Optimizing triage and treatment strategies in urinary tract infection

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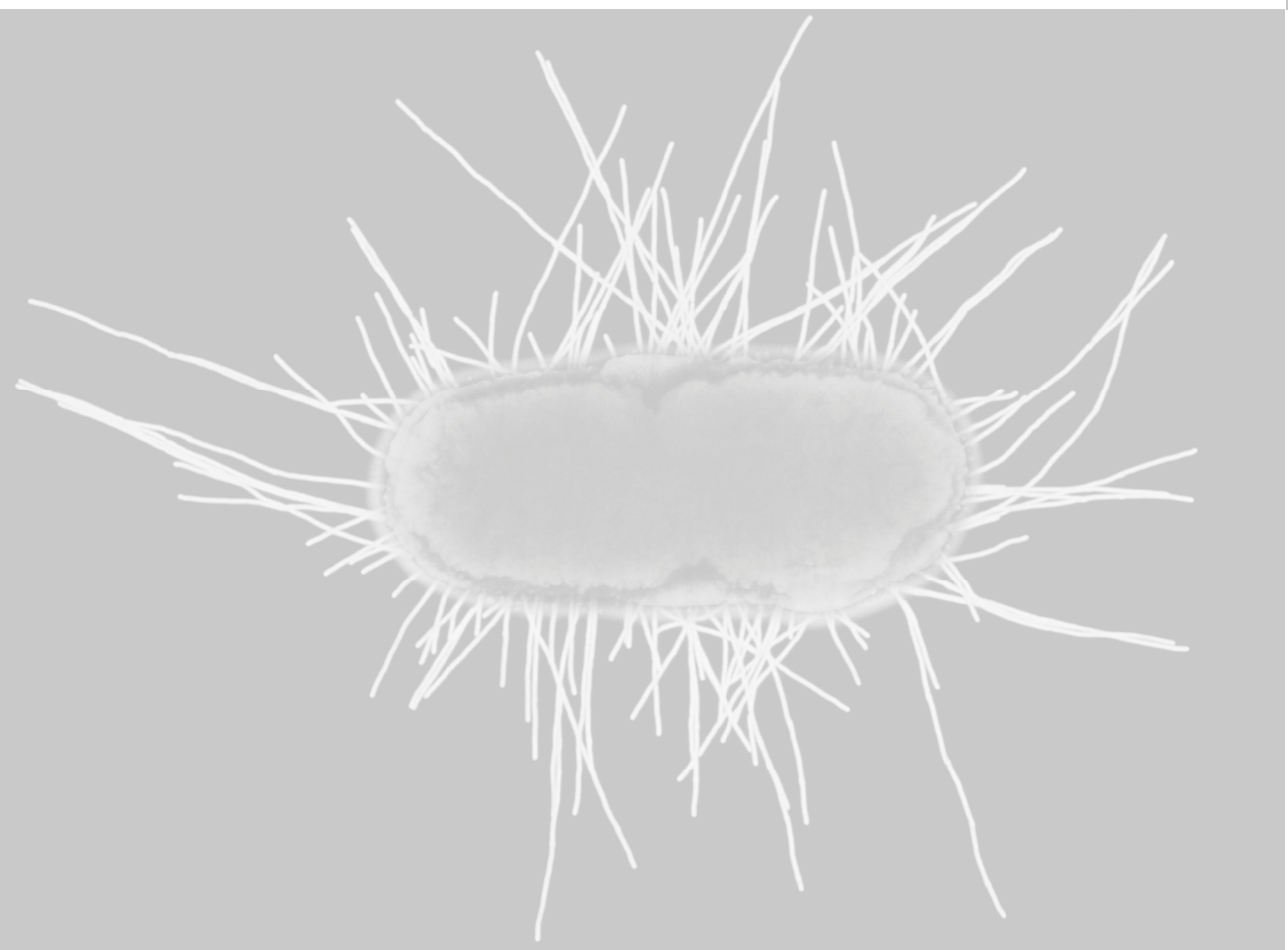

