



AIDA Work Package 2 protocol v7, 3 November 2014

CLINICAL TRIAL PROTOCOL

Randomised clinical trial comparing fosfomycin vs. nitrofurantoin for treatment of uncomplicated lower urinary tract infection in female adults at increased risk of antibiotic-resistant bacterial infection

Short title: Study comparing nitrofurantoin to fosfomycin for acute urinary tract infection in women

Funding source

European Commission, Bruxelles (B)

Grant agreement no: 278348

THEME: HEALTH.2011.2.3.1-1 [Investigator-driven clinical trials of off-patent antibiotics]

Project acronym: AIDA [*"Preserving old antibiotics for the future: assessment of clinical efficacy by a pharmacokinetic/pharmacodynamic approach to optimize effectiveness and reduce resistance for off-patent antibiotics"*]

Principal Investigator

Prof Dr Stephan Harbarth

Service Prévention et Contrôle de l'Infection

Hôpitaux Universitaires de Genève

Rue Gabrielle-Perret-Gentil 4

CH-1211 Genève 14

Fax: +41-22-3723987; Tel.: +41-22-3723357

Email: stephan.harbarth@hcuge.ch

Co-Investigators

Dr. Angela Huttner, Switzerland

Prof. Maciek Godycki-Cwirko, Poland

Prof. Leonard Leibovici, Israel

Prof. Johan Mouton, Netherlands

Study Products

Nitrofurantoin and fosfomycin (oral antimicrobial agents)



AIDA Work Package 2 protocol v7, 3 November 2014

CONFIDENTIALITY STATEMENT

The information contained in this document is the property of the Infection Control Program, Geneva University Hospitals, and is therefore provided to you in confidence as a potential reviewer or investigator. It is understood that this information will not be disclosed to others without written authorization from the Principal Investigator, except to the extent necessary to obtain consent from those persons to whom the Investigational Product may be administered.



AIDA Work Package 2 protocol v7, 3 November 2014

SIGNATURE PAGE

I, the undersigned, have reviewed this Protocol, including Appendices. I will conduct the clinical study as described and I will adhere to GCP/ICH and all the ethical and regulatory considerations stated (OClin and LPT_h).

Prof. Stephan Harbarth
Principal Investigator & Sponsor

Signature

3 November 2014
Date

Associate Professor
Title

Service Prévention et Contrôle de l'Infection
Hôpitaux Universitaires de Genève
Rue Gabrielle-Perret-Gentil 4
CH-1211 Genève 14
Institution and address

+41.22.372.33.57
Phone number

TABLE OF CONTENTS

Signature Page	3
SYNOPSIS	6
Study Flowchart	7
Abbreviations and definitions	8
1. JUSTIFICATION AND OBJECTIVES	9
1.1. Background information	9
1.2. Study rationale and hypothesis	12
1.3. Study settings	13
2. STUDY OBJECTIVES	13
3. STUDY DESIGN	13
3.1. Overall description	13
3.2. Study schedule	14
3.3. Randomisation	15
3.4. Study duration per patient	15
3.5. Data collected in the CRF	16
3.6. Trial time frame	16
3.7. Premature discontinuation of the study	17
3.8. Data monitoring board	17
3.9. Study supervision and expertise	17
3.10. Independent monitoring	17
4. STUDY POPULATION	17
4.1. Selection and recruitment procedures	17
4.2. Communication with clinicians involved in the care of trial participants	18
4.3. Patient inclusion criteria	18
4.4. Exclusion criteria	18
4.5. Inclusion of patients with mild and moderate renal insufficiency	19
4.6. Potential risks for pregnant or lactating women	21
4.7. Premature withdrawal of patients from the study	21
5. DEFINITIONS	21
5.1. Upper and lower urinary tract infections and urosepsis	21
5.2. Resistant bacteria and patients at increased risk	21
6. TRIAL MEDICATION	22
6.1. Selection of dosage and treatment duration	22
6.2. Name and composition of antimicrobial agents	22
6.3. Known side effects of the study medications	22
6.4. Dose adjustment	23
6.5. Pregnancy and breastfeeding	23
6.6. Contraception	23
6.7. Drug supply and storage	23
6.8. Measurement of compliance	23
6.9. Concomitant therapy	24
7. EVALUATION CRITERIA	24
7.1. Primary outcome	24
7.2. Secondary outcomes	24
7.3. Chemical and microbiologic methods	25
7.4. Antimicrobial susceptibility testing	25



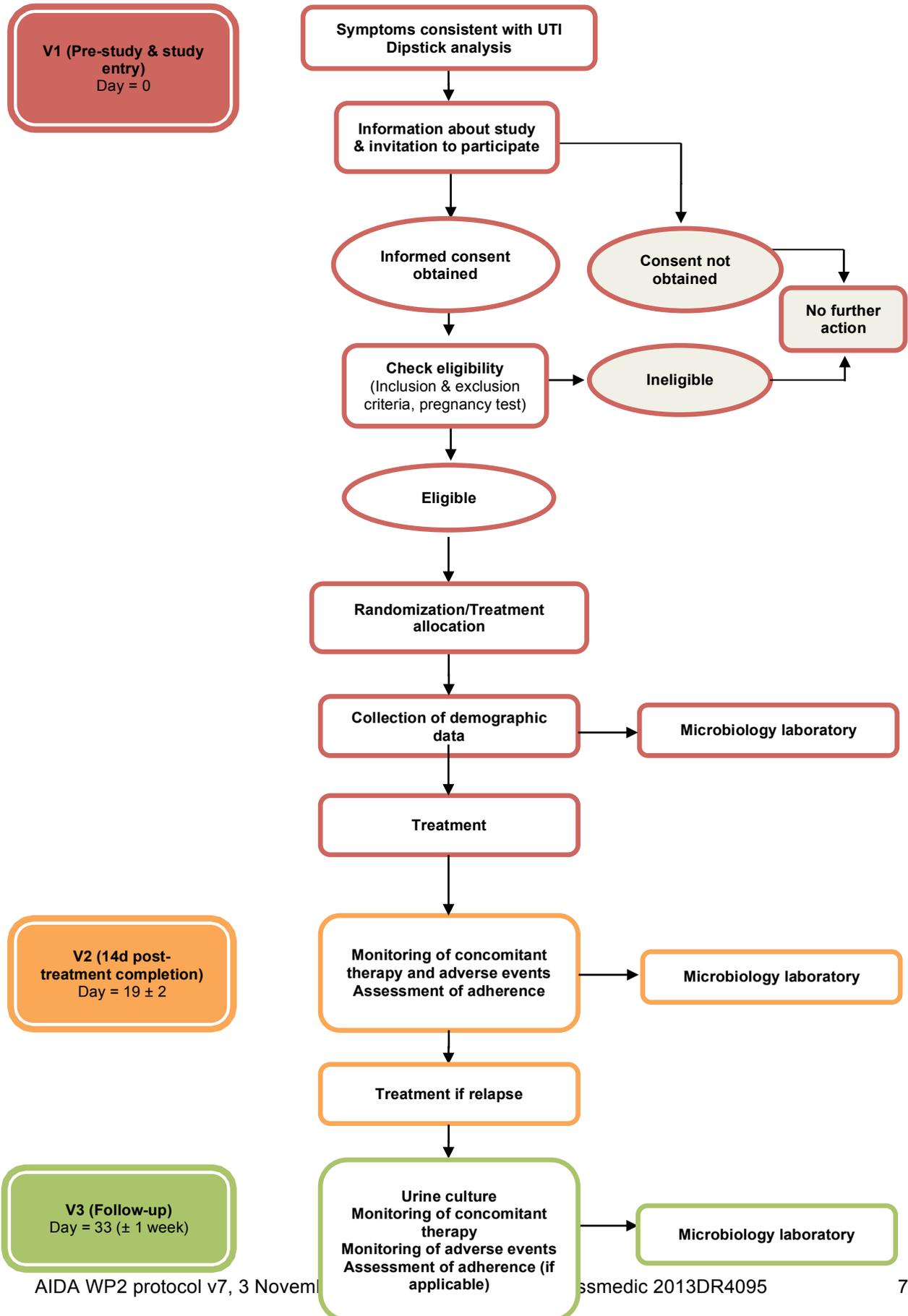
AIDA Work Package 2 protocol v7, 3 November 2014

8. DATA COLLECTION AND MANAGEMENT	25
8.1. Data collection	25
8.2. Data storage	25
8.3. Data quality control and quality assurance	25
8.4. Information for patients	26
9. ADVERSE EVENTS MANAGEMENT	26
9.1. Definitions of adverse events	26
9.2. Definitions of adverse event intensity	26
9.3. Definitions of adverse event causality	26
9.4. Recording and reporting of adverse events	27
9.5. Evaluation, management and follow-up of adverse events	28
10. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN	28
10.1. Number of patients and sample size	28
10.2. Data analysis	28
11. ETHICS	29
11.1. Guidelines and legislation	29
11.2. Informed consent	29
11.3. Ethics committee approval	29
11.4. Approval by Swissmedic	29
11.5. Personal data and data protection	29
11.6. Modification of protocol	30
12. PUBLICATION POLICY	30
12.1. Clinical trial registration	30
12.2. Publications	30
13. FINANCING AND INSURANCE	30
13.1. Funding source and ownership of data	30
13.2. Insurance	30
13.3. Compensation of subjects	30
REFERENCES	31
14. APPENDICES	34

