Optimizing triage and treatment strategies in urinary tract infection

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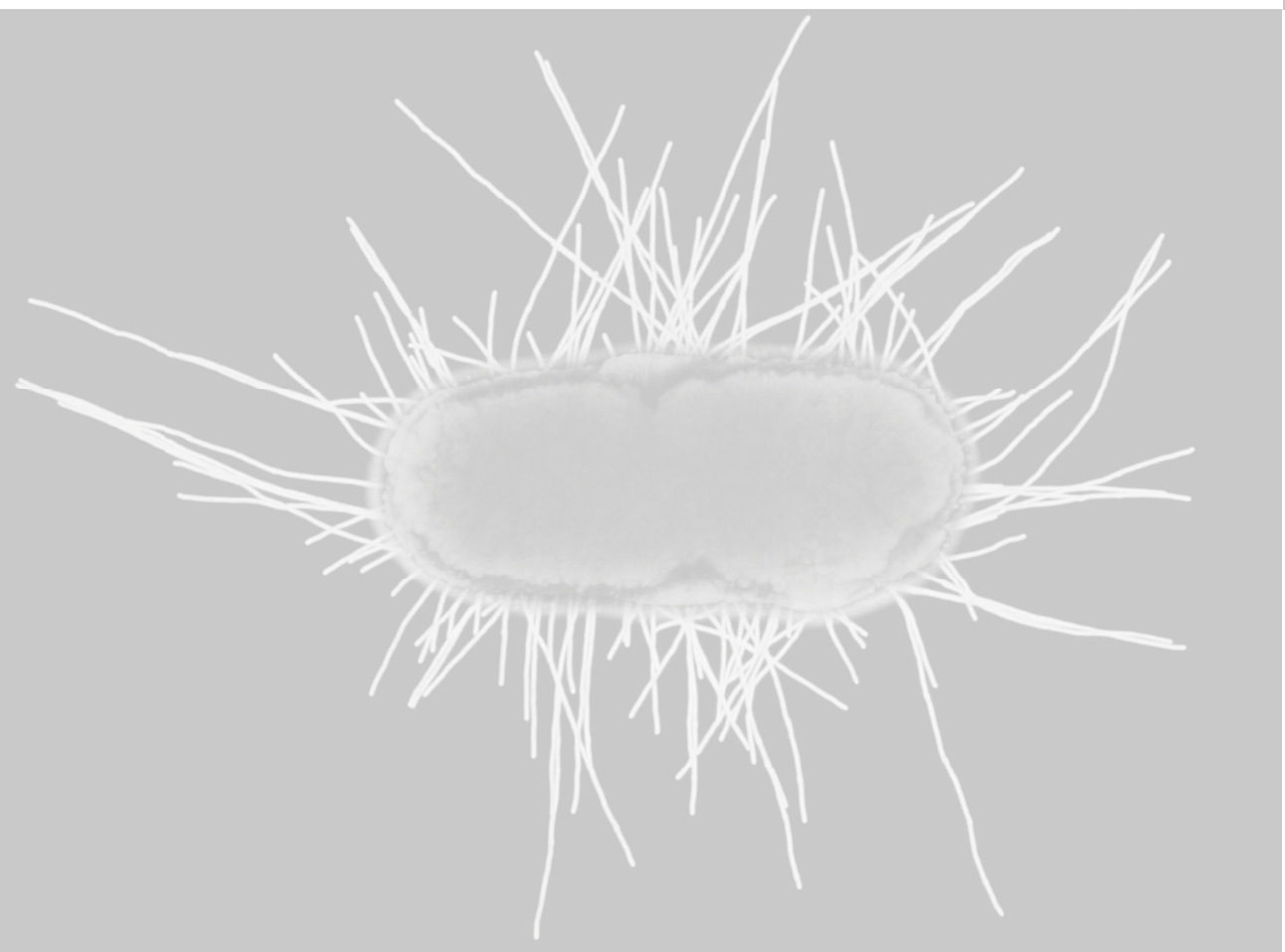


CHAPTER 10

Summary and general discussion

OPTIMIZING TRIAGE AND TREATMENT STRATEGIES IN URINARY TRACT INFECTION

Urinary tract infections (UTI) are among the most frequently encountered reasons for medical consultation in infectious diseases. The majority of UTI are confined to the bladder (i.e. acute cystitis) and belong to the routine daily practice of primary care. In otherwise healthy patients, acute cystitis can be self-limiting and in case antimicrobial treatment is indicated, a short course of antibiotics is usually sufficient.[1-3] In patients with underlying urologic abnormalities or recurrent cystitis, management can be more complex, especially of infections caused by drug-resistant uropathogens.[4]

Acute cystitis should be distinguished from infections extending beyond the bladder, such as acute pyelonephritis and prostatitis, which are tissue-invasive forms of urinary infection characterized by fever or other systemic symptoms.[5] Fever is a sign with little specificity and may indicate the mere presence of local kidney infection or of impending urosepsis. Prompt recognition and start of adequate antibiotic treatment of the latter condition is essential, to prevent progression to septic shock and death. However, the majority of patients with febrile UTI present with mild illness and respond favorably to antibiotic treatment.

