Beyond the cloudiness in urinary tract infection: definitions, diagnostics, and strategies for prevention

Bilsen, M.P.

Chapter 8

General discussion

The general aim of this thesis was to investigate current issues with the definition, diagnosis and treatment of urinary tract infection (UTI). The rationale for wanting to improve these aspects of UTI primarily lies in the significant physical and emotional burden faced by patients suffering from UTI. Beyond the burden on the individual patient, the high incidence of UTI puts a considerable strain on all layers of the health care system. The urgency to address these issues has only increased, given the escalating threat of antimicrobial resistance (AMR) to public health. The emergence of multidrug resistant organisms (MDROs) outpaces the development of novel antimicrobials. UTI is a key driver of AMR, not only due to its high incidence and tendency to recur, but also due to the inaccuracy of current urine diagnostics, particularly in older women. One of the root causes of inappropriate antimicrobial treatment is inappropriate diagnosis. Therefore, efforts to combat AMR should not only focus on developing novel antimicrobials, but also on improving diagnostics to support judicious antimicrobial use. Given the challenges in symptom assessment and the high prevalence of asymptomatic bacteriuria (ASB) in older women, accurate diagnostics for UTI are arguably most needed in this population. MDRO carriership is common in older adults, facilitating the spread of MDROs in the community, hospitals, and long-term care facilities (LTCF). [1, 2] To generate new, reliable data on novel diagnostics and treatment modalities for UTI, clear research definitions of UTI (and its various clinical phenotypes) are of paramount importance. Without an agreed reference standard, the internal and external validity of such studies is compromised.

This general discussion addresses the challenges related to the definition, diagnosis and treatment of UTI in three parts. For each part, the results of the studies in this thesis will be discussed, including implications for future research.

Part I: Defining UTI

Chapter 2 describes the results of a systematic review evaluating how UTI has been defined in recent studies. In total, 47 studies, published between 2019 and 2022, investigating prophylactic and therapeutic interventions in adults with UTI, were included. UTI definitions used in these studies were highly heterogeneous, consisting of various combinations of clinical signs and diagnostic tests (or a lack thereof). There are several factors that may explain this heterogeneity.

Firstly, the diverse clinical presentations and manifestations of UTI, taken together with a certain degree of subjectivity in symptoms, may lead to variations

in how researchers define UTI. As already mentioned in the introduction of this thesis, UTI is not a single clinical entity, but rather refers to a spectrum of disease manifestations. Secondly, there is a lack of consensus within the scientific community regarding thresholds for 'significant' pyuria and bacteriuria. This disagreement among experts was reflected in the various thresholds for pyuria and bacteriuria we found in the studies included in our systematic review. Thirdly, studies with distinct objectives (e.g. clinical trials and diagnostic accuracy studies) may use different criteria tailored to their specific research goals. A clinical trial evaluating the efficacy of a novel antimicrobial may define UTI based on the intended use of the antimicrobial for a specific population, e.g. including fever in the definition of UTI if the study drug has systemic properties. Diagnostic accuracy studies may define UTI based on more precise laboratory criteria. As our systematic review only included interventional studies, we could not deduce this from our data.

Differences between existing research guidelines may have led to conflicting definitions. European Medicines Agency (EMA) [3] and U.S. Food and Drug Administration (FDA) [4, 5] guidelines apply different symptom and laboratory criteria, leaving room for interpretation. Definitions of 'complicated UTI' are not uniform in these guidelines. In our systematic review, we found that 'complicated UTI' referred to two different clinical entities, i.e. UTI with systemic involvement and UTI with complicating host factors, likely due to the ambiguity of this term. However, the diversity observed in study definitions within our systematic review cannot be solely ascribed to conflicting guidelines, as the overall adherence to these guidelines proved to be low.