SYNOPSIS

PROTOCOL TITLE:	Randomised clinical trial comparing fosfomycin vs. nitrofurantoin for treatment of uncomplicated lower urinary tract infection (UTI) in female adults at risk of antibiotic-resistant infection
RATIONALE:	Developed before the establishment of a structured process for drug assessment, nitrofurantoin and fosfomycin are now being prescribed frequently given the rise in multi-resistant gram-negative pathogens. Doubts remain regarding fosfomycin's long-term clinical effectiveness. A randomized, controlled trial is needed to explore the clinical effectiveness and better define the side effect profiles of both nitrofurantoin and fosfomycin.
PRIMARY OBJECTIVES:	To demonstrate the superiority of 5 days of nitrofurantoin over single-dose fosfomycin for the treatment of lower, uncomplicated UTI in women at increased risk of antibiotic-resistant uropathogens.
TRIAL DESIGN:	Phase IV, open-label, data-analyst-blinded, randomized, multi-centre clinical superiority trial
PLANNED SAMPLE SIZE:	600 patients, 300 in each arm
SUBJECT SELECTION CRITERIA:	Non-pregnant female patients aged ≥ 18 years with uncomplicated lower UTI
TRIAL MEDICATION	Nitrofurantoin Fosfomycin
DOSAGE AND DURATION OF TREATMENT	Nitrofurantoin 100 mg tid for five days Fosfomycin 3 g (single dose)
MAIN PARAMETERS OF - EFFICACY:	Clinical response at 14 and 28 days after treatment cessation Bacteriological response at 14 and 28 days post treatment cessation
- SAFETY:	Adverse events
PROCEDURE & FOLLOW-UP:	Upon meeting inclusion criteria and providing informed consent, non-pregnant adult female patients with uncomplicated lower UTI will be randomized to receive either study drug. Clinical and bacteriologic assessments will be made at baseline and days 14 and 28 after therapy cessation; monitoring of adverse events will be performed throughout the study period. Questions will be asked at study visits regarding symptomatology, potential adverse events, use of additional medication, contacts with healthcare professionals, quality of life, daily activities, and days of work lost.
STATISTICAL ANALYSIS:	Conventional tests for superiority in the intention-to-treat analysis and per-protocol analyses. We will conduct a pre-defined subgroup analysis for patients with UTIs caused by extended-spectrum beta-lactamase (ESBL) producing and/or fluoroquinolone-resistant bacteria.
STUDY PERIOD:	Three-year study (summer 2013 to summer 2016)
SETTING:	Outpatient clinics, general practitioners' offices, and acute- and long-term-care facilities at three centres (Geneva, Lodz, and Tel Aviv); each site will recruit 200 patients.

STUDY FLOWCHART





UNIVERSITÉ
DE GENÈVE

HUG
Hôpitaux Universitaires de Genève



AIDA Work Package 2 protocol v7, 3 November 2014

ABBREVIATIONS AND DEFINITIONS

AE	Adverse event
AR	Adverse reaction
BhCG	Beta human chorionic gonadotropin
CI	Confidence interval
CRF	Case report form
GCP	Good clinical practice
GMP	Good manufacturing practice
ESBL	Extended-spectrum beta-lactamase producers
FQ	Fluoroquinolone
ICH	International Conference on Harmonization
ID	(Patient) identification
IRB	Institutional review board
ITT	Intent-to-treat
SAE	Serious adverse event
SAR	Serious adverse reaction
SOP	Standard operating procedure
SUSAR	Suspected, unexpected serious adverse reaction
UTI	Urinary tract infection

1. JUSTIFICATION AND OBJECTIVES

1.1. Background information

a) Off-patent antibiotics and aim of the AIDA project

In an era of rising antimicrobial drug resistance and scarce new antibiotics, older off-patent antibiotics (e.g. colistin, nitrofurantoin, doxycycline) are increasingly prescribed to patients. Many of these agents, however, were developed before the advent of a structured process for drug assessment and approval, in particular the establishment of clinical efficacy and effectiveness in randomized controlled trials (RCTs). A re-evaluation of these drugs is thus urgently needed. The AIDA consortium, funded by the 7th framework program of the European Commission, aims to answer the question of clinical effectiveness and optimal dosing of five off-patent antibiotics for infections caused by drug-resistant bacteria in three RCTs. The present clinical trial will compare fosfomycin to nitrofurantoin for the treatment of lower urinary tract infection (UTI) in adult women at risk of antibiotic-resistant bacteria.

b) Current challenges related to the treatment of acute uncomplicated UTI in female adults in an era of increasing antibiotic resistance

Acute uncomplicated UTI remains one of the most common indications for prescribing antimicrobials to women. Treatment of this infection is increasingly difficult, however, as antimicrobial resistance in uncomplicated UTI is on the rise. Mounting resistance rates of Gram-negative pathogens (e.g. *Escherichia coli*, *Klebsiella spp.*) causing UTI have been observed throughout Europe, in particular *Enterobacteriaceae* carrying extended-spectrum beta-lactamases (ESBL) and/or fluoroquinolone (FQ) resistance. In several European countries the rate of ciprofloxacin resistance in *E. coli* is approaching the resistance rate of trimethoprim-sulfamethoxazole (TMP-SMX), an antibiotic that has been largely abandoned as empirical therapy for upper UTIs.^{1, 2} FQ-resistant strains circulating in the community are often resistant to other agents such as TMP-SMX, amoxicillin, and doxycycline. The rate of co-resistance to ciprofloxacin in ESBL-producing isolates is often >80%.^{3, 4} Of note, a recently published retrospective study from Israel showed that reduction in ciprofloxacin use in the community in the context of a FQ restriction policy was associated with an increase in susceptibility to ciprofloxacin in urinary *E. coli* isolates.⁵ Thus, decreasing FQ overuse for lower UTI may have a favourable impact on FQ resistance, safeguarding FQ treatment options for more severe episodes of pyelonephritis and urosepsis.

c) Alternative agents

Several agents, such as nitrofurantoin, fosfomycin, and pivmecillin have been proposed as alternatives to commonly prescribed antibiotics for UTI. An important property of nitrofurantoin is that usually sensitive microorganisms do not readily become resistant to the drug, likely due to its multiple mechanisms of action. Although resistance can be induced in vitro, there has been only limited change in the resistance pattern of bacteria to nitrofurantoin over the years and there is usually no cross-resistance between nitrofurantoin and other chemotherapeutic agents.⁶ Similarly, fosfomycin tromethamine (hereafter referred to as fosfomycin), because of its unique mechanism of action, does not show significant cross-resistance with other antimicrobials used for treatment of lower UTI.⁷

d) Nitrofurantoin

Nitrofurantoin has been available for clinical use in a crystalline formulation since 1953 and is marketed as Furadantin. The sole use of this drug is in the treatment of UTIs, as after oral or intravenous (iv) administration, therapeutically active concentrations are attained only in urine. Therefore, it has been used for more than five decades for the treatment of uncomplicated cystitis and remains active against most uropathogens.

Nitrofurantoin is effective for the treatment of most infections localized to the urinary tract, such as urethritis, cystitis, and mild pyelonephritis. Although therapeutically active serum levels are not obtained, it is usually effective for renal infections, because renal medullary and urinary concentrations are almost identical.⁸ However, the use of nitrofurantoin in upper urinary tract infections has been questioned since these are more likely to be associated with bacteremia and nitrofurantoin achieves poor serum levels.⁹ ¹⁰ If renal infection is associated with features suggesting a possible bloodstream infection, other drugs such as the third-generation cephalosporins, aminoglycosides, quinolones, or trimethoprim-sulfa, which produce therapeutic serum levels, are indicated. Nitrofurantoin may also not be effective in patients with upper UTIs in whom one kidney has poor function. In such cases, even though overall renal function may be normal, effective concentrations of the drug may not be reached in the urine of a kidney with a unilateral creatinine clearance of less than 20 ml/min.¹¹

The popularity of nitrofurantoin is hampered by a recommended seven-day dosing regimen and concerns about efficacy and tolerance. A few studies have evaluated the efficacy and tolerance of nitrofurantoin, especially in a regimen shorter than 7 days, as is now more commonly preferred for the treatment of uncomplicated UTI in women. In a prospective, randomized, double-blind study comparing ciprofloxacin (100 mg twice daily for 3 days) with TMP/SMX (one double-strength tablet twice a day for 7 days) or nitrofurantoin (100 mg twice a day for 7 days) among 571 women with acute uncomplicated urinary tract infection (UTI), ciprofloxacin resulted in significantly higher eradication rates (91%) after 4–6 weeks than trimethoprim-sulfamethoxazole (79%) or nitrofurantoin (82%). However, clinical resolution 4–10 days after therapy and at the 4- to 6-week follow-up was similar among the three treatment groups.¹² In a randomised controlled trial (RCT) including 338 women, Gupta et al showed that a 5-day course of nitrofurantoin is equivalent clinically and microbiologically to a 3-day course of TMP/SMX (Figure 1) and should be considered an effective FQ-sparing alternative for the treatment of acute uncomplicated cystitis in women.¹³

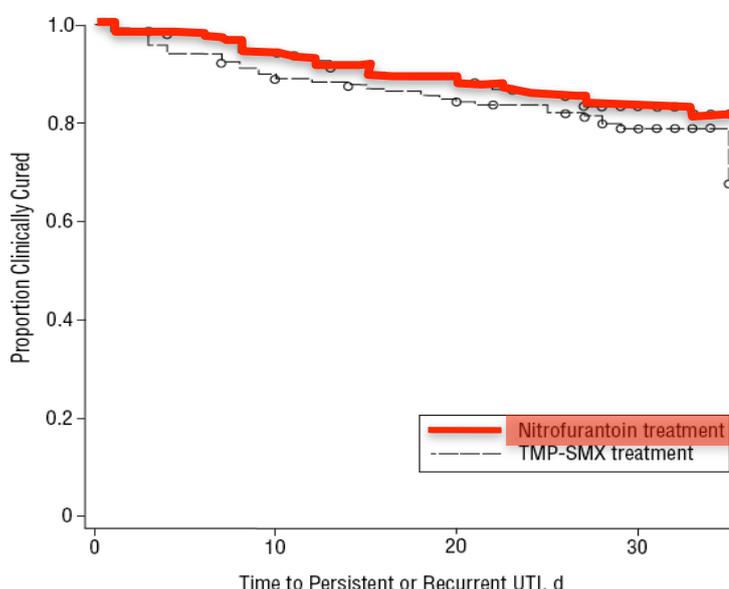


Figure 1. Clinical outcomes in women treated with trimethoprim/sulfamethoxazole (TMP-SMX) vs nitrofurantoin. The Kaplan-Meier curve shows equivalent rates of cure between nitrofurantoin- and TMP/SMX-treated women.¹³