The first part (**Chapters 2 to 5**) of this thesis focuses on research questions concerning the management of patients with febrile urinary tract infections (fUTI). In the second part, urinary tract infections complicated by multidrug-resistance (**Chapters 6 to 8**), and diagnosis of UTI (**Chapter 9**) are addressed.

Optimal triage strategy: when should a patient with community- acquired fUTI be hospitalized?

Although patients who present to the emergency department with fUTI generally have a low risk of a complicated course, many are admitted to the hospital for observation. Apparently, because of a small chance of life-threatening complications that cannot reliably be predicted, physicians tend to apply low thresholds for hospitalization. This suggests that many admissions may be avoidable, and that this practice leads to over-treatment of low severity patients and increased healthcare costs.[6,7] Accurate assessments of initial disease severity and the likelihood of disease progression are, therefore, crucial to provide a more personalized treatment strategy in the most appropriate setting.

Outpatient management is recommended for mildly ill patients who have minimal nausea, no vomiting, and stable coexisting medical conditions,[3,8] but literature to support this recommendation is limited as the majority of studies on outpatient management were restricted to healthy young to middle-aged women.[9-11] For suspected respiratory tract infection there are validated clinical tools, such as the *Pneumonia Severity Index* (PSI), to calculate the risk of clinical deterioration or death, that help the clinician decide whether hospital admission is indicated.[12] Such a clinical tool to identify those who require hospital admission is not available for fUTI. The predicting factors for mortality in the PSI, such as age, co-morbidity, and physical or laboratory

signs of sepsis are not specific for pneumonia. This risk assessment tool may, therefore, also be suitable for community-acquired infections other than pneumonia.

In **Chapter 2** we designed and validated a clinical severity assessment tool, called the '*Prediction Rule for Admission policy in Complicated urinary Tract InfeCtion LEiden*' (PRACTICE).[13] In a cohort of 787 consecutive fUTI patients, the PRACTICE identified those at very low risk for 30-day mortality and ICU admission. These risks were very low (<2.5%) in patients with a PRACTICE score below 100, yet 60% of patients in this group had been hospitalized. The use of the PRACTICE in guiding admission policy was subsequently evaluated in a stepped wedge cluster randomized trial, enrolling patients presenting to the emergency departments (ED) of seven hospitals. All participating centers started with a control period in which routine clinical practice with regard to hospitalization policy was applied. At the start of the intervention period, that was introduced at all participating centers in random order, the ED physicians were instructed to calculate the PRACTICE. Based on the patients' scores, recommendations were as follows: hospitalization for high risk (>100 points) and discharge to home for low-risk patients (<75 points). Preferably admission policy was done according to the PRACTICE, however, the attending physician was responsible for the final decision on treatment location.

Our hypothesis that the use of this prediction rule would reduce the hospitalization rate was confirmed in this study, as shown by a 20% absolute reduction. Unfortunately, the trial was stopped after inclusion of 370 patients due to safety concerns, because the percentage of patients who needed to be hospitalized for presumptive fUTI after initial home-based treatment (the secondary admission rate) of 27% exceeded the predefined stopping criterion.

Looking at the total of all patients included in the validation and intervention study, risks for mortality and ICU admission are still very low (Table 1a), much lower than the risks found in pneumonia patients in the initial validation study of the *Pneumonia Severity Index* (Table 1b).[12]

Table 1a. Clinical outcome of febrile urinary tract infection according to PRACTICE score risk class.

PRACTICE score in fUTI	Low risk 0-75	Intermediate risk 76-100	High risk >100	n
No. of patients	634	330	196	1157
Outpatient, No (%)	241 (38)	69 (21)	19 (10)	329
Inpatient, No (%)	393 (62)	261 (79)	177 (90)	831
30-day mortality, %	0.15	0.18	9.7	26
ICU admission, %	1.1	2.7	11.2	38

Table 1b. Clinical outcome of pneumonia according to PSI score risk class, adapted from Fine et al.[14]

PSI score in pneumonia	Low risk 0-70	Intermediate risk 71-90	High risk >90	n
No. of patients	1249	326	712	2287
Outpatient, No (%)	831 (66)	72 (22)	41 (6)	944
Inpatient, No (%)	418 (33)	254 (78)	671 (94)	1343
30-day mortality, %	0.32	0.92	14.9	113
ICU admission, %	4.3	5.9	13.2	167

Why did the implementation of the PRACTICE rule lead to more secondary hospitalizations in fUTI as compared to the PSI in pneumonia, which has been successfully introduced in routine patient care?