CHAPTER 1

Introduction and outline of the thesis

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INTRODUCTION

Urinary tract infections (UTIs) are a common reason for consultation in the emergency department (ED). The majority of UTI patients present with cystitis that can be diagnosed on clinical grounds only and treated with a short course of oral antibiotics; in case of a resistant causal uropathogen, the bladder infection may still be a self-limiting disease.[1] Although the majority of cystitis episodes are attended at the primary-care settings, they are also a frequent cause of ED consultation.[2] Fever in UTIs represents the presence of tissue invasion and inflammation such as pyelonephritis or prostatitis, both of which may be accompanied by urosepsis syndrome and progress to life-threatening septic shock. In febrile UTI, risk for a resistant uropathogen and complicated course should be evaluated to help guide clinical decisions regarding antimicrobial therapy and hospitalization.

In this chapter, we review the recent evidence for the optimization of diagnosis, triage decisions, and empirical therapy with a focus on febrile UTI at EDs.

DIAGNOSIS OF URINARY TRACT INFECTION

The clinical presentation is the cornerstone of diagnosis of UTIs. Classification of UTIs was recently updated to generalize the approach for clinical and research purposes.[3] Acute cystitis is characterized by dysuria, frequency, urgency and suprapubic pain without fever, and should be distinguished from invasive infection such as acute pyelonephritis, prostatitis, and urosepsis to allow a more rational use of antibiotics and other resources. The diagnosis is confirmed by the presence of a significant number of microbial pathogens within the urinary tract, but unfortunately the results of urine cultures are not immediately available at presentation in the ED to ensure correct diagnosis.

Leukocyturia supports a clinical suspicion of UTIs, but can be deceptive because of its low positive predictive value. A positive nitrite reaction is more accurate in diagnosing UTIs (positive likelihood ratio of 7.5–24.5), but its sensitivity is poor.[4] Particularly in elderly individuals, interpretation of urinary dipstick testing, urinalysis, and even urine culture is challenging because of the high prevalence (up to 60%) of asymptomatic bacteriuria. Additionally, adults aged 65 years and older may present with less clear symptoms. Caterino et al.[5] performed a retrospective cross-sectional analysis of the 2001–2008 National Hospital Ambulatory Medical Care Survey of adult patients visiting the ED with a diagnosis of UTIs, including cystitis and pyelonephritis, representing approximately 25 million ED visits for UTIs. In this study, urinary tract symptoms were identified in 32% of patients aged 18–64 years, in 24% in those aged 65–84 years, and 17% in those aged 85 and older. Age over 65 years and nursing home residence were associated with a lack of urinary tract symptoms.

Although studies of urine culture-proven UTIs in older inpatients showed a similar rate of urinary symptoms of 32%,[6] the absence of classic symptoms in this study raises the question

of correct diagnosis of UTIs in acute care setting. This finding was confirmed in a retrospective chart review, in which 43% of older women (70 and older) diagnosed with UTIs in the ED did not have a positive urine culture and 95% of these women were treated with antibiotics.[7] In these patients, the true cause of their complaints might have been overlooked, and the inappropriate use of antibiotics for presumed UTIs may contribute to the development of resistance. As older patients frequently have asymptomatic bacteriuria,[8] the percentage of patients with true UTIs among the symptomless patients might even be lower. Clearly, an effective strategy is needed to improve the diagnostic accuracy of UTIs in the ED.

ADDITIONAL VALUE OF BLOOD CULTURES

Urine cultures are recommended in case of invasive UTI to tailor antibiotic treatment. Bacteraemia is present in 19–29% of patients presenting with febrile UTI.[9-11]

In a prospective, multicenter study concerning adults with community-onset febrile UTI, the causative uropathogen was isolated from blood cultures only in 5% of patients with negative urine cultures. Antimicrobial pre-treatment [odds ratio (OR), 3.3; 95% confidence interval (CI), 1.5–7.1], an indwelling catheter (OR, 2.8; 95% CI, 1.0–7.5), and malignancy (OR, 2.7; 95% CI, 1.1–6.9) were identified as independent risk factors for these discordant culture results.[10] These findings were confirmed in a recent retrospective study, in which receiving antibiotic therapy at the moment of presentation (OR, 2.06; 95% CI, 1.18–3.61) was the only factor independently associated with discordant culture results (in 7% of patients).[11] These data show that blood cultures are of limited additional diagnostic value in most cases of febrile UTI. However, patients with a urinary catheter or malignancy or those who experience failure of antibiotic therapy for UTIs do have a higher risk for discordant cultures. We therefore recommend obtaining blood cultures for these specific patients.