e) Fosfomycin

Fosfomycin is a phosphonic acid, cell-wall active antimicrobial agent effective against Gram-positive and -negative microorganisms. In clinical practice, the compound is used for the treatment of uncomplicated UTIs caused by *E. coli* and *Enterococcus faecalis*. It has proven to be a very effective drug for the treatment of uncomplicated UTIs in adults, even given in a single 3-g dose. It also has reasonable cure rates for pyelonephritis and recurrent UTI, and has been effective in treating UTI in children, pregnant women, and the elderly. The excellent efficacy of fosfomycin in UTI has been attributed to the high urinary drug concentrations such that they remain above the minimal inhibitory concentration (MIC) for the most important urinary pathogens for at least 40 hours after a single 3-g dose. The vast majority of published studies investigate the use of fosfomycin in its oral formulation (fosfomycin tromethamine). For treatment of uncomplicated UTI (mostly in women), a 3-g dose of fosfomycin tromethamine has been compared with cephalexin (0.5 g qd for 5 days);¹⁴ amoxicillin–clavulanic acid (0.5 g tid for 5 days);¹⁵ piperidic acid (0.4 bid for 5 days);¹⁶ TMP/SMX (0.48 g bid for 3 days);¹⁷ trimethoprim at varying doses;¹⁸ nitrofurantoin (0.1 g bid for 7 days;²⁰ or 0.05 g qid for 7 days);²¹ and norfloxacin (0.4 g bid for 5 days²² or 0.4 g bid for 7 days²³). In all studies both the microbiological and clinical efficacy of the two drugs tested were similar, with microbiological eradication rates of 75–95% after 5–7 days of fosfomycin tromethamine treatment, and similar rates for clinical efficacy. After 4–6 weeks' observation, rates were still similar for all drugs at levels of 60–85% efficacy, at least in those studies that reported a follow-up. Thus, in many European countries, single-dose fosfomycin oral treatment has been approved for the treatment of acute uncomplicated lower UTI in adult women.

Concerns have arisen, however, regarding (1) fosfomycin's ability to achieve full microorganism eradication and (2) the emergence of microbiological relapse or re-infection after single-dose fosfomycin therapy.²⁴ Indeed, in a U.S. controlled, double-blinded trial whose results were never formally published, fosfomycin demonstrated a microbiologic eradication rate of only 77% (591/771) in patients with acute cystitis, as compared to 93% for both ciprofloxacin (219/222) and TMP/SMX (194/197). The inferred "clinical success rates" were 70%, 96% and 94%, respectively.²⁵ A further disadvantage of fosfomycin is that it is more expensive than nitrofurantoin. This is, however, an unreliable predictor of cost-effectiveness. Since treatment adherence to fosfomycin may be higher, this may be associated with fewer relapses and office visits as well as lower resistance rates.

f) Current UTI treatment recommendations

Although recommendations for management of uncomplicated UTI vary across countries, several current national guidelines (e.g. France, Netherlands) recommend FQ-sparing regimens in the treatment of uncomplicated lower UTI and encourage efforts to substitute FQs for UTI treatment with antibiotics of lesser ecologic impact, such as nitrofurantoin and fosfomycin.²⁶ These two agents are attractive alternatives, since both display antibacterial activity against many ESBL-producing and FQ-resistant Gram-negative bacteria. However, these regimens have not been rigorously compared in terms of efficacy, safety and effectiveness, apart from two clinical studies conducted more than 20 years ago in an era of low antibiotic resistance (0.1 g bid for 7 days;²⁰ 0.05 g qid for 7 days²¹). Previously gathered clinical data suggest that the microbiological failure may be

higher in female patients treated with a single dose of fosfomycin compared to a 5- to 7-day treatment with nitrofurantoin.²⁰ Conversely, a recent meta-analysis of randomized controlled trials has suggested similar clinical success rates of fosfomycin compared to several comparators.²⁷

Importantly, nitrofurantoin may have a higher rate of potential side effects, especially when used for longer treatment periods.²⁸ Probably because of risks of side effects and a lack of adequate clinical trials to demonstrate its efficacy, several dosing regimens are being advised, varying from 200 mg to 400 mg daily in 2 to 4 divided doses. Hitherto, rigorous comparisons with respect to the optimal dosing regimen have not been made. Current treatment and dosage regimens of nitrofurantoin for lower UTI are summarized below. Overall, there is now solid evidence that a 5-day course of nitrofurantoin is likely sufficient for treatment of uncomplicated lower UTI in women.

Table 1. The evolution of nitrofurantoin's role in various countries' clinical practice guidelines for uncomplicated urinary tract infection since 1999.

Country	Year	Dose	Duration (d)	Nitrofurantoin as first choice
USA ²⁹	1999	100 mg bid	7	
Netherlands ³⁰	1999	100 mg tid	3	✓
Scotland ³¹	2006	Not stated	3	✓
Netherlands ³²	2006	100 mg tid	5	✓
France ²⁶	2008	100 mg tid	5	
Belgium ³³	2008	100 mg tid	3	✓
USA & Europe ³⁴	2010	100 mg bid	5	✓

1.2. Study rationale and hypothesis

Lower UTIs are common in women. The treatment of uncomplicated UTI caused by antibiotic-resistant bacteria is a growing clinical problem. Two off-patent antibiotics, nitrofurantoin and fosfomycin, are considered alternatives, but superiority of either drug has not been clearly established. Since the emergence of ESBL-producing and FQ-resistant uropathogens, clinical and bacteriological outcomes have not been reported from randomized, controlled studies of either drug. Importantly, in the guidelines that were published in 2011 by the Infectious Diseases Society of America (IDSA) in collaboration with the European Society of Clinical Microbiology and Infectious Disease and other clinical societies, it was stated that specific recommendations for the role of fosfomycin in the treatment of multidrug-resistant uropathogens could not be included because sufficient data were lacking.³⁴

Thus, the high resistance rates exhibited by contemporary uropathogens necessitate the re-evaluation of these two older but still microbiologically active antibiotics in patients at increased risk of antibiotic-resistant uropathogens. Specifically, we will attempt to demonstrate the superiority of 5 days of nitrofurantoin over single-dose (3 g) fosfomycin for the treatment of lower, uncomplicated UTI in women at risk of antibiotic-resistant pathogens.

The study will be conducted in three countries; clinical and bacteriological outcomes without treatment modifications will be assessed. We will also include a significant number of secondary objectives that will aid in the clinical and bacteriological evaluation of nitrofurantoin and fosfomycin.

1.3. Study settings

We will recruit both ambulatory and hospitalized patients via general practitioners and several in- and outpatient hospital departments at three centres in Geneva (Switzerland), Lodz (Poland) and Tel Aviv (Israel). We aim to include 600 patients to achieve statistical significance (see Section 3.3 below); each study site will include 200 patients total. Each site will recruit and randomise patients independently of other sites.

2. STUDY OBJECTIVES

The primary objective of this investigator-initiated study is to demonstrate the superiority of 5 days oral nitrofurantoin over single-dose (3g) oral fosfomycin in the treatment of lower, uncomplicated UTI in adult women at increased risk of antibiotic-resistant uropathogens. Superiority will be determined based on assessments of clinical response 28 days post-treatment. (While fosfomycin is administered in a single dose, its longer half-life allows for a duration of activity in the urine comparable to that of nitrofurantoin.³⁵)

Secondary objectives of this study are to evaluate bacteriologic cure at days 14 and 28 after therapy, incidence of “true UTI” (as defined by initial symptoms consistent with UTI and a subsequently positive urine culture); duration of symptoms; lost days of work; hospital admission; incidence of pyelonephritis or urosepsis; development of adverse events; and emergence of antibiotic resistance during the 28-day post-therapy study period.

3. STUDY DESIGN

3.1. Overall description

This is an investigator-initiated, prospective, open-label, analyst-blinded, randomized clinical trial that will be conducted in three centres in Switzerland, Israel and Poland. Patients will be randomly assigned to treatment with single-dose fosfomycin or a five-day course of nitrofurantoin. This phase IV study will be performed according to Good Clinical Practice guidelines.

We will enrol non-pregnant female, adult patients with (1) at least one of four key symptoms of lower UTI (dysuria, urgency including nocturia, frequency, and suprapubic tenderness) that could be attributed to an uncomplicated UTI, and no alternative explanation (i.e. symptoms suggestive of STI or vulvo-vaginitis), and (2) a urine dipstick analysis positive for either nitrites or leukocyte esterase, at high risk of antibiotic-resistant pathogens. Enrolment will focus on patients with previous exposure to antibiotic treatment, healthcare facilities or prior identification of resistant pathogens (see Definitions section below). Women who have either moderate to severe chronic renal insufficiency or chronic urologic disorders, or who are on long-term antibiotic prophylaxis, will be excluded.

Patients who provide informed consent, have a negative BhCG urinary pregnancy test, and satisfy other entry criteria will be randomly assigned to receive either nitrofurantoin or fosfomycin. Before study inclusion, patients in both treatment groups should not receive any

AIDA Work Package 2 protocol v7, 3 November 2014

other antimicrobial drug. Thus, treatment will be administered in most circumstances empirically, until results of susceptibility tests are known.

All treatments are to be administered orally. Under no circumstances will fosfomycin be given intravenously. Assessments of microbiology, clinical signs and symptoms of disease, plus clinical and laboratory safety evaluations will be made at study entry. A second visit will take place on day 14 (± 2 days) post-treatment in order to assess clinical and bacteriologic progression. Final assessment will be made 4 weeks (± 7 days) after receiving the final dose of trial medication (see study flowchart).

Clinical response will be assessed in terms of resolution of signs and symptoms (see sections 7.1 and 7.2 for precise definitions). Bacteriological response will be assessed in terms of eradication of causative uropathogens in the urine 28 days post-treatment (day 33 ± 7). Again, while fosfomycin is administered in a single dose, its longer half-life allows for a duration of activity in the urine comparable to that of nitrofurantoin.³⁵ Thus, day 33 will also mark 28 days of follow-up from fosfomycin treatment “wrap-up.” Tolerability will be assessed by reviewing adverse events (see below).

