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Treatment duration and prognostics in febrile urinary tract infection

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Citation
Starre, W. E. van der. (2015, December 17). *Treatment duration and prognostics in febrile urinary tract infection*. Retrieved from https://hdl.handle.net/1887/37067

Version:	Corrected Publisher's Version
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Cover Page

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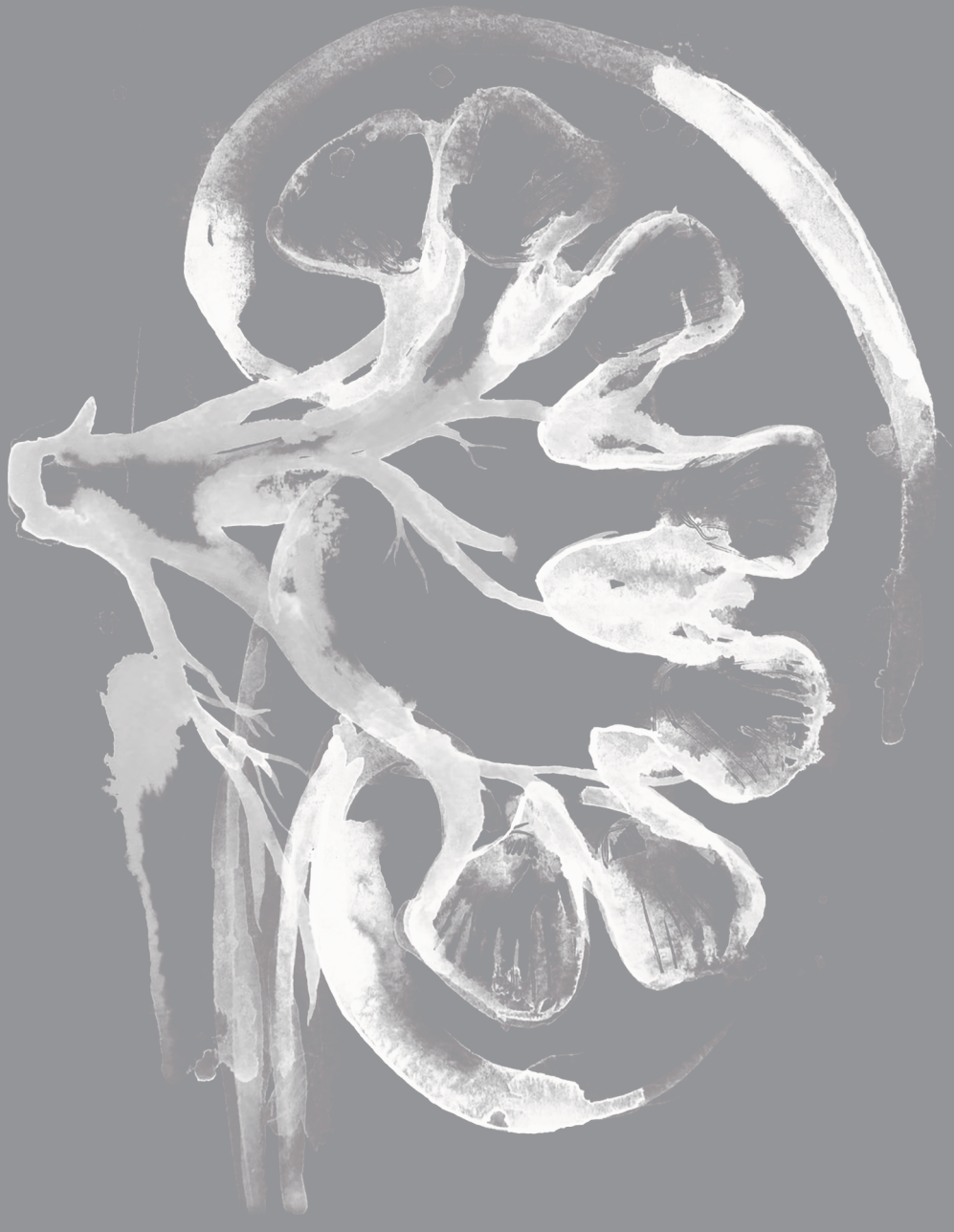
Title: Treatment duration and prognostics in febrile urinary tract infection
Issue Date: 2015-12-17



General introduction

Introduction

Urinary tract infection (UTI) is a common bacterial infection with substantial impact on quality of life and considerable health care expenditures across all ages.[1;2] Approximately half of all women will once experience an UTI during their lifetime. Moreover, elderly and patients with underlying illnesses like diabetes mellitus or urologic abnormalities are at increased risk.[3;4] It is expected that the incidence of UTI will continue to rise, given the increase in life expectancy and prevalence of diabetes mellitus in the next decades.