IMAGING OF THE URINARY TRACT

Clinical studies evaluating the role of radiologic imaging in patients with febrile UTI are scarce. The European Association of Urology recommends ultrasound evaluation to rule out urinary obstruction in all patients with pyelonephritis and additional radiologic testing, such as computed tomography (CT), if fever persists after 72 h of appropriate treatment.[12] A recent prospective study validated a clinical rule to predict the need for radiologic imaging in febrile UTI patients at the EDs.[13] This study advocates performing ultrasonography only in patients with either a history of nephrolithiasis, renal insufficiency (MDRD <40ml/min/1.73m3), or a urinary pH at least 7.0. The absence of these predictors ruled out the presence of pyonephrosis or obstructive uropathy, the findings that were present in 6% of febrile UTI patients. Another retrospective study in bacteraemic UTI patients showed significant urologic abnormalities in

32% of the patients.[14] In this cohort, complicated diabetes, renal disease, pre-existing urologic abnormalities, or nephrolithiasis were significant predictors for the presence of hydronephrosis or renal stones. CT findings of the kidneys might be of prognostic value as it correlates with the disease severity of acute pyelonephritis.[15] However, to date, there are no studies demonstrating that CT findings of the urinary tract significantly alter the therapeutic strategy. On the basis of these findings, we recommend performing an immediate ultrasonography of the urinary tract in febrile UTI patients with either a history of nephrolithiasis, renal insufficiency (MDRD <40 ml/min/1.73m3) or a urinary pH of at least 7.0 and in those who require ICU admission.

ADMISSION POLICY IN FEBRILE URINARY TRACT INFECTION

Fever in patients with UTIs reflects deeper tissue involvement and the presence of pyelonephritis, acute prostatitis, or urosepsis. Febrile UTI usually presents as a mild or moderate infection, which can be treated safely by oral antimicrobials in an outpatient setting; a minority of cases progress to septic shock. Therefore, a critical decision at the ED is whether the patient has to be hospitalized. This decision has consequences for resources, laboratory evaluation, risk for nosocomial infections, possible hospital-acquired disability in elderly patients and thus, healthcare costs.

Currently, admission policy is at the discretion of the emergency physician and guided by history, underlying disease, and on the severity of local and vital signs. Clinical tools helping to classify risks in patients with febrile UTI are being developed to guide triage decision. As a rule, women with uncomplicated acute pyelonephritis can be safely treated with oral antimicrobials at home. Recently, a prospective study in women and men consecutively demonstrated that all patients with febrile UTI with no suspicion of deterioration to severe sepsis as judged 'on gut feeling' by the attending physician can also be safely treated at home with oral antibiotics.[16]. In the current clinical practice, this assessment is based on the clinical parameters such as history, underlying disease, and on the severity of local and vital signs. We evaluated the use of a clinical prediction rule at EDs to help guide triage upon hospital admission policy in patients with febrile UTI. The results of this study are outlined in Chapter 2.

BIOMARKERS AS PREDICTOR OF BACTERAEMIA OR ADVERSE EVENTS

Two compounds that are used as biomarkers are procalcitonin and pro-adrenomedullin.

Procalcitonin

Procalcitonin (PCT) is a prohormone of calcitonin, used as a biomarker for the diagnosis of bacterial infection and sepsis, and for differentiation from viral infection or auto-immune disorders. PCT has been shown to differentiate lower UTI from pyelonephritis in children and

may predict subsequent renal scarring in this population.[17] In adults with febrile UTI, PCT is a marker of bacteraemia.[18] Recently, this finding has been confirmed in a study including women with acute pyelonephritis.