3.2. Study schedule

The study schedule and procedures at each visit are summarized below and in the table at the end of this section. No study-related test can be performed before a patient has provided written, informed consent to participate in the study.

a) First pre-study visit (V1)

V1 will take place on the date of study inclusion and before the start of trial treatment. Eligible patients will be approached and informed of the study. They will receive the Participant Information Sheet and will have the opportunity to ask questions. Inclusion and exclusion criteria will be assessed. The patients will be given sufficient time—to the extent that they are seeking immediate medical attention and relief for active symptoms—to consider the study's implications before deciding whether to consent and participate. Should patients refuse participation, they will be under no obligation to justify the refusal. Upon the patient's approval, a urine pregnancy test will be performed at this visit for all premenopausal patients.

Baseline characteristics will be recorded on a standardized electronic case report form (eCRF) and urine will be collected in the office, clinic, or ward; no special precautions are needed for this sample. A targeted physical examination will be performed. Immediately after urine collection, the sample will be refrigerated at 4°C, then transported to the local microbiology laboratory for further work-up. For patients who refuse to take part in the study, the general practitioner (GP) or research assistant will record the stated reason.

b) Second visit (V2): clinical and bacteriologic follow-up

A study visit will take place 14 days after treatment cessation (± 2 days). The patient will be interviewed regarding on-going symptoms, if any, compliance, concomitant medication, and any adverse events. Patients will be asked to provide urine for microbiologic culture. Should the investigator suspect treatment failure, further antibiotic treatment will be prescribed at this time.

c) Third and final visit (V3)

AIDA Work Package 2 protocol v7, 3 November 2014

The final visit will occur 28 days post-treatment (± 1 week). Patients will be asked to provide urine for microbiologic culture, and will be asked about any previously reported adverse events and further antimicrobial treatment. When patients are withdrawn from the study, the reason for withdrawal will be recorded.

Table 2. The AIDA Work Package 2 study schedule.

Periods	Pre-study	Follow-up	Follow-up
Visits	V1	V2	V3
Day	1/0 d pre-treatment	14 d post treatment completion (± 2)	28 d post treatment completion (± 1 week)
Invitation to participate and information about study	X		
Informed Consent	X		
Inclusion/ Exclusion	X		
Urine BhCG pregnancy test	X		
Treatment allocation	X		
Collection of demographic data	X		
Urine culture	X	X	X
Monitoring of signs and symptoms	X	X	X
Monitoring of adverse events		X	X
Monitoring of concomitant therapy		X	X
Assessment of adherence		X	X

3.3. Randomisation

Provided the enrolment criteria are fulfilled, the patient will be asked whether she wishes to participate in the trial. All patients who fulfil the inclusion criteria and agree to participate will receive an increasing sequential patient number and be randomly assigned to one of the two treatment groups in a 1:1 ratio.

Because this study is open-label to patients and investigators, randomisation will be based on investigator-blinded blocks of randomly varying size in order to protect against potential predictability of treatment assignments. Blocks will be small in order to decrease the potential for mid-block inequality, with sizes ranging from four to twelve. A statistician not involved in the study analysis will produce three randomised lists of treatment assignments (one per study site); the blocks' order and size will be generated by use of a computer-based randomised number system to achieve equal sample sizes in both treatment groups. The randomisation lists will be prepared prior to the initiation of the study. Only the statistician who developed the randomisation code will have a copy of the master randomisation lists. Each centre will receive the first 50 sealed envelopes for randomisation purposes before the beginning of the recruitment phase.

3.4. Study duration per patient

The maximum expected duration of patient participation in the study will be 33 days (± 1 week) from the day of the first administration of the trial medication.

3.5. Data collected in the CRF

The following table lists the data to be collected in each enrolled patient's case report form.

Table 3. Data to be collected in the CRF.

Demographic information <ul style="list-style-type: none"> • Age • Gender • Employment status
Study dates <ul style="list-style-type: none"> • Inclusion date • Start/end of treatment dates • Date of last follow-up
Enrolment <ul style="list-style-type: none"> • Inclusion criteria (checklist) • Exclusion criteria (checklist) • Study randomization number • Principal diagnosis
Clinical history & concomitant medications <ul style="list-style-type: none"> • Co-morbidities • History of past UTI episodes • Presence of invasive devices (e.g., urinary devices) • Results from diagnostic tests performed prior to inclusion • Concomitant medication, if any • Whether sexually active or not
Clinical course <ul style="list-style-type: none"> • Potential side effects of study medications • Symptomatology related to the present illness
Laboratory (chemistry) <ul style="list-style-type: none"> • Serum creatinine values, if known (both pre- and post-enrolment) • Liver function tests, if known • Results of urinary dipstick analyses
Laboratory (microbiology) <ul style="list-style-type: none"> • Results of urinary cultures (both pre- and post enrolment)
Compliance <ul style="list-style-type: none"> • Reported compliance with treatment (e.g., number of applications missed)
Follow up (regular end of study, subject/patient withdrew consent, withdrawal by investigator, protocol violation, lost to follow-up, death)

3.6. Trial time frame

Beginning of the study: summer 2013

End of patient enrolment: summer 2016

End of patient follow-up: summer 2016

Data analysis: summer 2016 – fall 2016

Preparation and submission of final manuscript: winter 2016

3.7. Premature discontinuation of the study

The study will be discontinued prematurely if there is a high frequency of unexpected or serious adverse reactions during the study, or if patients cannot be recruited in sufficient numbers.

3.8. Data monitoring board

The AIDA project has appointed a data-safety monitoring board (DSMB) that will be convened for the purpose of monitoring patient safety and treatment efficacy throughout the study. Board members are specialists in infectious diseases. They are otherwise uninvolved in the AIDA study.

3.9. Study supervision and expertise

The trial will be supervised by Prof. Dr Stephan Harbarth and co-investigators in each of the participating sites. Dedicated research assistants will help with patient inclusion and data collection. The principal investigator is well qualified and has published myriad articles about prevention and treatment of multidrug resistant organisms in peer-reviewed journals. He is a well-known infectious disease specialist with extensive experience in clinical trials and epidemiological research related to antibiotic resistance. He has been certified and received a GCP certificate at HUG for management of clinical trials in 2010.

3.10. Independent monitoring

The study team will contract with an external clinical research organization (CRO) for the independent monitoring of data collection to ensure the quality of these data and adherence to the study protocol. A clinical research associate (CRA) from the CRO will have access to all study documentation, including study case report forms and the study database. The CRA is bound to patient confidentiality. Results of the independent monitoring will be forwarded to Prof. Stephan Harbarth, the study sponsor.

4. STUDY POPULATION

4.1. Selection and recruitment procedures

Non-pregnant female patients over 18 years of age who (1) present with any of the four symptoms listed above, with no alternative explanation (e.g., vulvovaginitis on exam), and have (2) a urine dipstick analysis positive for either nitrites or leukocyte esterase, are eligible for inclusion. Symptoms should be of less than 7 days' duration. Any adult woman who fulfils the entry criteria, has no signs or symptoms of upper UTI (e.g. pyelonephritis), does not fulfil any of the other exclusion criteria (see below), and is able to give informed consent will be eligible for enrolment in this study.

Patient flow will be monitored in agreement with the CONSORT statement.³⁶ A screening log will be kept in a safe and password-protected database, in which the eligibility status of every patient screened will be recorded, regardless of whether or not she enters the study.

Women with suspected lower UTI may be recruited by means of direct communication between their primary physicians and the study team (see Section 4.2 below) or they may be recruited directly by means of a study flyer for consultation at the infectious diseases outpatient clinic of HUG.

4.2. Communication with clinicians involved in the care of trial participants

The GPs and clinicians of the concerned Services and Departments will be informed about the aim and interventions of this study. Patients in a given private practice or outpatient clinic will be enrolled in the study only with the previous agreement of the respective physician in charge. Other healthcare workers involved in the care of study participants will be informed as necessary. For hospitalized patients who decide to participate in the study, directors from different departments (e.g. internal medicine, surgery, rehabilitation and geriatrics) will be informed of the trial and will be asked to give written approval for inclusion of patients from their departments.

4.3. Patient inclusion criteria

Patients can be enrolled into the study provided that **all** of the following absolute criteria are fulfilled:

- Female gender
- Age \geq 18 years
- Written informed consent
- At least one of four key UTI symptoms that could be attributed to an uncomplicated UTI, and no alternative explanation (i.e. symptoms suggestive of STI or vulvo-vaginitis):
 - Dysuria
 - Urgency (including nocturia)
 - Frequency
 - Suprapubic tenderness
- Urine dipstick test positive for either nitrites or leukocyte esterase

Of note, the study will look to include patients at increased risk for resistant pathogens, e.g., FQ-resistant or ESBL-producing Enterobacteriaceae (see Definitions below), but this criterion is not an absolute requirement for participation in the study.

4.4. Exclusion criteria

Patients will **not** be considered for participation in the study if any of the following criteria listed below apply:

- Male sex
- Pregnancy or planned pregnancy
- Known carriage of nitrofurantoin- or fosfomycin-resistant uropathogen(s)
- Concomitant antimicrobial therapy
- Use of any antibiotics in the past 7 days
- Known or suspected hypersensitivity or allergy to fosfomycin or nitrofurantoin
- History of lung or liver reaction or peripheral neuropathy after use of nitrofurantoin or other nitrofurans in the past
- Pre-existing polyneuropathy
- G6PD deficiency
- Symptoms consistent with UTI in the preceding 4 weeks
- Active upper UTI (e.g. pyelonephritis, urosepsis: fever $>$ 38.0, flank pain, chills)
- Symptoms/signs suggestive of vaginitis or sexually transmitted infection
- Indwelling catheter, nephrostomy, ureter stent or other foreign material
- Otherwise complicated UTI:
 - A history of anatomical or functional abnormalities of the urogenital tract:
 - Congenital abnormalities

AIDA Work Package 2 protocol v7, 3 November 2014

- Polycystic kidney disease
- Obstruction or stricture of renal pelvis, ureter or urethra
- Kidney stones
- Cystocele
- Cystic diverticulae
- Change of anatomical proportions (e.g. after ureter implantation)
- Chronic vesico-urethral reflux
- Neurogenic bladder
- Severe chronic renal (creatinine clearance < 30 ml/min) or hepatic dysfunction
- Porphyria
- Immunosuppression:
 - Untreated infection with the human immunodeficiency virus (HIV)
 - Use of high-dose systemic corticosteroids or other immunosuppressive medication
 - Chemotherapy
 - Treatment with radiation
- Critical illness requiring intensive care
- Planned surgery within the next 6 weeks
- Inability to take oral drugs
- Participation in another prospective clinical trial
- Previous enrolment in the proposed study
- Inability to understand or to follow the study protocol

4.5. Inclusion of patients with mild and moderate renal insufficiency

We note that administration of nitrofurantoin is generally discouraged in those patients with even moderate renal insufficiency, i.e., a creatinine clearance between 30 - 60 ml/min. This recommendation stems almost entirely from the pharmacokinetic work of Sachs et al., who in 1968 administered oral nitrofurantoin to subjects with widely varying creatinine clearances.³⁷ Urinary concentration—and, it was concluded, likely clinical efficacy—decreased with renal function in near linear fashion, as shown in Figure 2. No nitrofurantoin toxicity was reported in the study. In their conclusions regarding toxicity, the authors cite another pharmacokinetic study by FP Chinard, whose results appear never to have been formally published: “Serum levels do rise in the presence of renal failure, but in the study conducted by Chinard, after 400 mg orally per 24 hours, concentrations did not exceed 5 to 6 µg per millilitre even in severely uremic patients.”