Classification

In the literature, various classifications of UTIs have been used, based on location of the infection, presence of fever and/or presence of complicating patient factors, which make the terminology and classification rather complex.

Firstly, based on the location, UTIs can be classified into 'lower UTI' and 'upper UTI'. When UTI is limited to the lower urinary tract (urethra and bladder), symptoms may include dysuria, urgency, frequency, hematuria and/or suprapubic pain, reflecting the presence of bladder infection (lower UTI or cystitis). If symptoms of lower UTI are accompanied by fever or chills, flank pain, nausea or vomiting, the upper urinary tract is also involved (upper UTI, kidney infection or pyelonephritis). In men, those symptoms may also reflect infection of the prostate (prostatitis). (Figure 1)

Another way of classifying UTIs is labelling UTI as 'uncomplicated' or 'complicated' by taking into account certain patient characteristics. The term 'uncomplicated' is usually restricted to premenopausal, non-pregnant women with no known anatomical or functional abnormalities of the urinary tract or other comorbidities.[5-7] However, some authors advocate to consider UTIs in women with well controlled diabetes mellitus or postmenopausal women without urological sequelae to be 'uncomplicated' too.[8] All other UTIs are by definition 'complicated', e.g. men and patients with urological abnormalities. To make it a some more complex, international guidelines use a combination of the above mentioned classifications: acute uncomplicated cystitis, acute uncomplicated pyelonephritis, complicated UTI and acute complicated pyelonephritis, and in addition for men several categories of prostatitis are distinguished.[6;8-13]

Given the broad range of classifications of UTIs in the literature, it makes sense to classify UTI patients uniformly according to their clinical presenta-

tion, in which fever is the main determinative clinical factor. Fever in UTI indicates that the infection is not limited to the bladder mucosa, but invasive and spread locally of systemically. Although an exact anatomical distinction can often not be made only on clinical symptoms, febrile UTI thus reflects the presence of a parenchymal inflammation of the urinary tract and the ensuing host response, in which the bladder, prostate, kidney, blood circulation, lymph nodes of the pelvis or a combination of those can be involved. In this thesis, we will use febrile UTI as the clinical syndrome of interest, because this is how patients present, and fever mainly determines the appropriate clinical approach. According to the discussed classifications, febrile UTI includes complicated UTI with fever, acute (un-)complicated pyelonephritis, acute prostatitis and urosepsis.

Pathogenesis

The majority of UTIs is caused by bacteria from the intestine that ascend through the urethra to the bladder and kidneys. *Escherichia coli* is by far the most common uropathogen, causing up to 80% of UTIs, followed by other bacteria such as *Klebsiella* species, *Proteus mirabilis* and *Pseudomonas aeruginosa*. Rarely, viruses and fungi are involved.[15;16]

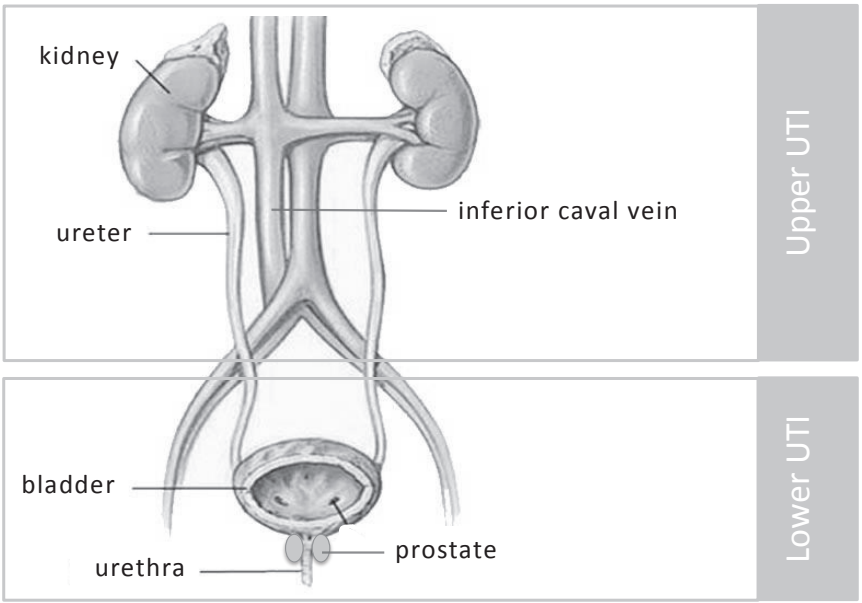


Figure 1. Lower UTI is limited to the urethra and bladder. Uropathogens may translocate to the prostate in men (prostatitis) and/or ascend to the kidney (acute pyelonephritis) and blood stream (urosepsis) causing a febrile upper UTI (adapted from [14]).

