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FOsfomycin for E.coli Febrile urinary tract infections as Alternative Stepdown Treatment (FORECAST): Study protocol for a randomized controlled trial

Febrile UTI in women

- UTI with systemic symptoms (febrile UTI):
  - pyelonephritis, urosepsis
- UTIs account for approximately 5 to 7% of all cases of severe sepsis
- Second infectious reason for hospital admittance
- *E. coli:* major pathogen of community-acquired urinary tract infections (66%)

Geerlings, S. E. Clinical Presentations and Epidemiology of Urinary Tract Infections. Microbiol. Spectr. 4, (2016).

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Treatment Febrile UTI

- Total antibiotic duration 7-10
- Empirical antibiotic treatment
  - Oral ciprofloxacin
  - Intravenous antibiotics if expected ciprofloxacin resistance ≥ 10%
- Stepdown treatment
  - Oral ciprofloxacin, co-trimoxazole, amoxicillin or augmentin

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Challenges in stepdown treatment

- Enterobacteriaceae resistance to ciprofloxacin, co-trimoxazole, amoxicillin or augmentin
- Ciprofloxacin restrictive use
- No oral antibiotic option → intravenous antibiotic therapy

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Resistance in the Netherlands ‘15

Clinical isolates Antibiotic	E. coli (43%)	K. Pneumoniae (7%)	P. Mirabilis (7%)
Ciprofloxacin	13%	6%	9%
Co-trimoxazole	25%	13%	27%
Augmentin	21%	11%	24%

*Nethmap 2015

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Fosfomycin

- Phosphoenolpyruvate analogue, Streptomyces spp., produced synthetically
- Inhibiting bacterial cell wall (peptidoglycan) synthesis, dose-effect relationship unknown
- Good safety profile
- Fosfomycin-trometamol: Single dose treatment in women with uncomplicated UTI (Cure +- 90%)

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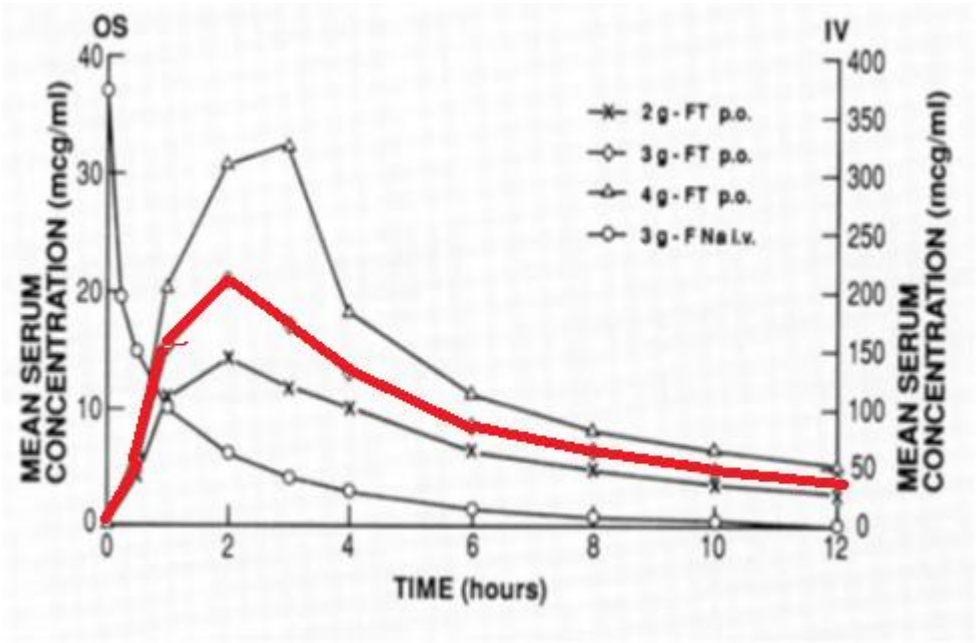
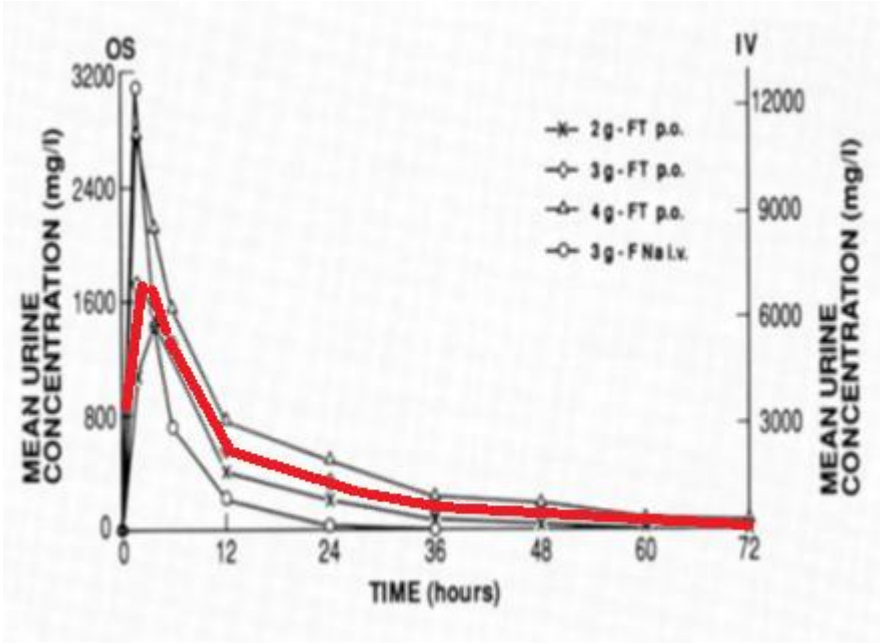
Surber, C. (2016). Product monograph of monurol, (version 4.0). Retrieved from http://www.paladin-labs.com/our_products/Monurol-Sachet-PM-En.pdf