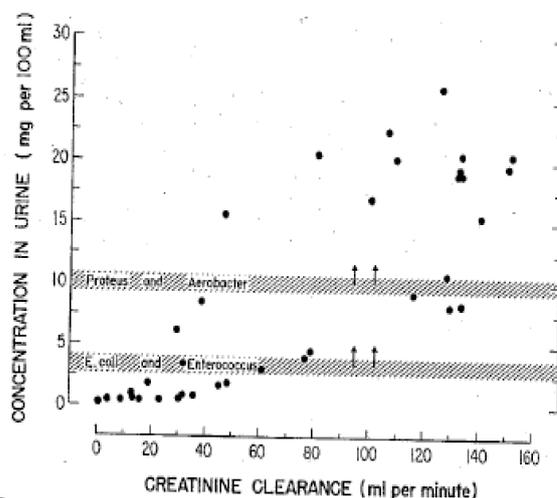


Figure 2. Highest concentration of nitrofurantoin achieved in the urine during collection periods of zero to two, two to four or four to ten hours, according to creatinine clearance. The shaded areas represent minimum inhibitory concentrations required for various bacteria as reported in the literature of the 1960s. From Sachs et al., Effect of renal function on urinary recovery of orally administered nitrofurantoin. *N Engl J Med.* 1968; 278(19): 1032-5.

Thus, nitrofurantoin toxicity is not a significant complication among those with renal insufficiency. Rather, the primary concern is clinical inefficacy due to subtherapeutic urinary nitrofurantoin concentrations. Data collection and presentation in this study were incomplete, however. Creatinine clearance values were calculated without correction for body-surface area, and analyses conflated data from healthy volunteers with those from patients with varying comorbid status, some of whom had already been on nitrofurantoin for unreported periods of time. The authors concluded by recommending the avoidance of nitrofurantoin in truly azotemic patients.

In the meantime, we observe in everyday practice a marked increase in the consumption of nitrofurantoin, particularly since 2010. This most recent increase is a direct result of the updated guidelines mentioned above: local Geneva guidelines recommended nitrofurantoin as the first choice for uncomplicated UTI in 2010 (Appendix 4), while European and U.S. guidelines followed suit in 2011. Nonetheless, nitrofurantoin use was on the rise even earlier. It is difficult to characterize and quantify nitrofurantoin's true use among certain populations, but it is known that its consumption is rapidly rising in two other groups for which it is also typically discouraged: men and the elderly. An evaluation of nationwide antimicrobial use among United States veterans in long-term-care facilities (> 95% men, all aged > 65 years) between 2007 and 2009 with a total of 7.5 million patient-days determined that, out of >100 antimicrobial agents, nitrofurantoin was in twelfth place for those most frequently administered (Huttner A et al., unpublished data). A recent population-based, point-prevalence study of antibiotic use among 37,371 elderly individuals in 363 long-term-care facilities in Canada revealed nitrofurantoin as the most commonly prescribed antibiotic—as well as the antibiotic most associated with very long treatment courses (>90 days).³⁸ Finally, local nitrofurantoin administration at Geneva's geriatrics hospital has increased exponentially in recent years (Figure 3), from 0.4 defined daily doses (DDD) per 1000 patient-days (pd) in 2007 to 11.9 DDD/1000 pd in 2012 (Huttner B, Harbarth S et al., unpublished data).

It is not unreasonable to infer that some of these +10,000 elderly persons have moderate renal insufficiency.

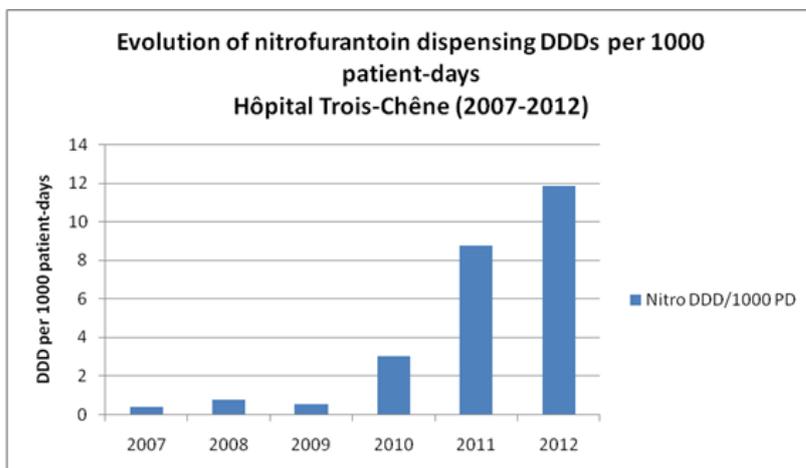


Figure 3. Nitrofurantoin dispensing at Geneva's geriatrics hospital over the last six years.

This pragmatic study concerns itself with the everyday reality of frequent nitrofurantoin and fosfomycin use. Because of the gaps in the extant—and methodologically somewhat superannuated—pharmacokinetic data, and because we have some indication that nitrofurantoin is already being administered to some patients with chronic moderate renal

insufficiency, we believe that a controlled evaluation of its effectiveness and potential toxicity in this population is warranted. We note also that a substudy aiming to provide a thorough and exhaustive pharmacokinetic profile of nitrofurantoin in women with acute uncomplicated cystitis (including some with decreased renal function) as well as healthy female volunteers will also be performed in the context of AIDA (ethics committee and Swissmedic approval permitting).

Any patient included in the study with a creatinine clearance in the range of 30 – 60 ml/min will be followed particularly closely, both for clinical efficacy and any potential toxicity.

4.6. Potential risks for pregnant or lactating women

Both study drugs belong to the pregnancy category B (see Swiss Medical Compendium, Appendix 4). Despite the fact that several clinical human studies have shown no evidence of fetotoxicity at normal doses with either drug,³⁹⁻⁴³ nitrofurantoin is nonetheless contra-indicated in the third trimester and during lactation, as an elevated risk of haemolytic anemia for the infant may exist. Fosfomycin is not contra-indicated in pregnancy, though its use during lactation is strongly discouraged. It is for this reason that the study will not include women who are either pregnant, wishing to become pregnant in the near term, or lactating.

4.7. Premature withdrawal of patients from the study

A patient has the right to withdraw from the trial at any time and for any reason without affecting the patient's right to treatment by the investigator. The investigator also has the right to withdraw the patient in the event of adverse events.

Reasons for withdrawal will be recorded in the CRF. Data collected on study subjects up to the time of withdrawal will remain in the trial database. If possible and if the patient agrees, follow-up information will be obtained outside the original protocol.

5. DEFINITIONS

5.1. Upper and lower urinary tract infections and urosepsis

Lower urinary tract infection includes infection of the urethra (urethritis), bladder (cystitis), and ureters. A “true” infection requires symptoms and/or signs consistent with UTI as well as a positive urine culture ($> 10^3$ colony forming units (cfu) /ml).⁴⁴

Upper UTI refers to an ascending infection that has reached the renal pelvis (pyelonephritis).

Urosepsis connotes the presence of the systemic inflammatory response syndrome in a patient with an upper urinary tract infection.

5.2. Resistant bacteria and patients at increased risk

Resistant bacterium. A bacterium with acquired (not intrinsic) resistance to at least one agent in one class of antibacterial agents.

Multidrug-resistant bacterium. In accordance with the European Centre for Disease Prevention and Control's recent proposal for standard definitions of acquired resistance, we define a multidrug-resistant pathogen as one that is resistant to at least one agent in ≥ 3 classes of antimicrobial agents.⁴⁵

AIDA Work Package 2 protocol v7, 3 November 2014

Patients at increased risk for carriage of resistant pathogen(s). Several studies have attempted to identify independent risk factors for carriage of resistant uropathogens. A logistic model examining > 200 prospectively enrolled patients with urinary tract infections found that receipt of antibiotics in the preceding month and advanced age were independent factors predictive of subsequent isolation of a resistant uropathogen.⁴⁶ Among female and male patients presenting to emergency departments with various types of UTI, Wright et al. identified age \geq 65 years (OR 3.0, 95% CI 1.7 to 5.4) and antibiotic use in the previous three months (OR 4.6, 95% CI 2.8 to 7.5) as independent risk factors. Diabetes was also a risk factor when patients with urinary catheters were excluded (OR 2.4, 95% CI 1.1 to 5.3).⁴⁷ In another analysis by the same group specifically for factors predicting carriage of TMP-SMX resistant *E. coli* among the same patients, recent hospitalization (OR, 2.5; 95% CI, 1.1–5.7) and current antibiotic use (OR, 4.5; 95% CI, 2.0–10.2) were also identified.⁴⁸

We thus define a patient at increased risk for resistant uropathogens as having at least one of the following characteristics:

- Any systemic antibiotic exposure (\geq one dose) in the previous twelve months
- Hospitalization in an acute or long-term-care centre in the previous twelve months
- The present episode of suspected UTI fulfils criteria for healthcare-associated infection⁴⁹
- Current or recent (in the preceding twelve months) carriage of resistant organisms (e.g., MRSA, ESBL, quinolone-resistant *E. coli*)
- Recent stay in a high-risk country:
 - o Residence for at least one month in the preceding twelve months in the following countries:
 - Any country in the Mediterranean basin, excluding France
 - South Asia
 - Southeast Asia
 - Middle East
 - Africa
 - Central & South America

6. TRIAL MEDICATION

6.1. Selection of dosage and treatment duration

After randomization, individual participants will be randomized to one of two treatment arms to receive either fosfomycin 3 g po single-dose vs. nitrofurantoin (100 mg po tid) for 5 days.

