic therapy N=115	Total N=240
Temperature, ° C	38.2[37.3;38.8]	38.3[37.7;38.9]	38.3[37.4;38.8]
Most common symptoms			
Urinary burning	104 (83%)	90 (80%)	194 (81%)
Urgency	54 (43%)	49 (43%)	103 (43%)
Frequency	89 (71%)	77 (67%)	166 (69%)
Dysuria	86 (69%)	75 (65%)	161 (67%)
Suprapubic, perineal, uretral pain	72 (58%)	75 (65%)	147 (61%)
Urine analysis			
White cell count , /mm^3	1000 [507;1000]	1000 [280;1000]	1000 [423;1000]
Organism isolated			
E.coli	97 (77.6)	105 (91.3)	202 (84.2)
Klebsiella spp.	14 (11.2)	5 (4.3)	19 (7.9)
Other	14 (11.2)	5 (4.3)	19 (7.9)
Positive blood culture	18 (18.2)	15 (16.3)	33 (17.3)
Blood white cell count , /mm^3	13100 [10000;17240]	13400 [10360;17020]	13100 [10000;17240]
Initial antibiotic treatment with 3rd generation cephalosporin	110 (88 %)	105 (91.3 %)	215 (89.6 %)

Primary outcome

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

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

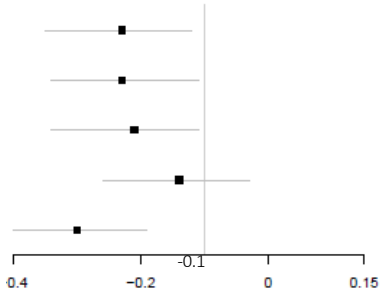
→ deleterious effect of 7-day vs 14-day antibiotic therapy

Failure causes

	14-day antibiotic therapy N=117	7-day antibiotic therapy N=108
Failures at Week 6	**21 (18%)**	**44 (41%)**
Clinical failure	0	5 (7.8%)
Bacteriological failure	8 (8.2%)	24 (37.5%)
Active antimicrobials taking	9 (9.3%)	22 (34.4%)
Missing data	14 (14.4%)	16 (25%)

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

Risk factors for failure

			Univariate models		Multivariate models	
Parameters/Values	N tot	N failure	OR (95%CI)	p	OR (95%CI)	p
Arm						
14-day antibiotic therapy	125	28	1			
7 day-antibiotic therapy	115	51	2.76 (1.58-4.83)	0.0004	2.77 (1.49-5.16)	0.001
Age>=50 yr						
No	63	11	1			
Yes	177	68	2.95 (1.44-6.04)	0.003	2.89 (1.19-6.98)	0.02
BMI>=30						
No	192	57	1			
Yes	30	15	2.37 (1.09-5.17)	0.030	1.66 (0.70-3.98)	0.25
Diabetes						
No	192	56	1			
Yes	48	23	2.23 (1.17-4.26)	0.015	0.96 (0.36-2.54)	0.94
Immunodepression						
No	220	71	1			
Yes	20	8	1.40 (0.55-3.58)	0.48		
Charlson score						
0	151	40	1			
1	42	21	2.77 (1.37-5.61)	0.005	2.53 (0.92-6.97)	0.07
>1	47	18	1.72 (0.86-3.44)	0.12	0.90 (0.36-2.24)	0.81
Urologic history						
No	162	47	1			
Yes	76	31	1.69 (0.95-2.98)	0.072	1.29 (0.67-2.48)	0.45

Parameters/Values	N tot	N failure	Univariate models OR (95%CI)	p	Multivariate models OR (95%CI)	p
Prostate size>=30g						
No	77	24	1			
Yes	136	46	1.13 (0.62-2.05)	0.69		
Prostate calcification						
No	192	62	1			
Yes	47	17	1.19 (0.61-2.32)	0.61		
Fever						
No	95	32	1			
Yes	145	47	0.94 (0.55-1.64)	0.84		
Positive blood culture						
No	158	51	1			
Yes	33	13	1.36 (0.63-2.96)	0.43		
Blood white blood cell count>10000/mm3						
No	59	20	1			
Yes	181	59	0.94 (0.51-1.76)	0.85		
Urine white cell count>1000/mm3						
No	106	30	1			
Yes	131	48	1.47 (0.84-2.54)	0.18		
Uropathogen identified *Ecoli*						
No	38	12	1			
Yes	202	67	1.08 (0.51-2.26)	0.85		
No functional signs (including fever) at D3						
No	136	44	1			
Yes	104	35	1.06 (0.62-1.82)	0.83		
Inital third generation cephalosorin treatment duration	239	79	1.05 (0.76-1.45)	0.77		
Inital third generation cephalosorin treatment during 3 days minimum						
No	139	44	1			
Yes	100	35	1.16 (0.67-2.00)	0.59		