First of all, the course of disease and the pathway leading to the failure of home treatment is probably different in these two infections. Whereas respiratory distress is probably the main cause of secondary hospitalization of pneumonia patients; inability to take oral medication and the need for volume resuscitation is more important for fUTI patients. These factors may have been underrepresented in the outcome of complicated course of fUTI as predicted by the PRACTICE in the validation cohort since the majority of low-risk patients were traditionally hospitalized and treated with intravenous fluids and antibiotics. Secondly, two re-admissions because of *E. coli* bacteremia might have been avoided. These two patients were contacted by the treating physician after receiving the blood culture results and asked to return to the hospital for intravenous treatment. Ciprofloxacin has however been shown to be equally effective orally as intravenously in bacteraemic UTI[15] so that hospitalization would not have been warranted. Last but not least, nearly half of secondary admissions (4 out of 10) were not related to deterioration of the course of the fUTI, but due to diagnostic errors at the ED. Patients with primary bacteremia caused by salmonella, staphylococci, and streptococci, presenting with aspecific symptoms, such as fever and back pain, were mistaken for pyelonephritis and sent home. Apparently, these patients were 'misdiagnosed' at first consultation as having fUTI, and subsequently were treated for other diagnoses at secondary admission. Our real-world study underlines the importance of the validation of clinical prediction rules in a new cohort to verify its predictive value and usefulness in a clinical setting.

Evidently, the diagnosis of fUTI is not as straightforward as the diagnosis of pneumonia, where the presence of an infiltrate on a chest X-ray is both definitive and confirmative. It is of importance to be aware that other infectious diseases can mimic the general symptoms of fUTI and to realize that the presence of leukocyturia or bacteriuria, a common condition especially in elderly patients, can distract attention from the correct diagnosis. Improved diagnosis of fUTI is needed, not only to optimize fUTI treatment and to ensure safe implementation of clinical prediction rules but also to improve antibiotic stewardship. Differentiation between asymptomatic bacteriuria (ASB) and symptomatic UTI is important because for ASB antibiotic

treatment is not indicated, except for pregnant women and patients undergoing urological procedures.[16] Antimicrobial treatment of ASB outside these settings leads to unnecessary side-effects, potential drug interactions, unnecessary costs, and, importantly, adds to the development and spread of antibiotic resistance.[17] Inappropriate treatment of ASB is substantial in the emergency care setting and ranges from 20% in patients aged >12 years, up to 43% in older adults.[18-20] Clearly, there is a considerable potential for reduction of antibiotic use in these patients.

How can the prediction rule for admission of febrile urinary tract infection patients be optimized?

Prognosis of the patient presenting with severe febrile illness depends on two factors. First, the severity of the acute host response to the infection and the ensuing inflammatory cascade eventually leading to shock and multi-organ failure which causes hyperacute mortality. Secondly, the patient´s general health condition, mainly defined by age and comorbidity, determines the 30-day mortality in patients who survive the first days of illness. The severity of the acute host response is underrepresented in the PRACTICE, because it was based on the 30-day mortality in the validation cohort. In **Chapter 3**, we hypothesized that the addition of an objective blood biomarker reflecting the severity of sepsis, such as procalcitonin (PCT), midregional pro-adrenomedullin (MR-proADM) or C-reactive protein (CRP),[21] might improve the decision rule in identifying patients who benefit from hospital-based treatment in the acute phase without compromising safety. Therefore, we conducted a secondary analysis of the study presented in **Chapter 2**.[22] In this study, only patients with blood samples collected upon ED presentation available for biomarker analysis were included (n=313).

MR-proADM exhibited the strongest predictive value for a severe course of fUTI, defined as a composite of all-cause 30-day mortality, ICU admission, and extended hospitalization (> 10 days). Combinations of MR-proADM, PCT or PRACTICE did not significantly increase predictive ability over the use of MR-proADM alone. Concentrations of MR-proADM and PCT were both significantly higher in patients who were hospitalized as compared to those who were treated as outpatients. In the subgroup of patients that were initially treated as outpatients but that required secondary admission, MR-proADM was significantly elevated as compared to those who completed outpatient treatment at home. PCT concentrations were similar in these two groups. CRP did not have any added value in any of the groups for clinical guidance, although CRP has found its way into clinical practice and is routinely measured in all patients with fUTI.

Since the ability of MR-proADM to identify patients at risk for secondary admission was not improved by combination with the PRACTICE score, we further assessed the sole use of MR-proADM in a virtual biomarker-guided treatment allocation study. Using a cut-off of 0.80 nmol/L, MR-proADM guided triage could decrease hospital admissions by 24% and would allow a higher proportion of patients to be safely treated as outpatients. The use of this cut-off would have resulted in only 2% of outpatient re-presentations to the ED, as well as no mortalities within 30 days, and no requirement for ICU admission. All of the patients with primary bacteremia who needed secondary admission in the primary study would have been hospitalized upon

first ED presentation if the MR-proADM cut-off was set at 0.80 nmol/L. We, therefore, consider MR-proADM to be the optimal biomarker for UTI triage, and 0.80 nmol/L the optimal cut-off concerning patient safety. However, though these results are promising, our virtual biomarker-guided triage can only be considered as hypothesis generating. The next step is to verify the use of MR-proADM to identify those who benefit from hospital admission in a clinical trial. Furthermore, any decision based on a biomarker or triage algorithm should be critically appraised for the use in an individual patient. Factors such as comorbidity, compliance, lack of family support, or risk of an antimicrobial resistant pathogen should all be considered in the final decision.