6.2. Name and composition of antimicrobial agents

This study will employ nitrofurantoin in its macrocrystalline formulation and fosfomycin tromethamine in all participating sites. Fosfomycin tromethamine comes in sachet form; in the sachet are roughly 5.6 g of fosfomycin tromethamine, equivalent to 3g of fosfomycin. The medication is prepared by adding water to the granules in the sachet. In Switzerland, Furadantine retard (nitrofurantoin), distributed by Vifor Pharma, and Monuril (fosfomycin), distributed by Zambon, will be used.

6.3. Known side effects of the study medications

The following information is supplied by the Swiss Medical Compendium (Appendix 4). In > 1% of cases, nitrofurantoin causes headache, as well as nausea with or without vomiting

and loss of appetite. Allergic reactions, primarily manifested by rash, pruritis, or urticaria, are seen in 1-2% of cases. In 0.1 – 1% of cases, nitrofurantoin may cause allergic pulmonary infiltrates of either acute or chronic presentation. Both presentations are described almost exclusively in patients taking nitrofurantoin for more than several weeks or months. The acute form usually presents after at least one month of nitrofurantoin intake, and tends to resolve within 2-3 weeks after discontinuing the medication. The chronic form tends to occur after six months of nitrofurantoin therapy; signs and symptoms recede only partially. A peripheral polyneuritis has been described among patients with renal insufficiency, anemia, diabetes mellitus, electrolyte imbalances, and vitamin B deficiency.

In > 1% of cases, oral fosfomycin may cause vulvo-vaginitis, headache, diarrhea, nausea, or stomach upset. In 0.1 – 1% of cases, it may cause rash (with or without pruritis or urticarial), abdominal pain, or paresthesias. The frequency of occurrence of serious allergic reactions such as anaphylactic shock and angioedema is unknown.

6.4. Dose adjustment

For fosfomycin, no dosage adjustment will be possible, as it will be administered as a single dose only. Nitrofurantoin's dose will not be increased. Should clinical failure be suspected, or in the case of an adverse event, clinicians will discontinue nitrofurantoin in favor of an alternate antimicrobial agent, which will be recorded in the patient's CRF.

6.5. Pregnancy and breastfeeding

Patients who are either pregnant, wish to become pregnant in the near future, or breastfeeding, are not eligible for study participation.

6.6. Contraception

Given both study drugs' inclusion in pregnancy category B, and in light of the fact that several clinical human studies have shown no evidence of fetotoxicity with either drug,³⁹⁻⁴³ active proof of contraception will not be required for participation in the study. Rather, patients who are sexually active will simply be asked to use an effective form of contraception (e.g., condoms or an oral contraceptive) throughout the course of their antibiotic treatment.

6.7. Drug supply and storage

Nitrofurantoin and fosfomycin are not investigational drugs, having been on the market for several decades. Because they are already recommended as first-line agents for uncomplicated cystitis in women, they are frequently prescribed and covered by all Swiss health insurance companies. Thus, outpatients will be given a prescription by the study investigator for either antibiotic and then instructed to obtain the medication from the pharmacy, as they would normally do. Inpatients will be prescribed the study drug by the study investigator, and the insurance company billed correspondingly, as per routine.

Because the study will not provide the study medications, there will be no special storage or labelling procedures. Patients will receive the medication directly from hospital or outpatient pharmacies. Nonetheless, patients will be instructed to bring the medication package to the first follow-up visit, so that the medication lot number and expiration date can be documented.

6.8. Measurement of compliance

Compliance will be reported by the patients by means of oral communication with investigators at planned study visits.

6.9. Concomitant therapy

Concomitant, non-antimicrobial therapy will be recorded at study entry and upon follow-up visits. Concomitant antimicrobial therapy is a study exclusion criterion.

7. EVALUATION CRITERIA

7.1. Primary outcome

The primary outcome is clinical response 28 days after completion of therapy. Clinical response is defined in the table below.

Table 4. Definitions of clinical and bacteriologic responses.

Clinical response	Definition
Clinical cure	Complete resolution of symptoms with no recurrence of symptoms or signs of UTI
Clinical failure	Need for additional, or change in, antibiotic treatment due to a UTI OR discontinuation due to lack of efficacy
Indeterminate	Either persistence of symptoms without objective evidence of infection (absence of bacteriuria or pyuria) OR any extenuating circumstances precluding a classification or clinical cure/failure
Bacteriologic response	Definition
Bacteriologic cure	Eradication of the infecting strain with no recurrence of bacteriuria ($<10^3$ cfu/mL) during follow-up
Bacteriologic recurrence	Bacteriuria $\geq 10^3$ cfu/mL However, bacteriologic recurrence without urinary tract symptoms will be designated asymptomatic bacteriuria and left untreated.

Because clinical outcomes are often difficult to assess (e.g., a patient may report overall improvement but persistent, subclinical dysuria while at the same time denying a need for additional, or change in, antibiotic treatment), patients' reported symptoms will be recorded in detail. Cases deemed "indeterminate" may be orally (and anonymously) presented to a panel of blinded study investigators (e.g., from alternate study sites) to determine whether the outcome can be classified more clearly as cure or failure. Cases defying further classification will remain "indeterminate."

7.2. Secondary outcomes

Secondary outcomes are listed in the box below; bacteriologic response is defined in the table above. Emergence of antibiotic resistance will be determined through a documented change in the cultured pathogen during the study period from phenotypic susceptibility to phenotypic resistance toward the index antibiotic initially assigned. Resistance to other antibiotic classes will also be assessed.

Primary outcomes

Clinical response 28 days after completion of therapy (day 33 \pm 7 days)

Secondary outcomes

Clinical response 14 days after completion of therapy (day 19 \pm 2)

Bacteriological response 14 and 28 days post treatment (days 19 \pm 2 and 33 \pm 7 days)

Incidence of "true UTI" among all included patients

Duration of symptoms after treatment initiation

Lost days of work in the 33-day study period

Hospital admission in the 33-day study period
Progression to pyelonephritis or urosepsis (see definitions below) in the 33-day study period
28-day mortality
Incidence of adverse events, with particular emphasis on toxicity of nitrofurantoin, including chronic hepatitis and pneumonitis
Emergence of antibiotic resistance

7.3. Chemical and microbiologic methods

Urine samples for urinalysis will be collected locally and analysed immediately according to the site's local guidelines. In Geneva, urine samples for culture will be collected in a sterile fashion and transported to the local microbiology laboratory normally serving the patient's medical care site. At the Geneva University Hospitals' Bacteriology Laboratory, urine cultures are performed according to CLSI guidelines⁵⁰ (see Appendix 2 for detailed protocol).

7.4. Antimicrobial susceptibility testing

At each site, local procedures will be followed. In Geneva, uropathogen susceptibility testing is performed according to EUCAST standards.⁵¹

8. DATA COLLECTION AND MANAGEMENT

8.1. Data collection

This study will use electronic data capture by means of an electronic case report form (eCRF), such as that developed by SecuTrial®, an encrypted, web-based platform for clinical trials used widely in Switzerland and abroad. Only approved study investigators and study nurses will have access to the eCRF; extent of data access will be contingent upon the user's role in the study.

Anonymisation of patient data. No individually identifiable health information will enter the electronic CRF. Patients will be given an anonymous study number under which their data will be recorded into this database. The principal investigator will maintain a master list containing a crosswalk conversion that will allow, in the case of an adverse event, for the matching of a patient's study number to personally identifiable information such as name and birthdate. This list will be kept separate from and outside of the electronic CRF and database.

8.2. Data storage

All data relevant to this study will be stored for 10 years from the end of the trial. Electronic data will be password protected, and paper documents will be stored in a locked cabinet.

8.3. Data quality control and quality assurance

Throughout the study, a quality control and assurance assessment will be performed to guarantee the strict application of the protocol and conformity of the data entered into the CRF with the source documents. With the exception of the data on adherence to the study treatment (which is directly recorded into the CRF), other data will be available from the medical and nursing charts, which are mostly electronically available in Geneva. This allows for frequent and regular validation of study CRF data.

8.4. Information for patients

After the study data have been analysed, participants will be informed of the overall findings of the study.

9. ADVERSE EVENTS MANAGEMENT

Throughout the course of the clinical trial, particular attention will be paid to adverse events and adverse drug reactions. Definitions in this section are in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (www.ich.org).

9.1. Definitions of adverse events

Adverse event (AE): Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse drug reaction (ADR): A response to a drug which is noxious and unintended and which occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function (definition applicable to marketed medicinal products).

Unexpected adverse drug reaction (UADR): An adverse reaction, the nature or severity of which is not consistent with the applicable product information (summary of product characteristics).

Serious adverse event (SAE) or serious adverse drug reaction (SAR): A serious adverse event or reaction is any untoward medical occurrence that, at any dose:

- results in death
- is life-threatening (this term refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe),
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect

9.2. Definitions of adverse event intensity

Intensity	Definition
Mild	Patient is aware of signs and symptoms but they are easily tolerated
Moderate	Signs / symptoms cause discomfort such that they interfere with usual activities
Severe	Patient is unable to work or perform usual activities

9.3. Definitions of adverse event causality

Causality code	Definition
----------------	------------

AIDA Work Package 2 protocol v7, 3 November 2014

Not assessable	A report suggesting an AE, which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.
Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship, which makes a causal relationship improbable, and in which other drugs / treatments, chemicals or underlying disease(s) provide plausible explanations.
Possible	A clinical event, including laboratory test abnormality, with a reasonable temporal relationship to administration of the drug / treatment, but which also could be explained by concomitant diseases or other drugs / treatments or chemicals.
Probable	A clinical event, including laboratory test abnormality, with a reasonable temporal relationship to administration of the drug / treatment, unlikely to be attributable to concomitant disease(s) or other drugs / treatments or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
Certain	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to study treatment and which cannot be explained by concomitant disease(s), other drugs / treatments or chemicals. The response to withdrawal of the treatment (dechallenge) should be clinically plausible. The event must be definitive either pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacologic phenomenon.) Rechallenge, if performed, is satisfactory.