PCT predicted the severity of sepsis and bacteraemia (area under the curve (AUC) of 0.75 and 0.72, respectively), but disease classification systems as Sequential Organ Failure Assessment score (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE) performed better in predicting 28-day mortality.[19] Ha et al. showed that PCT outperformed CRP in the prediction of bacteraemia in adults with acute pyelonephritis.[20] Debate on the value of PCT for triage decisions has not yet been closed, as in the study by Lemiale,[21] PCT could not predict a complicated course in outpatients with acute pyelonephritis.

Pro-adrenomedullin

Pro-adrenomedullin (proADM) is a promising inflammatory biomarker that, because of its shorthalf-life in serum, is measured best by its stable midregional fragment of pro-ADM (MR-proADM). Both proADM and MR-proADM levels are elevated in patients with sepsis.[22,23] A prospective multicenter study recently showed that MR-proADM accurately predicts a complicated course as reflected by bacteraemia and need for ICU admission, as well as 30-day mortality, in patients presenting with community-acquired febrile UTI. Predictive value of MR-proADM was superior to PCT and the more conventional biomarkers C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and leukocyte count.[24]

BIOMARKER-GUIDED TRIAGE

As biomarkers are objective, can be readily available in the ED if laboratory infrastructure is organized, and can predict complicated course, they might guide the physician in deciding the location of treatment. Claessens et al. report that biomarkers PCT, CRP, and midregional pro-natriuretic peptide did not help guide physicians to decide upon the need for hospital in patients with acute pyelonephritis.[25] MR-proADM might perform better, as its predictive value was superior to other biomarkers. Litke et al. retrospectively evaluated a virtual triage algorithm including patients with (un)complicated cystitis and febrile UTI.[26] Combination of proADM (>1.5 nmol/l) or urea (>14 mmol/l) with objective clinical admission criteria, such as inability to take oral antibiotics or evidence of serious complications or comorbidity necessitating hospitalization, could have reduced the hospitalization rate by 12% without compromising the safety.

Prospective interventional trials are needed to address this question, especially in patients with invasive UTI. Currently, a prospective, randomized study on pro-ADM-enhanced triage is conducted in Switzerland.[27] As outlined in Chapter 3, we evaluated the potential use of pro-ADM in patients presenting with febrile UTI.

THERAPY OF COMMUNITY-ONSET URINARY TRACT INFECTION

Antibiotic resistance among Gram-negative microorganisms complicates the management of UTI. The WHO published a first global assessment this year that showed alarming resistance rates throughout the world.[28] This report underlined the fact that surveillance of antimicrobial resistance is well organized in Europe and the USA, but remains poor in other regions. Resistance to third generation cephalosporins, most frequently used for the intravenous treatment of febrile UTI, and to fluoroquinolones exceed 50% in five of the six WHO regions. These numbers have to be interpreted with caution, because of variances in sample collection, interpretation of laboratory findings, and regional coverage, but they confirm the previous reports of increasing resistance worldwide.[29,30]

Awareness of the sensitivity rates of *Escherichia coli* isolates in the local region is essential for the appropriate empirical selection of agents to treat UTIs. These data obtained from the regional microbiology laboratories should be incorporated in the local treatment guidelines available in the ED. Restrictive use of antibiotics and adherence to guidelines are essential to reduce the antibiotic pressure worldwide and stop or slow down the development of resistance. The available antibiotics should be preserved for those patients who really need them, highlighting the importance of differentiating asymptomatic bacteriuria from UTI in the ED.

Acute uncomplicated cystitis

Recently updated guidelines from the Infectious Diseases Society of America (IDSA) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) recommend the use of nitrofurantoin, fosfomycin, and sulfamethoxazole–trimethoprim (SMX–TMP) as the first-line treatment for acute uncomplicated cystitis.[31] These agents reach adequate levels in the urine and have low propensity for collateral ecological damage. An additional advantage is that these agents usually remain active in the case of extended-spectrum beta-lactamase (ESBL)-producing Gram-negative bacteria. The empiric use of SMX–TMP is recommended if local resistance rate of uropathogens does not exceed the threshold of 20% or if the causative pathogen is known to be susceptible.[31] Fluoroquinolones and b-lactam agents (including inhibitor combinations) should be reserved for patients who failed in first-line therapy or with contraindications.