Adverse events related to antimicrobials

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

To conclude

- 7 days of antimicrobials was not inferior to 14 days to cure males with febrile UTI (per protocol and ITT analysis), 6 weeks after treatment initiation.
- 7 day-duration may even be deleterious as compared to 14 day-duration
- Risk factors for failure were shorter (7 days) duration of antibiotic treatment and age> 50 years, in multivariate analysis
- Many missing data, but sensitivity analysis corroborates results
- Rectal with resistant bacteria carriage to be further analyzed

Thanks to the 24 participating centers

	N (%)
Saint-Louis, Paris	76 (27%)
Beaujon, Clichy	34 (12%)
Kremlin Bicetre, Villejuif	29 (10%)
Tours	23 (8%)
Clamart	14 (5%)
Perpignan	13 (5%)
Lariboisière, Paris	11 (4%)
Other (17 centers)☼	84 (29%), mean 4.2 patients/center

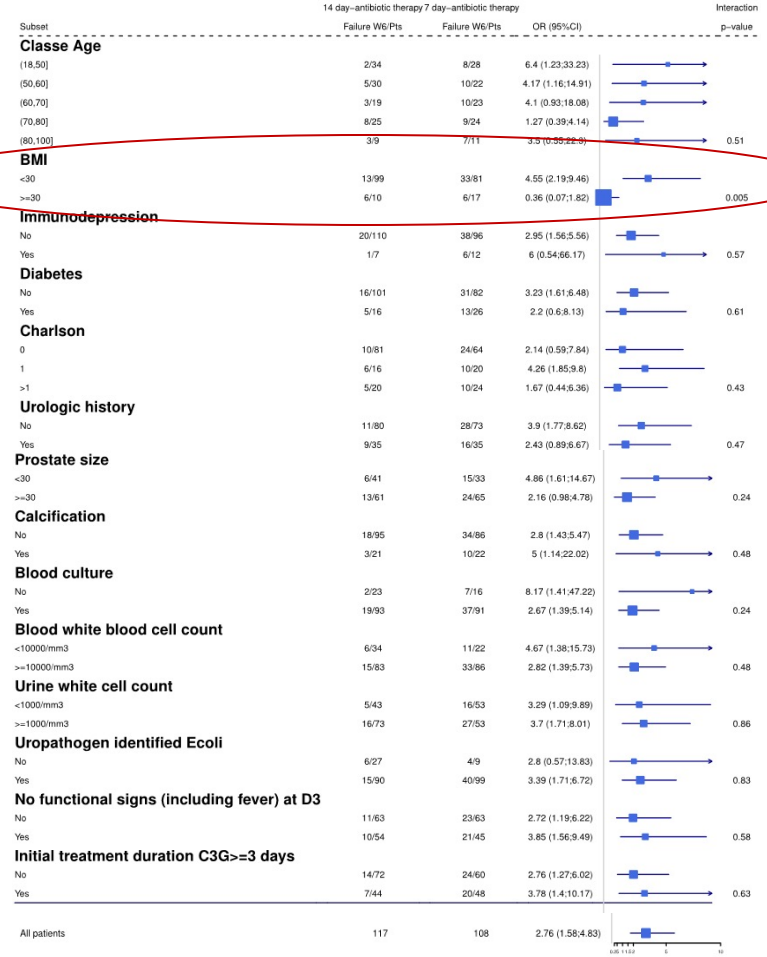
☼: Annecy, CHI Créteil, Cochin, Colmar, Diaconesses, Grenoble, H. Mondor, J.Verdier, Lille, Necker, Pau , Quimper, Rouen, La Roche sur Yon, St-Antoine, Sud Francilien, Villefranche sur Saone.