Optimal treatment duration: how long should a patient with community-acquired fUTI be treated?

Although the benefits of using antibiotics are indisputable, its excessive use leads to resistance of pathogens. Antimicrobial resistance is a serious and growing public health threat, and thus it is essential to develop strategies to maintain the effectiveness of the available antimicrobials. The determination of the optimal duration of treatment is a simple and effective approach to antibiotic stewardship. Therefore, the general approach to treatment duration of common infections should be that "shorter is better". With respect to febrile UTI or acute pyelonephritis, trials for testing treatment duration have usually focused on otherwise healthy young women and have addressed optimal treatment duration by comparing the same drug for various durations of therapy or compared various treatment durations of several antimicrobial agents.[23] As such, recommendations about optimal treatment duration of UTIs in men, the elderly, hospitalized patients, and patients with comorbidities or bacteremia, remain unclear.

We conducted a randomized placebo-controlled double-blind multicenter non-inferiority trial to determine whether the efficacy and safety of a 7-day course of ciprofloxacin were similar to those in a 14-day ciprofloxacin course in an unselected population of both men and women.[24] Patients with community-acquired fUTI were recruited at regional hospitals and primary care centers, and clinical and microbiological cure rates were assessed. Clinical cure in this study was defined as being alive, free of fever and UTI symptoms, and without additional antimicrobial therapy (for relapse of UTI).

The results of this study are discussed in **Chapter 4**. We found that community-acquired fUTI can be safely and efficaciously treated with a 7-day instead of a 14-day course of oral ciprofloxacin in women, including the elderly with severe comorbidities, and irrespective of the severity of disease at presentation. Both treatment regimens were highly effective in women: 94% vs 93% clinical cure at 2-3 weeks after the end of treatment (for 7 versus 14 days, respectively) and a comparable high bacteriological cure rate. In men, however, 7-day treatment did not reach non-inferiority with a 14-day course of treatment, as shown by an increase in the rate of clinical (14% vs 2%) and bacteriological treatment failure after a 7-day compared to a 14-day treatment course, irrespective of comorbidities or complicating factors. Surprisingly, clinical cure rates assessed after longer follow-up (70–84 days post-treatment) were similar between 7 and 14 days of treatment in both women *and* men. In other words, the need for additional antibiotic UTI treatment during

longer follow-up is similar, irrespective of whether the initial treatment of fUTI was 7 or 14 days. Our findings suggest that fUTI in men likely involves the prostate, as involvement of the prostate is a known cause for recurrence of UTI even after appropriate antimicrobial treatment.[25]

These results extend the findings of a previous highly similar Swedish study performed in women with acute pyelonephritis, showing non-inferiority of 7- and 14-day antimicrobial treatment.[26] Compared to our study, their patient group was younger, had fewer comorbidities, and fewer of their patients had complicated UTI. In a recent study regarding the duration of antimicrobial therapy for Gram-negative bacteremia, a subgroup analysis in 282 patients with a urinary source of bacteremia confirmed that a different treatment duration is indicated for men and women.[27] After adjustments for confounders, there was no significant difference in the risk of treatment failure between short and long duration of therapy in women, but a 7- to 10-day course of therapy for men was associated with a significant increase in the risk of treatment failure compared to >10 days of therapy.

Unfortunately, due to the limited number of patients enrolled, our study lacks statistical power to draw confident conclusions on the various subgroups. Overall, we can conclude that in women - including postmenopausal women and those with significant comorbidities- febrile UTI can be treated successfully with a 7-day course of oral ciprofloxacin. In men, however, a short course leads to significantly more clinical failures than a 14-day course of ciprofloxacin, so men should be treated for at least two weeks. Additional studies to confirm optimal treatment duration in subgroups, and to determine optimal treatment duration with other classes of antimicrobial agents are needed. These studies should include outcome measures set at three months or even longer instead of the traditional 2-6 weeks.

Can biomarkers in blood provide guidance on optimal duration of antibiotic treatment for fUTI?