Pharmacokinetic profile

Serum



Urine



*Bergan, T, Thorsteinsson SB, A. E. (1993). Pharmacokinetic Profile of Fosfomycin Trometamol. Chemo, 39, 297–301

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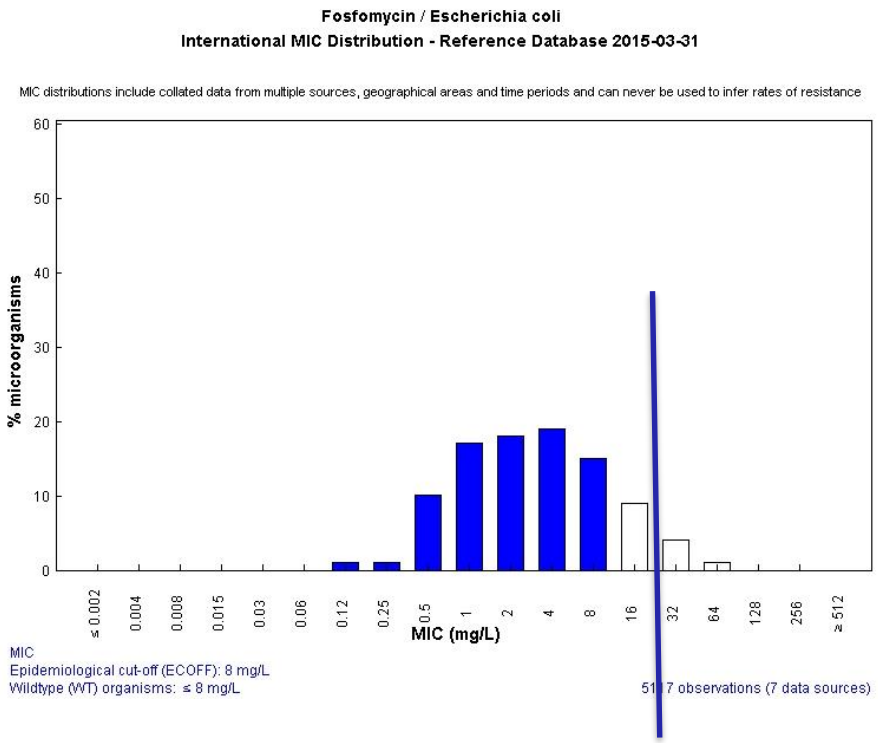
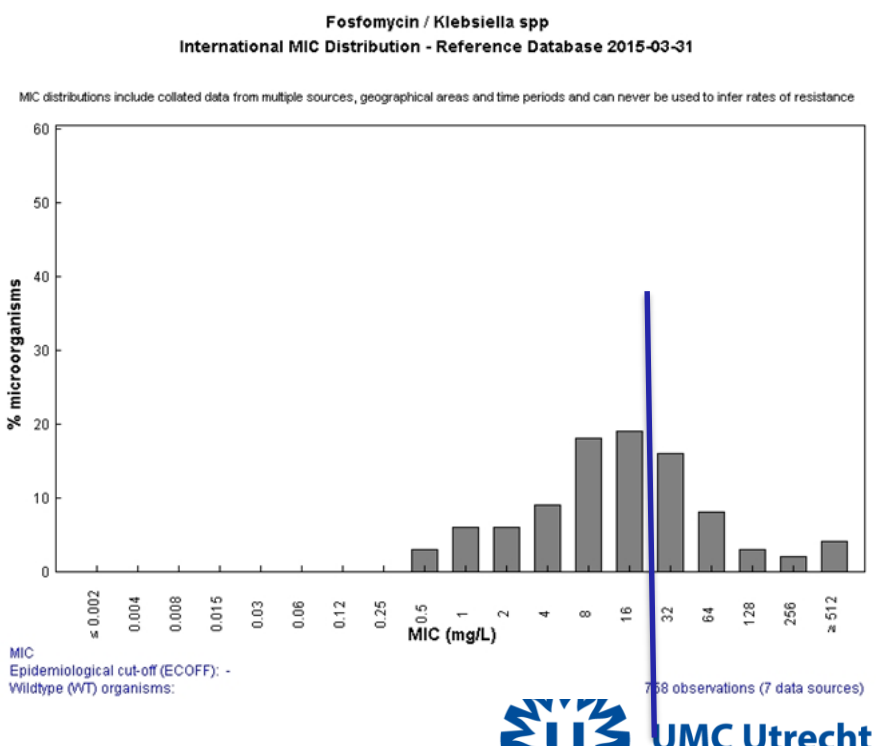
Resistance, following EUCAST