9.4. Recording and reporting of adverse events

In accordance with the “*Verordnung über klinische Versuche mit Heilmitteln (VKlin)*,” all adverse events and adverse drug reactions will be recorded. A list of these events will be made available on a yearly basis to the Ethics Commission at Geneva University Hospitals (by the investigators) and to Swissmedic.

The record of adverse events will contain all AEs (signs and symptoms) that are either volunteered by patients or observed during or following study drug administration and during the course of the study on the appropriate CRF page.

The description will include

- the subject identification number
- name and start date of study drug administration
- the nature of the sign or symptom;
- the date of onset; date of resolution (duration);
- the severity / intensity
- the investigator’s judgement on possible relationship to study treatment or other therapy
- the action taken (if any), and the outcome.

All Suspected Adverse Drug Reactions that are both serious and unexpected (SUSAR) will be reported to the Ethics Commission at Geneva University Hospital and to Swissmedic within 7 days of first obtaining knowledge (if the event was life threatening or resulted in death) and within 15 days for all other events.

9.5. Evaluation, management and follow-up of adverse events

Consenting participants will be urged upon enrolment to contact the study investigator immediately in the case of any adverse event throughout the course of the study period. (Contact information is present in the informational study brochure.) The study investigator will immediately assess whether (1) the patient requires immediate medical attention, (2) the adverse event is likely to be an adverse drug reaction (i.e., whether a causal relationship with the study drug is probable), and (3) immediate discontinuation of the study drug is indicated. Should the answer to any of these three questions be affirmative, the patient will be asked to discontinue the study drug immediately. Depending on the investigator's assessment of the clinical severity of the event, a formal physical examination will be arranged either immediately or in the short term. Every adverse event will be followed up until the event is either resolved or adequately explained.

10. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

10.1. Number of patients and sample size

Assuming 90% and 80% clinical cure rates at day 28 after therapy completion with nitrofurantoin and fosfomycin, respectively (alpha 0.05, beta 0.80; two-tailed), and a roughly 12% attrition rate, we will need 600 patients, 300 in each treatment group, to show an absolute advantage of 10% over fosfomycin.

10.2. Data analysis

Blinding of the data analyst

Of note, this pragmatic trial is open-label for reasons of practicality; both patients and study investigators will be aware of the study drug administered. However, to increase validity where possible, the final analysis of study data will be blinded. Once study data are complete, a study investigator will export the anonymized data into Stata 12 (StataCorp, College Station, TX). This new statistical file will be structured in such a way that an independent data analyst (who has not had access to the study CRF) will be blinded to which medication each group received. The only element that will not lend itself to a blinded analysis is compliance, given fosfomycin's administration as a single dose. Models including compliance as a variable will not be assessed in a blinded fashion.

The alternative hypothesis is anticipated:

H₁: Nitrofurantoin will have a 10% advantage over fosfomycin in clinical and bacteriologic cure rates 28 days post treatment.

Two different patient populations will be analysed: the intention-to-treat (ITT) patient population and the microbiologically evaluable, per-protocol patient population. The ITT population will include all patients who were enrolled in the study. The per-protocol analysis will include all patients for whom all the microbiological data specified in the protocol are available. Patients with a negative urine culture immediately prior to starting antibiotic treatment will be excluded from the per-protocol analysis.

Comparisons of clinical, bacteriologic and other stated outcomes for patients receiving nitrofurantoin or fosfomycin will be performed using both crude and adjusted analyses. Categorical variables will be compared by Chi-squared or Fisher's exact test where appropriate, continuous variables by Student's t-test.

Due to the very low likelihood of unexpected SAEs related to the study drugs, which have both been on the market and widely used for several decades, no interim analysis will be performed, and stopping rules have not been pre-specified. Immediate attention will be paid to any suspected unexpected serious adverse reaction (SUSAR) occurring during the study period as described above.

11. ETHICS

11.1. Guidelines and legislation

This study will be conducted in accordance with the ethical principles stated in the most recent version of the Declaration of Helsinki, the ICH Guideline for Good Clinical Practice (E6), the CONSORT statement, and the relevant Swiss legislation (LPTh, Oclin).

11.2. Informed consent

An informed consent, written in accordance with the origins of the Declaration of Helsinki and the applicable laws of Switzerland, Poland and Israel will be obtained from all patients.

The patient will sign the Informed Consent Form (Appendix 1) before s/he enters the study. The Investigator will explain the nature, purpose and risks of the study and provide the patient with a copy of the patient information, which will state, in simple terms, the aim of the study and related procedures (Appendix 1). It will be made clear to the patient that she is free to refuse participation in the trial, and may withdraw consent at any time and for any reason without incurring any penalty or withholding of treatment.

The patient will be given sufficient time to consider the study's implications before deciding whether to participate. Patients who are approached about participation in the study, but do not wish to participate will be recorded and compared with the trial participants in order to document any enrolment bias.

11.3. Ethics committee approval

The present protocol and accompanying documents (patient information, informed consent, etc.) will be submitted to the Central Ethics Commission (Institutional Review Board, IRB) of the Geneva University Hospitals. The study will commence only once full approval has been granted from both the University's IRB and Swissmedic. Further, both peripheral sites will submit the study protocol to their local IRBs and appropriate governmental regulatory committees for approval before study launch.

11.4. Approval by Swissmedic

Only upon receiving approval from the Central Ethics Commission will Swissmedic be notified of this study for registry. The study will not be launched until Swissmedic grants full approval.

11.5. Personal data and data protection

All data obtained in the context of the clinical trial are subject to data protection. The patient's name and other personal data (excluding age and sex) will not be disclosed by the investigators. The storage of data for statistical assessment will likewise be performed only under the patient's anonymized study identification (see Section 8.1). Only the Site Investigator will have the means to identify a patient's name or other personal details via the study identification.

AIDA Work Package 2 protocol v7, 3 November 2014

If it becomes necessary in the course of the study to identify a patient's name for medical reasons, all individuals involved will be subject to an obligation to maintain secrecy. If personal data are stored and processed, the requirements of pertinent data protection legislation will be observed.

11.6. Modification of protocol

The Investigators and Sponsor will not implement any deviation from, or changes of, the protocol without mutual agreement and in a written form of an amendment to study protocol. The only exceptions are where it is necessary to eliminate an immediate hazard to study patients, or when the changes involve only logistical or administrative aspects of the study (e.g. change in monitor(s), change of telephone number(s)). The amendment will be signed and dated by those that signed the first version of the final protocol. Protocol amendments will be submitted to the concerned IECs and competent authorities in line with pertinent regulatory requirements.

12. PUBLICATION POLICY

12.1. Clinical trial registration

This clinical trial will be registered in an international registry of clinical trials. Registration will be performed before inclusion of the first patient.

12.2. Publications

At the end of this trial, at least one publication in a peer-reviewed journal and several presentations of the trial results at international conferences are planned.

13. FINANCING AND INSURANCE

13.1. Funding source and ownership of data

This is an investigator-initiated study. The grant provider of this investigator-initiated project (European Commission) and the manufacturers of the antibiotic agents have no role in collection, analysis, or interpretation of data; in writing of the report; or in the decision to submit the paper for publication.

13.2. Insurance

This investigator-initiated study meets criteria for the Geneva University Hospitals' insurance policy for clinical studies (Appendix 3, Centre de Recherche Clinique's "Bulletin 1"). This policy will cover any damage to health arising from participation in this clinical trial. Any damage to health, which might have arisen from this clinical trial, will be reported immediately by the investigator to the insurance company.

13.3. Compensation of subjects

For women who were recruited from the community, a total of 50 CHF will be given as remuneration, with 16.70 CHF pro rata should study participation be terminated early.

REFERENCES

1. Cuevas O, Cercenado E, Gimeno M, Marin M, Coronel P, Bouza E. Comparative in vitro activity of cefditoren and other antimicrobials against Enterobacteriaceae causing community-acquired uncomplicated urinary tract infections in women: a Spanish nationwide multicenter study. *Diagnostic microbiology and infectious disease*. 2010; **67**(3): 251-60.
2. Blaettler L, Mertz D, Frei R, Elzi L, Widmer AF, Battegay M, et al. Secular trend and risk factors for antimicrobial resistance in Escherichia coli isolates in Switzerland 1997-2007. *Infection*. 2009; **37**(6): 534-9.
3. Spanu T, Luzzaro F, Perilli M, Amicosante G, Toniolo A, Fadda G. Occurrence of extended-spectrum beta-lactamases in members of the family Enterobacteriaceae in Italy: implications for resistance to beta-lactams and other antimicrobial drugs. *Antimicrobial agents and chemotherapy*. 2002; **46**(1): 196-202.
4. Paterson DL, Mulazimoglu L, Casellas JM, Ko WC, Goossens H, Von Gottberg A, et al. Epidemiology of ciprofloxacin resistance and its relationship to extended-spectrum beta-lactamase production in Klebsiella pneumoniae isolates causing bacteremia. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2000; **30**(3): 473-8.
5. Gottesman BS, Carmeli Y, Shitrit P, Chowers M. Impact of quinolone restriction on resistance patterns of Escherichia coli isolated from urine by culture in a community setting. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2009; **49**(6): 869-75.
6. Garau J. Other antimicrobials of interest in the era of extended-spectrum beta-lactamases: fosfomycin, nitrofurantoin and tigecycline. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases*. 2008; **14 Suppl 1**: 198-202.
7. Popovic M, Steinort D, Pillai S, Joukhadar C. Fosfomycin: an old, new friend? *European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology*. 2010; **29**(2): 127-42.
8. Stamey TA. Recurrent urinary tract infections in female patients: an overview of management and treatment. *Rev Infect Dis*. 1987; **9 Suppl 2**: S195-210.
9. Drayer DE. Pharmacologically active drug metabolites: therapeutic and toxic activities, plasma and urine data in man, accumulation in renal failure. *Clin Pharmacokinet*. 1976; **1**(6): 426-43.
10. Naumann P. The value of antibiotic levels in tissue and in urine in the treatment of urinary tract infections. *The Journal of antimicrobial chemotherapy*. 1978; **4**(1): 9-17.
11. Gilbert DN. Urinary tract infections in patients with chronic renal insufficiency. *Clin J Am Soc Nephrol*. 2006; **1**(2): 327-31.
12. Iravani A, Klimberg I, Briefer C, Munera C, Kowalsky SF, Echols RM. A trial comparing low-dose, short-course ciprofloxacin and standard 7 day therapy with cotrimoxazole or nitrofurantoin in the treatment of uncomplicated urinary tract infection. *The Journal of antimicrobial chemotherapy*. 1999; **43 Suppl A**: 67-75.
13. Gupta K, Hooton TM, Roberts PL, Stamm WE. Short-course nitrofurantoin for the treatment of acute uncomplicated cystitis in women. *Archives of internal medicine*. 2007; **167**(20): 2207-12.
14. Elhanan G, Tabenkin H, Yahalom R, Raz R. Single-dose fosfomycin trometamol versus 5-day cephalexin regimen for treatment of uncomplicated lower urinary tract infections in women. *Antimicrobial agents and chemotherapy*. 1994; **38**(11): 2612-4.