This leads us to question why adherence to existing guidelines is generally low. Apart from the lack of clarity within and cohesiveness between these guidelines, these guidelines were developed to facilitate clinical development programmes for novel antimicrobials or new uses and/or regimens for licensed antimicrobials. As such, researchers conducting studies for other purposes, e.g. evaluating novel diagnostic tests, may not feel compelled to follow these guidelines for their specific study objectives. Moreover, if there are no institutional or journal requirements mandating the use of specific guidelines or definitions, researchers may choose more flexible or alternative approaches. Other existing research guidelines are limited in their applicability, as they were developed for surveillance purposes or for studies conducted in specific settings, such as LTCFs. [6, 7]

The findings of our systematic review led us to establish a reference standard for UTI, intended for research purposes rather than clinical practice. As previously noted in the introduction section of this thesis, a reference standard is crucial for identification of homogeneous groups of patients for clinical research. Without a reference standard, bias is introduced into estimates of diagnostic accuracy and efficacy, affecting the internal validity of a study, and results cannot be readily compared with other studies (or synthesised for meta-analysis), compromising its external validity. Moreover, a reference standard creates a common language for international researchers.

We conducted a Delphi study, described in **Chapter 3** of this thesis, to achieve consensus on a reference standard. Used in various fields, the Delphi method has four main characteristics: an expert panel is questioned about the issue of interest, the process is anonymous to reduce the effect of dominant personalities, the questionnaires are iterative in nature, and the design of the subsequent rounds is informed by a summary of the group response of the previous round. [8] This study included 57 UTI experts from various countries across Europe and North America, representing medical specialties including infectious diseases, urology, microbiology, geriatrics, family medicine, and emergency medicine. After three questionnaire rounds, a high degree of consensus (94%) on the final reference standard was reached.

There are some notable differences between this reference standard and the aforementioned research guidelines. UTI diagnosis involves many factors, and in clinical practice there are levels of probability when diagnosing UTI. To reflect this, our reference standard includes a scoring system with possible, probable, and definite UTI categories, echoing the categorisation that can be found in the now widely-used *European Organisation for Research and Treatment of Cancer and the Mycoses Study Group* (EORTC/MSG) consensus definitions of invasive fungal diseases. [9] For clarity purposes, our reference standard steers away from the term 'complicated UTI' and instead distinguishes between UTI with and without systemic involvement. We chose this distinction to align more closely with clinical practice and to ensure that future UTI studies should then be able to focus upon clearly phenotyped cohorts. For instance, a recent randomised trial comparing a novel aminoglycoside to meropenem for the treatment of 'complicated UTI', applied the FDA definition, in which 'complicated' may either refer to UTI with systemic signs (e.g. fever) or UTI with complicating host factors (e.g. urological comorbidity). As a consequence, they included a heterogeneous group of study

participants with and without systemic involvement and various complicating host factors. [10] Aside from the probably unnecessary treatment of acute cystitis with broad-spectrum intravenous antibiotics in some study participants, this limits the interpretation of study results and the external validity of the study.

Another major difference between our reference standard and previous guidelines is the incorporation of different levels of pyuria. This decision was primarily based on study outcomes described in **Chapter 4**, in which we demonstrate that the low pyuria thresholds used in previous guidelines have low specificity for UTI in older women, and the degree of pyuria can help to distinguish UTI from ASB in this population. Considering the predominance of UTI in older women and the high need for reliable data in this understudied population, we believed that a new reference standard should take the high prevalence of ASB in older women into account and integrated this into our scoring system for pyuria (and bacteriuria) domains.

Despite compelling evidence that the absence of pyuria effectively rules out UTI [11, 12], our systematic review (**Chapter 2**) showed that pyuria was seldomly incorporated into study definitions, and if it was, the presence of leukocyte esterase on a urine dipstick was usually considered sufficient. As leukocyte esterase results exhibit poor correlation with absolute degrees of pyuria, and the quantification of pyuria is crucial for enhancing comparability across future studies, our reference standard is based on leukocyte quantification and omits urine dipstick items. While quantification of pyuria should also be encouraged in UTI studies conducted in primary and long-term care settings, our supplementary reference standard does include urine dipstick items, to ensure the broad applicability of our reference standard. Finally, our reference standard applies lower bacteriuria thresholds than any of the aforementioned standards. This decision was based on clear expert panel consensus and previous evidence demonstrating lower colony-counts in 'clear-cut' cases of UTI. [11, 12] The multifaceted scoring system of our reference standard mitigates the risk of a lower bacteriuria threshold leading to misclassification of ASB as UTI.