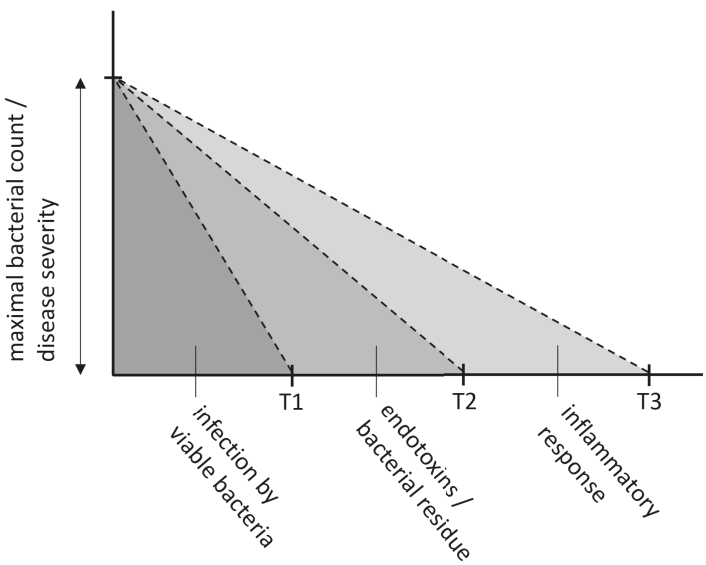
Procalcitonin (PCT) has been shown to provide useful guidance for duration of antibiotic treatment in patients with respiratory tract infections and sepsis.[28-30] PCT has also been shown to be a biomarker of bacteremia in patients with febrile UTI,[31-33] but little is known about its value as a biomarker for required treatment duration of fUTI. MR-proADM is a predictor of a complicated course of disease in fUTI, the need for ICU admission, and mortality,[21,34] but its use has not been tested for guidance of antibiotic treatment duration.

In **Chapter 5**, we assessed whether PCT measurement on days 0 and 3 could more accurately identify patients at risk of treatment failure and in need of a prolonged course of antibiotics compared to either MR-proADM or C-reactive protein. We found that the biomarker signatures of both PCT and MR-proADM correlated significantly with parameters that reflect the severity of invasive urinary tract infection, such as temperature, presence of bacteremia, shaking chills, and the need for initial administration of antibiotics intravenously rather than orally. Also, the course of PCT and MR-proADM correlated with signs of clinical recovery, such as time to defervescence and length of hospital stay. As opposed to PCT and MR-proADM, the popular biomarker CRP did not show any correlation with relevant clinical parameters. Although these findings seem

promising for the potential use of PCT and MR-proADM to aid the clinician with determining the length of antibiotic therapy, neither of these biomarkers could identify patients at risk for treatment failure in our study. This is likely due to the fact that all patients in our study were treated with antibiotics for at least 7 days, after which treatment success was already high (89% overall).

Historically, empiric treatment was based on the anticipated time to clinical recovery, while taking into account the interindividual variability of the severity of disease at the start of treatment by adding a 'safety margin' of some days to the average recovery time. Traditionally, the standard duration of antimicrobial treatment for acute pyelonephritis was 6 weeks until in 1987 a 2-week regimen was shown to be equally effective.[35] Only recently, additional studies including ours have provided evidence for a shorter therapy,[23,24,26] and this has already led to the introduction of a 7-day treatment regimen for all female patients with fUTI as the standard of care.[8] Some studies lend additional support for an even shorter fluoroquinolone regimen for mild to moderate pyelonephritis.[36,37] Our study design, unfortunately, did not allow for further assessment whether a (probably female) subgroup of patients could have been treated shorter than 7 days.

Figure 1. Hypothetic model of febrile urinary tract infection.



T0 medical consultation and start of antimicrobial treatment, T1 killing of all viable bacteria, T2 resolution of endotoxin / bacterial residue, T3 resolution of inflammatory response.

In Figure 1 a hypothetical model of febrile urinary tract infection is presented. Severity of the acute febrile UTI is on the Y-axis, which is a sum of the bacterial load and the intensity of the host response to the bacterial infection. On the X-axis, is the time necessary for bacterial killing

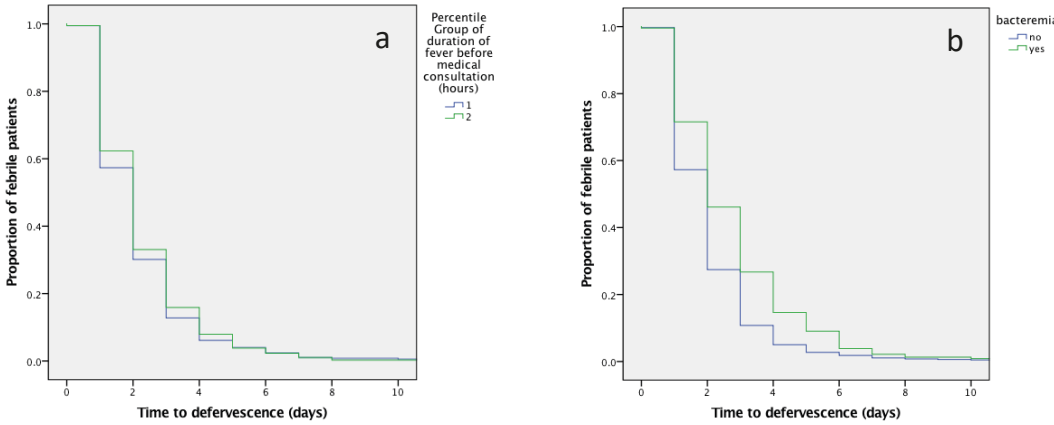
(T1), resolution of bacterial endotoxins and residue (T2) and for recovery from the symptoms of the infection (T3). After the start of antimicrobial treatment, the killing of bacteria results in the release of bacterial components that continue to trigger the host proinflammatory response. Since there is a considerable interindividual variability in disease severity, the starting point on the Y-axis differs substantially between patients. However, the rate of reduction of the bacterial load in response to the provided antimicrobial as represented by the gradient of the line will probably be quite similar in different patients. After all, all patients were treated either with an intravenous β-lactam antibiotic with or without aminoglycoside or with oral ciprofloxacin. These antibiotics have an excellent bioavailability and tissue concentrations well above the minimum inhibitory concentrations of the causative uropathogen have been reached, except in patients with pyonephrosis or renal abscess.