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*EUCAST EUCAST
E.coli: MIC S<32mg/l>R, CSLI R<64mg/L>R

Resistance in the Netherlands ‘15

Clinical isolates Antibiotic	E. coli (43%)	K. Pneumoniae (7%)	P. Mirabilis (7%)
Ciprofloxacine	13%	6%	9%
Co-trimoxazole	25%	13%	27%
Augmentin	21%	11%	24%
Fosfomycin	<1%	31%	16%

*Nethmap 2015

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Safety

- Little side effects
  -fosfomycin-trometamol (oral)
  -intravenous fosfomycin (24 gr/24 hour)

- Tolerability

- Interactions: metoclopramide

- Intoxication

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Clinical effectivity

Fosfomycin-trometamol	Trials	Effect
Cystitis	Meta-analysis RCT*	Non-inferior to nitrofurantoin/trimethoprim
Complicated UTI	Observational studies**	Moderate/high effectivity (70-90%)

*Falagas, M. E., Vouloumanou, E. K., Togias, A. G., Karadima, M., Kapaskelis, A. M., Rafailidis, P. I., & Athanasiou, S. (2010). Fosfomycin versus other antibiotics for the treatment of cystitis: A meta-analysis of randomized controlled trials. *Journal of Antimicrobial Chemotherapy*, *65*(9), 1862–1877. doi:10.1093/jac/dkq237

**Giancola, S. E., Mahoney, M. V., Hogan, M. D., Raux, B. R., McCoy, C., & Hirsch, E. B. (2017). Assessment of Fosfomycin for Complicated or Multidrug-Resistant Urinary Tract Infections: Patient Characteristics and Outcomes. *Chemotherapy*, 100–104. doi:10.1159/000449422

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The FORECAST trial:

Randomized controlled, multicentre, double-blind, double-dummy, non-inferior, investigator-initiated trial

To demonstrate non-inferiority of oral fosfomycin compared to oral ciprofloxacin as a step-down treatment for febrile urinary tract infection for the cumulative endpoint survival clinical cure (resolution of symptoms) 6-10 days post-treatment.