The open-ended question is whether our reference standard will be implemented in future UTI studies. While the low adherence to previous standards suggests a need for a new reference standard, the implementation of our reference standard is not assured. However, several aspects of our reference standard increase the likelihood of successful implementation. Firstly, by involving a large and diverse

group of stakeholders, we incorporated viewpoints from multiple different medical specialties and countries, increasing applicability and endorsement of the reference standard. The same approach has resulted in the widespread adoption of consensus definitions for invasive fungal diseases in major trials assessing antifungal drug efficacy, validation studies of diagnostic tests, and epidemiological research. [13] Similarly, our reference standard is versatile and applicable across various study types, in contrast to the EMA and FDA standards, which were specifically developed for the approval of new antimicrobials. Another strength of our reference standard lies in its clarity, specifically, its avoidance of ambiguous terms such as 'complicated UTI'. Ideally, the use of our reference standard would serve as a quality criterion for journals and ethical committees. It is important to reiterate that our reference standard was not developed for clinical practice and should, therefore, not be utilised in such settings. Our reference standard was not validated for clinical use and does not consider the practical aspects of clinical practice. For instance, a urine culture result may not be available at the time of patient presentation.

To ensure continued use of the reference standard in future studies, the reference standard will have to be updated once new evidence emerges. For instance, if the novel urine biomarkers described in **Chapter 5** of this thesis will have been validated in a broader population, they could be integrated in an updated reference standard. Additionally, further calibration of the reference standard in future studies may result in adjustments to certain domains or the weighting of specific criteria. While our reference standard was partially validated and calibrated using fictional case vignettes, future studies could involve a more extensive and diverse set of case vignettes. Alternatively, they could assess the alignment of the reference standard with actual clinical cases, as adjudicated by a separate expert panel.

Part II: Diagnostic challenges

As summarised in the introduction of this thesis, diagnosing UTI is perhaps most challenging in older women. One approach to addressing these diagnostic challenges in clinical practice is by examining how existing diagnostic tests can be optimised.

Due to their convenience, urine dipsticks are frequently used in primary care and LTCF settings, but they lack accuracy. [14] While automated microscopy and

urine flow cytometry are more precise methods for quantification of pyuria, currently applied reference values do not take the high prevalence of ASB (with concomitant pyuria) in older women into account. In **Chapter 4**, we describe the results of a case-control study, conducted across multiple primary care offices, LTCFs and emergency departments, in which we evaluated the diagnostic accuracy of automated microscopy and urine flow cytometry for UTI in women ≥ 65 years. Our main findings were as follows: both diagnostic methods had (equally) high diagnostic accuracy for UTI in this population, the level of pyuria could aid in distinguishing UTI from ASB, and the specificity of the commonly used pyuria threshold (10 leukocytes/µl) for UTI was poor (36%). These results are difficult to compare with prior studies, as they generally use the presence of bacteriuria as a proxy reference standard for UTI, which does not distinguish UTI from ASB. As has been stated, ramifications of inappropriately diagnosing UTI include antimicrobial overtreatment and failing to address the true cause of symptoms. In our study, a threshold of 200 leukocytes/µl increased the specificity to 86% (95% confidence interval (CI) 78 – 92), while maintaining a high sensitivity of 89% (95%CI 80 – 96), corresponding with a positive likelihood ratio of 6.3 (95%CI 3.9 – 10.3) and a negative likelihood ratio of 0.1 (95%CI 0.06 – 0.3).