If the hypothetical model is correct, then the duration of symptoms of the infection will depend on the initial disease severity and may be assessed at first presentation. One could have predicted that our biomarker approach might have been successful in guiding treatments up to one or a few days after clinical recovery. The biomarker signature, however, lacked the ability to do so after the 7 days of treatment, when a strong margin surpasses the time for the biomarker signature to return to normal. Differences between patients in severity of illness at presentation and corresponding biomarker levels are likely to have normalized after 7 days of treatment, and definitely after 14 days.

If we look at all patients who participated in the PRACTICE study (validation and interventional cohort) and the FUTIRST trial combined (N = 1485),[13,24] the mean time to defervescence after the start of treatment was 2.3 days (SD 1.8). Once on antibiotic treatment, 40%, 68%, and 85% of the patients become afebrile within 1, 2, and 3 days, respectively.

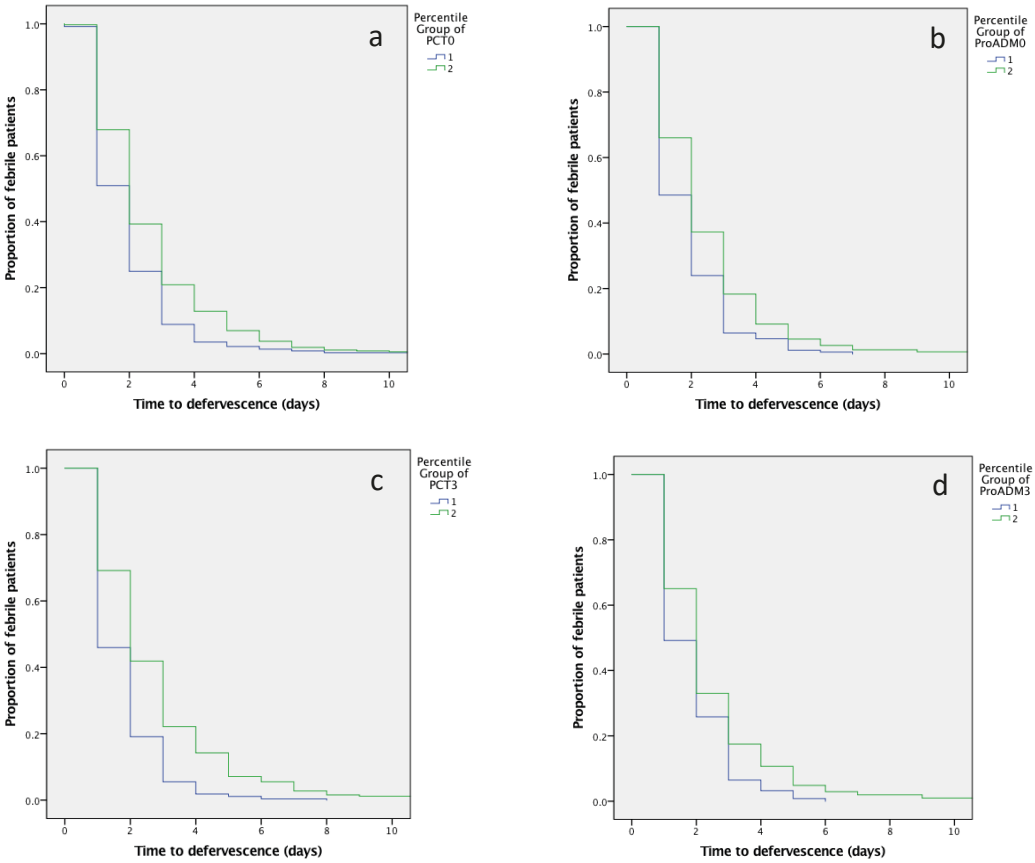
The time to defervescence is not correlated to duration of fever before presentation, as illustrated by the survival plot for two percentile groups in Figure 2a. Apparently, the bacterial load and the intensity of the provoked systemic inflammatory response before patients seek medical consultation, is not directly proportional to the duration of the infection. Patients with bacteremia and probably a higher bacterial load, needed more time to become afebrile after the start of treatment (mean fever duration 2.8 (SD 2.2) days in patients with bacteremia vs. 2.1 (SD 1.5) days in patients without bacteremia, $p < 0.01$; Figure 2b).

Figure 2. Survival function for the different levels of percentile group of a. duration of fever (hours) before medical consultation (N = 765, median 26, IQR 12 - 60, P = 0.24) and b. patients with (N = 232, 26%) and without (N = 660, 74%) bacteremia (P < 0.01).