AIDA Work Package 2 protocol v7, 3 November 2014

15. Cooper J, Raeburn AL, Brumfitt W, Hamilton-Miller JM. General practitioner study: fosfomycin trometamol versus amoxicillin clavulanate in acute urinary tract infections. *Chemotherapy*. 1990; **36 Suppl 1**: 24-6.
16. Jardin A. A general practitioner multicenter study: fosfomycin trometamol single dose versus piperimic acid multiple dose. *Infection*. 1990; **18 Suppl 2**: S89-93.
17. Crocchiolo P. Single-dose fosfomycin trometamol versus multiple-dose cotrimoxazole in the treatment of lower urinary tract infections in general practice. Multicenter Group of General Practitioners. *Chemotherapy*. 1990; **36 Suppl 1**: 37-40.
18. Harvard Davis R, O'Dowd TC, Holmes W, Smail J, Slack RC. A comparative double-blind randomised study of single dose fosfomycin trometamol with trimethoprim in the treatment of urinary tract infections in general practice. *Chemotherapy*. 1990; **36 Suppl 1**: 34-6.
19. Minassian MA, Lewis DA, Chattopadhyay D, Bovill B, Duckworth GJ, Williams JD. A comparison between single-dose fosfomycin trometamol (Monuril) and a 5-day course of trimethoprim in the treatment of uncomplicated lower urinary tract infection in women. *International journal of antimicrobial agents*. 1998; **10**(1): 39-47.
20. Stein GE. Comparison of single-dose fosfomycin and a 7-day course of nitrofurantoin in female patients with uncomplicated urinary tract infection. *Clinical therapeutics*. 1999; **21**(11): 1864-72.
21. Van Pienbroek E, Hermans J, Kaptein AA, Mulder JD. Fosfomycin trometamol in a single dose versus seven days nitrofurantoin in the treatment of acute uncomplicated urinary tract infections in women. *Pharmacy world & science : PWS*. 1993; **15**(6): 257-62.
22. de Jong Z, Pontonnier F, Plante P. Single-dose fosfomycin trometamol (Monuril) versus multiple-dose norfloxacin: results of a multicenter study in females with uncomplicated lower urinary tract infections. *Urologia internationalis*. 1991; **46**(4): 344-8.
23. Boerema JB, Willems FT. Fosfomycin trometamol in a single dose versus norfloxacin for seven days in the treatment of uncomplicated urinary infections in general practice. *Infection*. 1990; **18 Suppl 2**: S80-8.
24. Neuner EA, Sekeres J, Hall GS, van Duin D. Experience with fosfomycin for treatment of urinary tract infections due to multidrug-resistant organisms. *Antimicrobial agents and chemotherapy*. 2012; **56**(11): 5744-8.
25. Fosfomycin for urinary tract infections. *The Medical letter on drugs and therapeutics*. 1997; **39**(1005): 66-8.
26. [AFSSAPS Practice recommendations for diagnosis and antibiotic therapy of adult community urinary tract infections]. *Medecine et maladies infectieuses*. 2008; **38 Suppl 3**: S203-52.
27. Falagas ME, Vouloumanou EK, Trogias AG, Karadima M, Kapaskelis AM, Rafailidis PI, et al. Fosfomycin versus other antibiotics for the treatment of cystitis: a meta-analysis of randomized controlled trials. *The Journal of antimicrobial chemotherapy*. 2010; **65**(9): 1862-77.
28. Patel SS, Balfour JA, Bryson HM. Fosfomycin tromethamine. A review of its antibacterial activity, pharmacokinetic properties and therapeutic efficacy as a single-dose oral treatment for acute uncomplicated lower urinary tract infections. *Drugs*. 1997; **53**(4): 637-56.
29. Warren JW, Abrutyn E, Hebel JR, Johnson JR, Schaeffer AJ, Stamm WE. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Infectious Diseases Society of America (IDSA). *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 1999; **29**(4): 745-58.
30. van den Broek PJ, van Everdingen JJ. ['Urinary tract infections'--revised CBO guideline. Dutch Institute for Quality Assurance]. *Nederlands tijdschrift voor geneeskunde*. 1999; **143**(49): 2461-5.
31. Beckford-Ball J. Management of suspected bacterial urinary tract infection. *Nursing times*. 2006; **102**(36): 25-6.

AIDA Work Package 2 protocol v7, 3 November 2014

32. van Pinxteren B, van Vliet SM, Wiersma TJ, Goudswaard AN. [Summary of the practice guideline 'Urinary-tract infections' (second revision) from the Dutch College of General Practitioners]. *Nederlands tijdschrift voor geneeskunde*. 2006; **150**(13): 718-22.
33. Acute cystitis in women: Belgian guidelines.
34. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2011; **52**(5): e103-20.
35. Borsa F, Leroy A, Fillastre JP, Godin M, Moulin B. Comparative pharmacokinetics of tromethamine fosfomycin and calcium fosfomycin in young and elderly adults. *Antimicrobial agents and chemotherapy*. 1988; **32**(6): 938-41.
36. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Annals of internal medicine*. 2010; **152**(11): 726-32.
37. Sachs J, Geer T, Noell P, Kunin CM. Effect of renal function on urinary recovery of orally administered nitrofurantoin. *The New England journal of medicine*. 1968; **278**(19): 1032-5.
38. Daneman N, Gruneir A, Newman A, Fischer HD, Bronskill SE, Rochon PA, et al. Antibiotic use in long-term care facilities. *The Journal of antimicrobial chemotherapy*. 2011; **66**(12): 2856-63.
39. Cunha BA. Nitrofurantoin--current concepts. *Urology*. 1988; **32**(1): 67-71.
40. Cunha BA. New uses for older antibiotics: nitrofurantoin, amikacin, colistin, polymyxin B, doxycycline, and minocycline revisited. *The Medical clinics of North America*. 2006; **90**(6): 1089-107.
41. Reeves DS. Treatment of bacteriuria in pregnancy with single dose fosfomycin trometamol: a review. *Infection*. 1992; **20 Suppl 4**: S313-6.
42. Thoumsin H, Aghayan M, Lambotte R. Single dose fosfomycin trometamol versus multiple dose nitrofurantoin in pregnant women with bacteriuria: preliminary results. *Infection*. 1990; **18 Suppl 2**: S94-7.
43. Usta TA, Dogan O, Ates U, Yucel B, Onar Z, Kaya E. Comparison of single-dose and multiple-dose antibiotics for lower urinary tract infection in pregnancy. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics*. 2011; **114**(3): 229-33.
44. Nicolle LE. Uncomplicated urinary tract infection in adults including uncomplicated pyelonephritis. *The Urologic clinics of North America*. 2008; **35**(1): 1-12, v.
45. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases*. 2012; **18**(3): 268-81.
46. Leibovici L, Greenshtain S, Cohen O, Wysenbeek AJ. Toward improved empiric management of moderate to severe urinary tract infections. *Archives of internal medicine*. 1992; **152**(12): 2481-6.
47. Wright SW, Wrenn KD, Haynes M, Haas DW. Prevalence and risk factors for multidrug resistant uropathogens in ED patients. *The American journal of emergency medicine*. 2000; **18**(2): 143-6.
48. Wright SW, Wrenn KD, Haynes ML. Trimethoprim-sulfamethoxazole resistance among urinary coliform isolates. *Journal of general internal medicine*. 1999; **14**(10): 606-9.
49. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *American journal of infection control*. 2008; **36**(5): 309-32.
50. (CLSI). CaLSI. Urinalysis; Approved Guideline—Third Edition. CLSI document GP16-A3. 2009; **29**(4).



AIDA Work Package 2 protocol v7, 3 November 2014

51. Institute CaLS. Performance Standards for Antimicrobial Susceptibility Testing; Seventeenth Informational Supplement. CLSI document M100-S17. 2007; **27**(1).

14. APPENDICES

Appendix 1: Informed consent, AIDA Work Package 2 randomised controlled trial.

Appendix 2: Prestations du Laboratoire Central de Bactériologie des Hôpitaux Universitaires de Genève: Urine native / stabilise. Geneva, 9.3.2007.

Appendix 3: Bulletin 1, Centre de Recherche Clinique Info, Bulletin 1: Mise au point concernant l'assurance pour les essais cliniques. Geneva, February 2009.

Appendix 4: Traitement des infections urinaires non compliquées chez la femme en pratique ambulatoire: Recommandations cantonales dans le contexte de l'émergence des bactéries productrices de bêta-lactamase à spectre élargi (BLSE), 2010.

Appendix 5: Swiss Medical Compendium: information for nitrofurantoin and fosfomycin.