Scientific commitee

- Professeur Louis BERNARD (Maladies Infectieuses, Tours)
- Dr Franck BRUYERE (Urologie, Tours)
- Dr Jean-Paul FONTAINE (Urgences, Paris)
- Docteur Manuel ETIENNE (Maladies Infectieuses, Rouen)
- Docteur Matthieu LAFAURIE (Maladies Infectieuses, Paris)
- Professeur Agnès LEFORT (Médecine Interne, Clichy)
- Professeur Jean-Michel MOLINA (Maladies Infectieuses, Paris)
- Professeur Jean-Louis PONS (Microbiologie-Bactériologie, Paris)
- Professeur Albert SOTTO (Maladies Infectieuses, Nîmes)
- Professeur Pierre TATTEVIN (Maladies Infectieuses, Rennes)

Merci de votre attention

Effects of randomization on the risk of failure



Subset	14 day−antibiotic therapy Failure W6/Pts	7 day−antibiotic therapy Failure W6/Pts	OR (95%CI)	Interaction p−value
Classe Age				
(18,50]	2/34	8/28	6.4 (1.23;33.23)	
(50,60]	5/30	10/22	4.17 (1.16;14.91)	
(60,70]	3/19	10/23	4.1 (0.93;18.08)	
(70,80]	8/25	9/24	1.27 (0.39;4.14)	
(80,100]	3/9	7/11	3.5 (0.35;22.9)	0.51
BMI				
<30	13/99	33/81	4.55 (2.19;9.46)	
>=30	6/10	6/17	0.36 (0.07;1.82)	0.005
Immunodepression				
No	20/110	38/96	2.95 (1.56;5.56)	
Yes	1/7	6/12	6 (0.54;66.17)	0.57
Diabetes				
No	16/101	31/82	3.23 (1.61;6.48)	
Yes	5/16	13/26	2.2 (0.6;8.13)	0.61
Charlson				
0	10/81	24/64	2.14 (0.59;7.84)	
1	6/16	10/20	4.26 (1.85;9.8)	
>1	5/20	10/24	1.67 (0.44;6.36)	0.43
Urologic history				
No	11/80	28/73	3.9 (1.77;8.62)	
Yes	9/35	16/35	2.43 (0.89;6.67)	0.47
Prostate size				
<30	6/41	15/33	4.86 (1.61;14.67)	
>=30	13/61	24/65	2.16 (0.98;4.78)	0.24
Calcification				
No	18/95	34/86	2.8 (1.43;5.47)	
Yes	3/21	10/22	5 (1.14;22.02)	0.48
Blood culture				
No	2/23	7/16	8.17 (1.41;47.22)	
Yes	19/93	37/91	2.67 (1.39;5.14)	0.24
Blood white blood cell count				
<10000/mm3	6/34	11/22	4.67 (1.38;15.73)	
>=10000/mm3	15/83	33/86	2.82 (1.39;5.73)	0.48
Urine white cell count				
<1000/mm3	5/43	16/53	3.29 (1.09;9.89)	
>=1000/mm3	16/73	27/53	3.7 (1.71;8.01)	0.86
Uropathogen identified Ecoli				
No	6/27	4/9	2.8 (0.57;13.83)	
Yes	15/90	40/99	3.39 (1.71;6.72)	0.83
No functional signs (including fever) at D3				
No	11/63	23/63	2.72 (1.19;6.22)	
Yes	10/54	21/45	3.85 (1.56;9.49)	0.58
Initial treatment duration C3G>=3 days				
No	14/72	24/60	2.76 (1.27;6.02)	
Yes	7/44	20/48	3.78 (1.4;10.17)	0.63
All patients	117	108	2.76 (1.58;4.83)	

Outcome 14 weeks after initiation of active antibiotic therapy

	14-day antibiotic therapy (n=125)	7 day-antibiotic therapy (n=115)	Total (n=240)
Cure	59 (47%)	68 (59%)	127 (53%)
Causes of failure			
Microbiological failures	13 (10.4%)	28 (24.3%)	41 (17.1%)
Taking antibiotics active on the uropathogen	10 (8%)	22 (19.1%)	32 (13.3%)
Clinical failure	0	5 (4.3%)	5 (3.9%)
Missing data	39 (66%)	29 (43%)	68 (54%)