As described in **Chapter 5**, the biomarkers PCT and MR-proADM, assessed at presentation and after three days of treatment, were also positively correlated with the time to defervescence in this larger study population. The strongest relationships were seen between PCT and time to defervescence (PCT at presentation t = 0.17, P < 0.01; PCT assessed at day 3 t = 0.22, P < 0.01). This is illustrated by the survival plots in Figure 3.

Figure 3. Survival function for the different levels of percentile group of a. PCT concentrations measured at presentation (N = 747, median 0.43, IQR 0.13 - 1.84, P < 0.01); b. MR-proADM concentrations measured at presentation (N = 324, median 0.95, IQR 0.68 - 1.47, P < 0.01); c. PCT concentrations measured at day 3 (N = 525, median 0.23, IQR 0.08 - 1.04, P < 0.01); d. MR-proADM concentrations measured at day 3 (N = 227, median 0.69, IQR 0.52 – 0.98, P < 0.01).



Finding the optimal time point between T1 and T3 (as close to T1 as possible) in our model in Figure 1, is key to minimize antibiotic treatment duration. It is likely that after the start of antimicrobial treatment, when the bacterial count decreases to below the threshold at which a fever response is provoked, the patient becomes afebrile while there are still viable bacteria present. If treatment duration is too short, these bacteria may grow back above the threshold level of symptoms and cause prompt relapse of disease. Measurement of bacterial compounds such as lipopolysaccharide (LPS) or bacterial DNA will not differentiate between viable bacteria that can cause relapse, or residue of killed bacteria after exposure to antibiotics. Therefore, it is advisable to use a biomarker that reflects both bacterial load and host response for guidance on treatment duration.

Based on our data, as well as previous experience in patients with acute respiratory tract infections and critically ill patients admitted to the ICU ward,[38,39] PCT appears to be the most

promising marker to help minimize antibiotic treatment duration in fUTI. Obviously, a prospective clinical trial including sufficient study subjects with community-acquired febrile urinary tract infection would be the next step forward in this matter.

Complex and multidrug-resistant urinary tract infections

The management of patients with recurrent urinary tract infections is challenging, even more so in the era of rising antimicrobial resistance. Multidrug-resistance is leading to an increased need for intravenous treatment of UTIs with last-resort antibiotics and subsequent hospitalizations. Prophylaxis with low dose oral antibiotics, as recommended by current guidelines, is often limited by multidrug-resistance of uropathogens, and may even extend the development of resistance. In patients with recurrent UTI due to multi-drug resistant uropathogens, intravesical gentamicin instillation is a valuable treatment option for either the suppression or prevention of UTI. Locally administered aminoglycosides circumvent systemic toxicity while development of antimicrobial resistance is unlikely because of high levels of the antibiotic in the urine and lack of antibiotic pressure on commensal gut flora. In **Chapter 6** the effectiveness, safety, and feasibility of prophylactic treatment with intravesical gentamicin after self-catheterization are described in patients with refractory recurrent urinary tract infections caused by multidrug-resistant (MDR) microorganisms.

We found that overnight intravesical gentamicin instillation reduced the number of UTI episodes in these patients, was well accepted, feasible, and safe. Systemic uptake of gentamicin was not detected, and no relevant side effects were reported. Although the number of infections was significantly reduced, there were nonetheless patients who had 'breakthrough infections'. The mean number of UTI episodes during six months of treatment was 1.0 (SD 1.2), which was a reduction of 79%. A total of eight patients stopped the prophylactic treatment because of clinical failure due to various causes. In two patients refractory to gentamicin instilments, other causes for their urinary symptoms were diagnosed. Three patients experienced recurrent exogenous reinfections (different uropathogens) with microorganisms less sensitive or resistant to gentamicin, such as *Enterococcus faecalis* and *Candida albicans*. The remaining three patients had recurrent or persistent symptoms and positive cultures with the same gentamicin-sensitive micro-organism consistent with an endogenous focus: two male patients with suspected chronic bacterial prostatitis, and one female patient with a suspected endogenous focus in the upper urinary tract (outside the reach of the antibiotic agent). Two other patients did not have clinical failure; yet, they had persistent asymptomatic positive cultures under gentamicin instillation and were found to have infected kidney stones. In all of these patients, failure of gentamicin instilments became apparent within six weeks. Therefore, a trial period of six weeks of gentamicin prophylaxis seems reasonable. In case of persistent urinary symptoms, further diagnostic evaluation is warranted. Apparently, intravesical gentamicin can also be used for diagnostic purposes to localize the site of bacterial persistence. In patients with persistent gentamicin-sensitive bacteriuria between instillations, a source in the upper urinary tract is likely, and further analysis should be performed, including imaging of the urinary tract and urine cultures obtained by selective sampling of both ureters.