Widespread use of fluoroquinolones contributes to the development of resistance; therefore, it is important to reserve its use for patients with suspected invasive UTIs with a risk of bacteraemia.

Despite these recommendations, ciprofloxacin and levofloxacin are the most common prescribed drugs for acute cystitis in the USA.[32] We endorse antibiotic stewardship to reduce the inappropriate use of antibiotics. Simple interventions in the emergency room, such as the introduction of an electronic ordering set and feedback, have been shown to significantly and sustainably improve the adherence to guidelines (overall adherence to UTI treatment guideline increased from 44 to 82% and prescription of fluoroquinolones for uncomplicated cystitis decreased from 44 to 13%).[2]

Febrile urinary tract infection

In patients with febrile UTI, a urine culture with an antibiogram should be performed, to adjust empirical antimicrobial therapy according to the resistance pattern of the causative pathogen. In areas where the prevalence of resistance to fluoroquinolones is below 10%, ciprofloxacin is the recommended first-line outpatient treatment for acute uncomplicated pyelonephritis.[31] As a result of the high bioavailability, good penetration in renal and prostate tissue and blood, oral ciprofloxacin can be used even in the case of bacteraemia.[33]

In regions with higher level of ciprofloxacin resistance, a dose of a long-acting parental antimicrobial, such as a 1 g dose of ceftriaxone or a 24-h dose of an aminoglycoside, can be given once during the initiation of therapy while culture results are pending.[31]

Patients with systemic symptoms requiring hospitalization should better be started on an intravenous antimicrobial regimen. The optimal treatment differs regionally and should be adapted to local resistance prevalence. Most guidelines advise the use of second-generation cephalosporins with or without an aminoglycoside, third-generation cephalosporins, or carbapenems. Guideline-adherent initial treatment with a broad-spectrum agent should be tailored on the basis of susceptibility results and switched to a culture-directed oral agent as soon as possible, because this has been shown to reduce the length of hospital stay in a recent Dutch multicenter study.[34] This approach might have a favourable impact on the patient outcome and healthcare costs.

Identification of risk factors for resistant uropathogens

To select the appropriate empirical antibiotic treatment, it is essential to estimate the risk of the involved uropathogen resistant to antibiotics. Several recent studies addressed the identification of risk factors for resistance to fluoroquinolones in patients presenting to the ED with community-onset acute pyelonephritis, with reported resistance ranging from 12 to 34%.[35-40] Risk factors for resistance to fluoroquinolones imply prior use of antibiotics and healthcare-associated UTI, including a history of hospital admission within the last 3–6 months, the presence of an indwelling urinary catheter, nursing home residence, or recent invasive urinary instrumentation (Table 1).

Risk factors for community-acquired febrile UTI due to ESBL-producing enterobacteriaceae are similar, as shown in Table 1.[40-42] Interestingly, recent travel to an area where

ESBL is endemic was a strong predictor of ESBL producing uropathogens in Norway, where the prevalence of ESBL is low.[42] The range of prevalence of ESBL-positive isolates in these reports was 1.3–10.3%. Inappropriate initial antibiotic treatment did not lead to more clinical and microbiological failure in patients with ESBL-positive isolates in a Korean study,[41] but a resistant causative uropathogen is associated with a prolonged duration of hospitalization.[37,40,41] We recommend considering the adjustment of empirical therapy in patients presenting to the ED with febrile UTI and risk factors as presented in Table 1.

For patients at risk for fluoroquinolone resistance, intravenous therapy with an extended-spectrum cephalosporin is an option; in case of risk for ESBL-producing bacteria, the rational

choice would be to add an aminoglycoside to the regimen or to use a carbapenem [31]. Severity of disease, possibility of follow-up, and monitoring of treatment failure should be taken into account. In the case of a recent history of UTI with resistant bacteria, alternative treatment should also be considered.

Table 1. Risk factors for FQ-R and ESBL-producing uropathogens in community-onset acute pyelonephritis.