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Inclusion criteria

- Competent women (≥18 years)
- Hospitalised
- Adequate intravenous antibiotic therapy for ≥48 - ≤120 hours
- Candidate for safe iv to oral switch as judged by the attending physician

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Inclusion criteria

- Urine (≥10^4 CFU/ml) OR blood culture: *Escherichia coli* , ciprofloxacin S AND fosfomycin
- ≥ local symptom:
  - lower abdominal pain, low back pain, flank pain or costo-vertebral angle pain or tenderness on physical examination, dysuria, urinary urgency, urinary frequency, suprapubic/pelvic discomfort, macroscopic hematuria, new urinary incontinence or worsening of pre-existing incontinence)
- ≥forthcoming systemic symptoms:
  - Fever/low temperature (≥38.0 C° or <36 C°), rigors, delirium, hemodynamic instability as a result of sepsis requiring intravenous fluids, increase in CRP (> 30 mg/L) or leucocytes (> 12*10^9/L)
- FUTI as presumptive diagnosis and primary reason for hospitalization by attending physician

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Exclusion criteria

- Pregnant or nursing women
- Glomerular filtration rate < 30 ml/min/1,73 m3 or renal replacement therapy
- Concomitant systemic antibacterial treatment
- Ascertained or presumptive hypersensitivity to the active compounds and/or any excipient of the products or to any quinole
- Participation to any trial with an investigational product involved in the 30 days before the screening visit
- Specific comorbidity or diagnosis
- Patients with inadequate understanding of the study risks or its requirements or unwilling to plan a follow-up visit
- Contraindications/interactions for any of the active compounds or medication
- Every other laboratory result, clinical condition, disease or treatment that, in investigator's opinion, make the subject non suitable for the study

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Intervention

10 days of total antibiotic (iv+oral) treatment, of which 5-8 days of study medication

Duration (hours) ↓	Study arm		Control arm	
12 H	Sachet fosfomycin-trometamol 3g	Tablet placebo	Sachet placebo	Tablet ciprofloxacin 500mg
12 H		Tablet placebo		Tablet ciprofloxacin 500mg

Primary endpoint

The cumulative endpoint survival and clinical cure (resolution of symptoms) 6-10 days post-treatment

Definition:

Alive with resolution of local and systemic-related AF-UTI symptoms present at the day of admission, without additional antibiotic therapy

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Expected endpoint, RCT's

Trial	Population	Intervention	Bacteremia	Cure rate
Sandberg 2012	Women with community-acquired pyelonephritis	Oral ciprofloxacin 2d500mg 7 vs 14 days	27%	96 vs 97%
Nieuwkoop 2017	Women with community acquired pyelonephritis	Ciprofloxacin 2d500mg 7 vs 14 days	19%	92 vs. 94%

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Sample size calculation

- Expected endpoint: cure rate of 92,5% in ciprofloxacin group vs 92,5% in fosfomycin group
- Non-inferiority margin: 10%
- Power (ß-1): 80%
- Alpha (type I error), two-sided: 5%
- Sample size needed: 109 per group
- Accounting for 10% of lost participants = 120 per group = N=240

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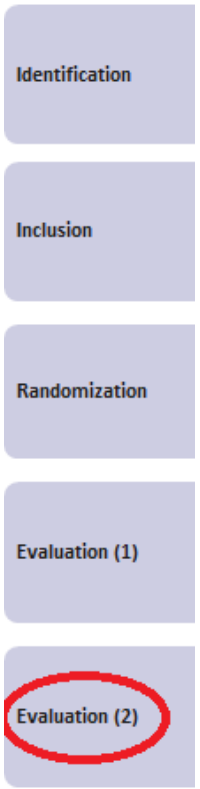
Secondary endpoints	Time (days)
Microbiological cure (y/n)	6-10
Fosfomycin resistance (y/n), ciprofloxacin resistance (y/n), ESBL-producing bacteria (y/n) in urine culture	6-10
Early study medication discontinuation	6-10
Survival and clinical cure	30-35
Mortality (y/n)	30-35
ICU admissions	30-35
Readmissions (y/n)	30-35
Relapses (y/n)	30-35
Reinfections (y/n)	30-35
Additional antibiotic use (y/n)	30-35
Hospitalization (days)*	30-35
Study protocol related adverse events (y/n)	30-35