The incidental breakthrough infections in the other patients may have been due to our treatment protocol, in which the frequency of instilments was reduced after two weeks from daily to every other day, and later to twice a week. Apparently, the short interval of one or two days between instillations is enough for the colonization with new bacteria that are not eradicated by the next antibiotic instilment. This finding could not be explained by resistance to gentamicin, and often the symptoms of UTI cleared up after seven days of consecutive daily instilments.

Treatment with overnight gentamicin instilments also had a positive effect on antimicrobial resistance. The percentage of MDR pathogens dropped from 79% to 24% after start of gentamicin prophylaxis, without an increase in resistance to gentamicin. The observed decrease in the antibiotic resistance in the breakthrough UTIs may be attributed to the decrease in the overall oral antibiotic use. More than half (56%) of the patients did not need to use any systemic antibiotics during the prophylactic treatment period and, due to the more favorable susceptibility profile, the majority of patients that needed systemic antimicrobial treatment, could be treated with first-line oral antibiotics.

Unfortunately, our attempt to perform a randomized, controlled trial failed because of the lack of patients willing to participate in a randomized trial that held the risk of being assigned to standard treatment (oral prophylaxis) that had failed them before. The study design was therefore changed to a prospective non-controlled trial. Obviously, a randomized controlled trial would have provided more insight into the efficacy of the treatment. It should be noted that the study participants represent a very specific population, with a high rate of complex urologic comorbidities, such as patients with renal transplant or neobladder, and that 59% of patients were on intermittent catheterization. In the majority of patients, treatment was complicated by multidrug-resistance or allergy to several oral antibiotics. Our data provide evidence that overnight intravesical gentamicin instilments are an effective and safe treatment option for complex and refractory cases, but not until after the standard management as advised by the guidelines has been attempted.[40]

Recurrent UTI by the same strain can arise from re-infection by bacteria that derive from the patients intestinal flora. In case of recurrent MDR infections, targeting the primary (intestinal) niche by decolonization may be a valuable approach to prevent relapsing infections. In **Chapter 7** a case of a 34-year old diabetes patient on peritoneal dialysis is described. This patient had recurrent urinary tract infections caused by a Verona Integron-encoded Metallo-β-lactamase (VIM)-positive *Pseudomonas aeruginosa*.[41] Because the only antibiotic available for systemic use (colistin, MIC 4 mg/ml) is nephrotoxic, a planned kidney-pancreas transplantation was considered contraindicated due to high infection risk and the patient was removed from the transplantation waiting list.

After chronic prostatitis or colonization at other sites than the gut were ruled out, he was treated with overnight intravesical gentamicin instilments and fecal microbiota transfer (FMT) in an attempt to eradicate MDR *Pseudomonas aeruginosa* from the intestinal tract. This treatment prevented recurrences of urinary tract infections with multidrug-resistant (MDR) *P. aeruginosa*,

but failed to eradicate intestinal colonization with MDR *E. coli*. Our findings contradict previous positive reports on FMT for decolonization of drug-resistant enterobacteriaceae.[42]

Microbiota analysis showed that our patient had intact microbiota diversity and composition at phylum level prior to FMT, in contrast to the diminished microbiota seen in patients with recurrent *Clostridium difficile* infection (CDI). Previous antibiotic treatment had not resulted in a distinct disturbance of the intestinal flora. Only minor changes of the microbiota composition were observed after FMT with a slight increase of cyanobacteria and tenericutes. We hypothesize that diminished diversity appears not to play a role in MDR carriership as opposed to recurrent CDI. Therefore, one might question the efficacy of fecal transplantation in patients with a normal microbiota diversity.

Extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae are a major concern worldwide and reported prevalence in clinical isolates is increasing. Urinary tract infections are the most common clinical manifestations of ESBL-producing *Escherichia coli*. The risk among healthy asymptomatic carriers of ESBL-producing *E. coli* to develop clinical infections due to colonizing strains is not yet well known. **Chapter 8** describes extended spectrum cephalosporin-resistant *E. coli* isolates from patients with urinary tract infection, broilers (meat chickens), individuals living and/or working on broiler farms, and individuals in the general population.[43] Multivariate analysis, based on ESBL/plasmidic-AmpC resistance genes, virulence profiles, and phylogenetic groups, revealed that most UTI isolates formed a clearly distinct group. The results show that transmission occurs between broilers and individuals on broiler farms, but also indicate that the role of broilers as a source of foodborne transmission of ESC-resistant *E. coli* to the general population and as cause of urinary tract infections is likely relatively small.

In the past few years, automated, standardized, quantitative urine analysis has been introduced in clinical practice and has shown high efficiency and accuracy compared to traditional sediment analysis. In **Chapter 9**, a retrospective case record study is presented that established a diagnostic scoring tool based on the combination of one of these relatively new automated urine analysis (IRIS Diagnostics iQ200 Elite) and clinical signs.[44] This scoring tool could rule out urinary tract infection in the majority of patients in the derivation cohort, and therefore could potentially improve antibiotic stewardship in suspected UTI cases. Validation in a new cohort of patients is required before the score can be implemented in clinical practice.

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