Periurethral colonization with a uropathogen usually is one of the critical initial steps in the pathogenesis of UTI. Most uropathogens originate from the rectal microbiota and enter the bladder via the urethra.[17] The urinary tract is normally well protected against microbial invasion by a variety of host defense mechanisms. The main defense mechanisms of the host against colonization of the bladder are dilution and micturition. However, several behavioural and environmental risk factors can facilitate the colonization and influence the susceptibility of the host. Anatomical or functional abnormalities that prevent complete emptying of the bladder, like urethral stenosis, benign prostate hypertrophia may increase the chance of colonization with uropathogens. Behavioural risk factors associated include voiding dysfunction, bladder catheterization and sexual intercourse.[18-20] After colonization, the next step in pathogenesis is the adhesion of uropathogens to the epithelial bladder and kidney cells and invasion into the tissue. After adherence, uropathogens are protected against wash-out by urine flow. Whether subsequent UTI occurs is the result of a dynamic interaction between the host and uropathogen.

Uropathogens have proven themselves to be a formidable opponent to the human host defense, capable of survival and rapid adaption in the relatively hostile environment of the urinary tract due to virulence factors. Virulence factors enable bacteria to overcome local host defences, enter and multiply within the urinary tract and invade the uroepithelium. Examples of such virulence factors, which have been studied in particular in *Escherichia coli* strains, include adhesins like fimbriae, siderophores, polysaccharide coatings, proteases and toxins.[21;22] Fimbriae, hair-like organelles, play a major role in the adhesion of *Escherichia coli* to the uroepithelial cells. The most important are type-1 fimbriae and P-fimbriae. Type-1 fimbriae cause adhesion to epithelial cells of the vagina, urethra and bladder, whereas P-fimbriae (type-2 fimbriae) adhere to kidney cells. In more than 70% of all *E. coli* strains of patients with acute pyelonephritis, such P-fimbriae are found.[15]

Despite the discussed first line of host defense, uropathogens may thus sometimes persist in the urinary tract due to effective virulence characteristics. Then, antimicrobial properties of the uroepithelium and the innate immune system of the urinary tract become critical to the host response to uropathogens. The uroepithelium produces several antimicrobial peptides, amongst others cathelicidin LL37, β-defensins and uromodulin, as part of the innate immune response.[23;24] Such antimicrobial peptides possess a direct

toxic activity. In addition, defensins e.g. can enhance innate responses by causing mast cell degranulation and by promoting neutrophil chemotaxis. Uromodulin adheres to fimbriae of uropathogenic *E. coli*, thus preventing its attachment to the epithelium. Uromodulin also has an immunomodulatory function.[25] If the antimicrobial peptides fail to completely kill and wash-out the invading pathogens, the innate immune response is initiated in order to eliminate the invading microbes. Toll-like receptors (TLR) are key initial molecules in the pathogenic cascade of UTI.[26] Bacterial recognition leads to cytokine (like IL-6, IL-8) and chemokine responses and recruitment of inflammatory cells.
The role of adaptive immunity in UTI remains controversial, but does not seem to play a primary role in the protection against bacteria, as is also reflected in the frequent recurrent UTIs observable especially in young women.[25;27]

Both antimicrobial properties of the urinary tract and the innate immune response to the presence of bacteria in the kidney may be influenced by genetic predisposition, as has been shown recently.[28-32]