*Except earlier scheduled admissions



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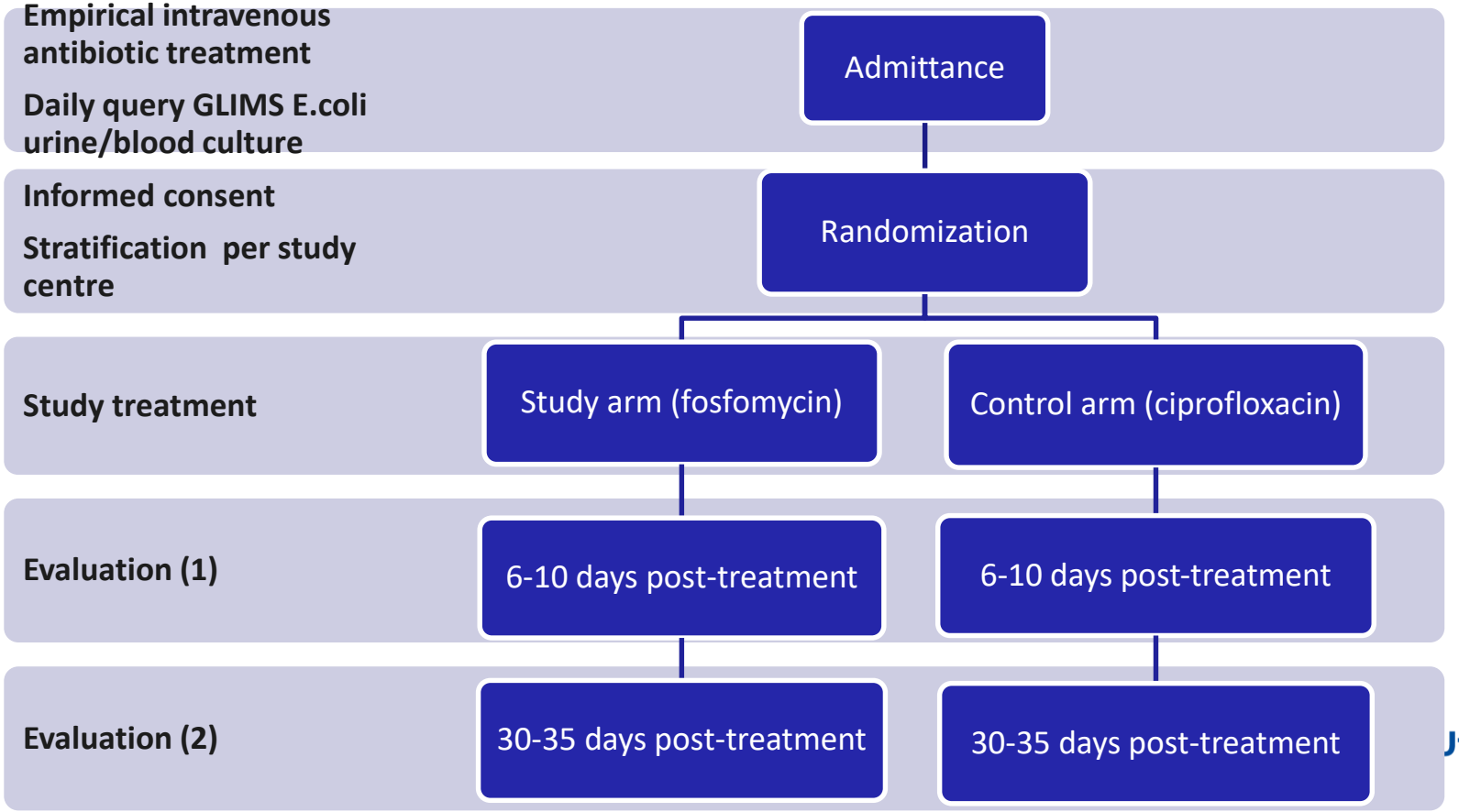
Logistics



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