	Risk factor for	Multivariate odds ratio	Reference
Male sex	FQ-R	3.1	37,40
Exposure to antibiotics in the proceeding 3–6 months (fluoroquinolone strongest predictor)	FQ-R ESBL	2.3-17.5 3.1-4.2	35,37-42
Prior hospitalization within 6 months	FQ-R ESBL	2.0-4.8 7.4	35,36,38,40
Indwelling urinary catheter	FQ-R ESBL	3.1 4.4	35,36,41
Isolation of fluoroquinolone resistant *Escherichia coli* in the urine within the preceding 3 months	FQ-R	5.8	39
Nursing home residence	FQ-R	3.1-4.8	38,40
Recent travel to Asia, the Middle East or Africa (within 6 weeks)	ESBL	21	42
Underlying comorbidity such as diabetes, chronic kidney disease, haematological or neurological disease	FQ-R ESBL	2.9 3.2-16.8	37,39-42

ESBL, extended-spectrum beta lactamase; FQ-R, fluoroquinolone resistance.

CONCLUSION

Though UTI is part of the daily practice in EDs, there remain controversies upon its management. Policies to risk stratify patients to guide the choice of empirical antibiotic treatment and decisions upon need for hospitalization and need for microbiologic, radiologic, and urologic diagnostics should be improved. Blood cultures and ultrasound of the urinary tract might be restricted to specific patient groups. Women with acute uncomplicated pyelonephritis can be managed as outpatients, whereas this is less clear in other patient groups. Biomarkers such as pro-ADM might be of use in guiding admission policy. Empirical therapy of febrile UTI should be based on local susceptibility data, taking individual risk factors for resistance into account.

OUTLINE OF THE THESIS

The current thesis aims at optimizing care for patients with urinary tract infections, with a focus on admission policy, diagnostics and treatment duration in patients presenting with febrile UTI, and on UTIs caused by resistant uropathogens.

In **Chapter 2** we validated a clinical severity assessment tool, called the 'Prediction Rule for Admission policy in Complicated urinary Tract InfeCtion LEiden' (PRACTICE) in patients with febrile urinary tract infection. Subsequently, the use of the PRACTICE guiding admission policy was evaluated in a stepped wedge cluster randomized trial, enrolling patients presenting to the emergency department.

Chapter 3 focuses on improvement of risk assessment and triage decisions by the use of biomarkers. In this study, we compared the biomarkers MR-proADM, procalcitonin, CRP and the PRACTICE prediction tool in their ability to predict a clinically severe course of disease, initial hospitalization and subsequent readmission during the treatment of febrile UTI.

Chapter 4 describes a randomized placebo-controlled, double-blind, non-inferiority trial on treatment duration of febrile urinary tract infection. 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 hospitalized patients.

In **Chapter 5** we assessed the use of the biomarkers procalcitonin, MR-proADM and CRP to predict clinical cure or failure in these patients with community-acquired febrile urinary tract infection.

The study in **Chapter 6** reports on the effectiveness, the safety and the feasibility of prophylactic intravesical gentamicin treatment for patients with complex recurrent urinary tract infections caused by multidrug-resistant bacteria.

Chapter 7 describes a patient with recurrent urinary tract infections caused by multi-drug resistant *Pseudomonas aeruginosa*, which hampered a planned kidney transplant. He was treated with combined intravesical gentamicin, intravenous colistin and fecal microbiota transfer, and fecal microbiota profiles before and after treatment were analyzed.

In **Chapter 8** extended spectrum cephalosporin-resistant *Escherichia coli* isolates from patients with urinary tract infection, broilers, humans on broiler farms, versus isolates from humans in the general population were compared with respect to virulence factors, phylogenetic groups, and resistance genes.

In **Chapter 9** a retrospective case record study is presented on the use of automated urine microscopy analysis in the clinical diagnosis of urinary tract infection in an academic setting, aiming at defining an optimal diagnostic score based on both clinical and automated urine analysis parameters.

Finally, the results of the thesis are summarized and discussed in **Chapter 10**.

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