Treatment

In the last decade, treatment of UTI has become more and more complicated by rising antimicrobial resistance of Enterobacteriaceae, the most common uropathogens of UTI. In the Netherlands, fluoroquinolones, amoxicillin-clavulanic acid and trimethoprim-sulfamethoxazole are yet the preferred agents for oral treatment of febrile UTI. Fluoroquinolones are recommended as first choice empirical agent, particularly because there is a relatively low rate of antimicrobial resistance.[5;33-35] However, the extensive use of antimicrobials in veterinary and human health care practice has resulted in the emergence and dissemination of resistant pathogens in the community, endangering the efficacy of (oral) treatment options.[36;37] In the Netherlands, a country known for its restrictive use of antibiotics and overall low rates of antimicrobial resistance, *Escherichia coli* resistance to fluoroquinolones increased from 3% in 2001 to 10-17% in 2014 with even higher rates at urology services.[38;39] In order to select the most appropriate empirical antimicrobial oral therapy, it is very important to know which patients are at particularly risk for e.g. fluoroquinolone-resistant uropathogens. However, data on host-related and/or environmental risk factors for fluoroquinolone resistance in community-acquired febrile UTI are limited.

With a lack of new antimicrobial classes in development,[40] it is increasingly important to develop strategies to maintain and even increase effectiveness of available antimicrobials. Optimization of treatment duration represents one such important strategy, because the development and spread of antimicrobial resistance is closely related to the total amount of antimicrobials used in countries.[41] The duration of antimicrobial therapy exerts differential selecting pressure on gut flora which leads to selection of resistant strains and reduction of resident commensal bacteria paving the road for e.g. *Clostridium difficile* infection.[42] Moreover, the potential adverse effects of unnecessary extended treatment periods reach beyond the individual treated: the longer antimicrobials are taken and excreted into the environment, the more pressure is exerted on the ecological balance of bacteria outside the human gut.[43]

Although febrile UTI is a relatively common and potentially severe infection, yet the optimal duration of treatment has not been established with the exception of uncomplicated cystitis and acute pyelonephritis in otherwise healthy women. Young women without comorbidities can be treated for febrile UTI with a 1-week regimen of fluoroquinolones provided a low level of fluoroquinolone resistance,[44] or, if proven susceptible, with a 2-week course of trimethoprim-sulfamethoxazole.[35;45-47] In contrast, there is less conformity on therapeutic approaches for other patient categories, as most randomized trials have excluded male patients, the elderly, and those with urinary tract abnormalities or underlying systemic illnesses.
Because of a lack of randomized treatment duration trials, current guidelines usually recommend antimicrobials for 7-14 days, with longer durations in special circumstances such as chronic bacterial prostatitis.[5;48-50]

It can be concluded that, despite the importance of minimal yet optimally efficacious duration of treatment, the evidence on optimal treatment duration of febrile UTI is scarce. We therefore initiated the FUTIRST- (*Febrile Urinary Tract Infection Randomized Short Treatment*) trial, a randomized, placebo-controlled double-blind non-inferiority study including consecutive adults presenting with a community-acquired febrile UTI. Patients were recruited at 35 primary care centers and 8 affiliating regional emergency departments in the Leiden-The Hague region (Figure 2). They were randomly assigned to receive ciprofloxacin 500 mg orally twice daily for 7 days or for 14 days. The aim of this study was to determine whether the efficacy and safety of a 7-day antimicrobial regimen (short treatment) is similar to a 14-day regimen

(standard treatment) in a unselected population with community-acquired febrile UTI.[51]

Apart from that, we performed a prospective observational multicentre cohort study. The aim of this study is to clarify the clinical relevance of urine and blood biomarkers, as well as genetic markers, for the prediction of severity and course of febrile UTI. Although several markers of febrile UTI (e.g. MR-proADM) have been identified, little is known of clinical relevance and specificity of biomarkers for disease progression and prognosis of the patient. The benefit of addition of urine and/or blood (bedside) biomarkers to readily-available clinical information will be evaluated with respect to patient's prognosis and management. Moreover, although selective genetic control of innate immunity (e.g. IL-6, IL-8) is presently being unravelled, little is known of the clinical relevance of such combined underlying genetic mechanisms.
To obtain these data, the participating patients were thoroughly followed clinically, and microbiological data and blood and urine samples were collected at different time points (Table 1).

Patients were recruited both in primary care and at regional emergency departments (Figure 2), reflecting a real-life, full spectrum of invasive UTI. The prognostic value of a certain biomarker measured in a febrile UTI patient at e.g. the emergency department is not one-to-one applicable to a febrile UTI patient presenting at a primary care center. The inclusion of both patients with a relatively mild illness as well as those with a life-threatening condition would allow us to investigate the prognostic value of biomarkers in various subgroups separately.

Table 1. Flowchart of data collection in febrile UTI patients (adapted from [51])

	Days after enrollment			
Assessment	**0**	**3-4**	**24-32**	**84-92**
Enrollment	x			
Demography	x			
Clinical data	x	x	x	x
Urine culture	x		x	
Blood culture	x			
Plasma sample	x	x	x	
Urine sample	x	x	x	
DNA sample	x			
Adverse events	x	x	x	x
Survival		x	x	x
Contact - in person	x	x	x	
Contact - by phone				x

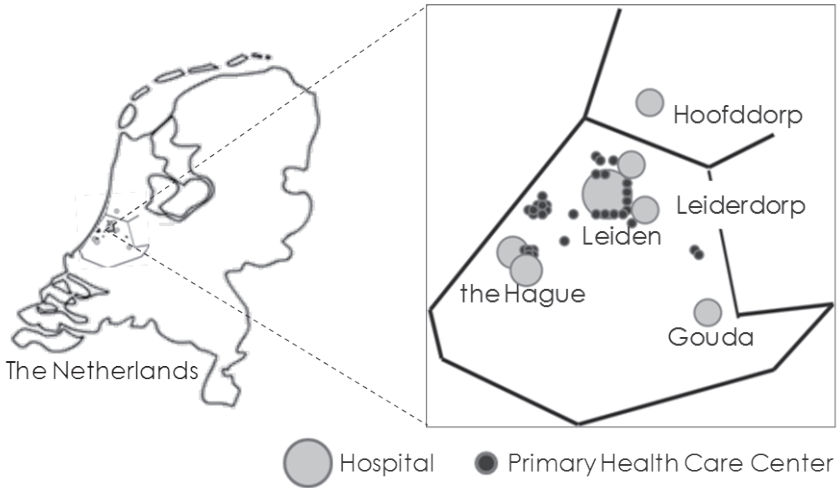


Figure 2. Participating study sites (adapted from [51])

Outline of the thesis

The aim of this thesis is to clarify the clinical relevance of urine and blood biomarkers, as well as genetic markers, for the prediction of severity and course of febrile UTI. Furthermore, this thesis focuses on the optimal duration of antimicrobial treatment.

In **Chapter 1**, we assess potential risk factors for resistance to fluoroquinolones in patients with febrile *Escherichia coli* UTI. Both host-related risk factors and environmental risk factors like contact with health care workers and animals were included.[52]
The review in **Chapter 2** highlights the main evidence from randomized trials on the optimal treatment duration of community-acquired febrile UTI.[53]
Chapter 3 describes the FUTIRST-trial, a randomized, placebo-controlled non-inferiority multicentre trial on treatment duration of febrile UTI.[51] In this trial, short treatment duration (7 days) is compared to standard (14 days) duration of oral ciprofloxacin with respect to clinical and microbiological cure both in primary care and in admitted patients.
The cohort study in **Chapter 4** evaluates the effect of pre-existing diabetes on presentation and microbiological and clinical outcome of febrile UTI. The effect of diabetes and concurrent illnesses is assessed separately.[54] Do diabetic patients with febrile UTI indeed have a complicated course or not?
Although several markers of febrile UTI (e.g., procalcitonin) have been identified, little is known of clinical relevance and specificity of biomarkers for disease progression and prognosis of the patient. **Chapter 5** evaluates the prognostic value of the plasma biomarker midregional pro-adrenomedullin (MR-proADM) in predicting bacteraemia, need for hospital admission and a complicated course of the infection. Moreover, this study compares the prognostic value of MR-proADM with more conventional biomarkers like C-reactive protein (CRP), leucocyte count and procalcitonin (PCT).[55]
Chapter 6 focuses on the host defense of febrile UTI, especially on its relation with the occurrence of bacteraemia. The study investigates the urinary production of cytokines (IL-6, IL-8) and antimicrobial peptides (cathelicidin LL37, β-defensin 2 and uromodulin) in febrile UTI. Moreover, the influence of plasma vitamin D level and genetic variations in host defense on the production of these urinary proteins and the clinical course is assessed.[56]
Sepsis is associated with activation of the coagulation cascade. Microparticles expressing procoagulant tissue factor (MP-TF) are released in blood concurrently with markers of inflammation and coagulation, and could play a

major role in the onset of sepsis-related morbidity. In **Chapter 7**, we evaluate whether the release of MP-TF into blood is accompanied by inflammatory and procoagulant changes in febrile *E. coli* UTI.[57]

Finally, in the general discussion, the major findings of all studies are summarized and remaining questions and the implications for future research are discussed.

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