The potential consequences of these findings for clinical practice differ per health care setting. In hospitals, pyuria is usually quantified (via automated microscopy or urine flowcytometry) in patients with suspected UTI, although some laboratories forego quantification if initial dipstick screening does not yield abnormal results. While the latter diagnostic strategy could contribute to underdiagnosis of UTI, the primary concern in older women is overdiagnosis, or rather, inappropriate diagnosis. Based on our findings in **Chapter 4** and the widespread availability of pyuria quantification in most hospitals, we propose that pyuria should be quantified in all women ≥ 65 years with suspected UTI in this setting, and a higher threshold (e.g. 200 leukocytes/µl) should be employed. Alternatively, the test result could be accompanied by a message reminding the ordering clinician that intermediate degrees of pyuria are also found in older women with ASB. Evidently, a one-size-fits-all threshold for pyuria is a concept better left in the past, and age-, sex-, and setting-specific reference values warrant further study.

However, the majority of women with suspected UTI present in primary care, and rates of ASB are highest in women residing in LTCF. [15, 16] Therefore, the potential impact of pyuria quantification and novel thresholds is arguably highest in these healthcare settings. Nevertheless, there are feasibility concerns

to address. While automated microscopy has the advantage of a reduced labour intensity, reduced interobserver variability, and higher throughput than manual microscopy, automated microscopy still requires some preanalytical steps and trained personnel to operate and maintain these automated systems. The Dutch primary care guideline on UTI [17] does recommend manual microscopy in case of leukocyte-esterase-positive and nitrite-negative urine dipstick results, but favours a urine dipslide (i.e. a slide coated with agar media for bacteriuria determination) in this scenario due to the ease-of-use. Alternatively, primary care physicians and geriatricians could send urine samples to central laboratories for pyuria quantification. However, this approach incurs additional financial and logistical costs, as pyuria quantification should be performed within a few hours for reliable results. [18]

In light of the feasibility challenges related to pyuria quantification in primary care offices and LTCFs, novel biomarkers are particularly needed in these settings. In **Chapter 5**, we have explored the diagnostic potential of twelve urine biomarkers in the same study population as described in **Chapter 4**. Urine biomarker concentrations were measured through liquid chromatography-mass spectrometry (LC-MS) and enzyme-linked immunosorbent assay (ELISA). We identified five urine biomarkers with high diagnostic accuracy for UTI in older women. Urinary interleukin 6 (IL-6), azurocidin, neutrophil gelatinase-associated lipocalin (NGAL), tissue inhibitor of metalloproteinases 2 (TIMP-2), and C-X-C motif chemokine 9 (CXCL-9) accurately differentiated older women with UTI from asymptomatic women, including those with ASB. Azurocidin exhibited the highest diagnostic accuracy (sensitivity 86% and specificity 89% at a cut-off of 16.7 ng/mmol creatinine). These biomarkers all play different roles in the innate immune response. [19-21] Interestingly, patients with ASB exhibited higher biomarker concentrations than asymptomatic patients without bacteriuria, but lower concentrations than patients with UTI, suggesting that ASB may cause a state of low-grade inflammation. A similar distribution was seen for pyuria concentrations in **Chapter 4**. IL-6 and azurocidin have been studied most extensively in this population, and our findings are consistent with prior studies. [22, 23]

However, some hurdles must be overcome before these novel biomarkers can be used in routine clinical practice, especially in non-hospital settings. Currently, these biomarkers are measured using ELISA and LC-MS. These methods are costly and require trained laboratory technicians. Less expensive and easier tests will

need to be developed, for instance in the form of point-of-care testing. A point-of-care test is a test that can be rapidly and easily performed at the patient's bedside. [24] These tests are already being developed. For instance, the Utriplex test is a point-of-care urine dipstick test measuring human neutrophil elastase, matrix metalloproteinase 8 and cystatin C. Its diagnostic accuracy was disappointing in a prior paediatric study, likely explained by misclassification as a result of their reference standard ('acute illness' with urine culture yielding a uropathogen ≥ 105 CFU/mL). However, this study illustrates that point-of-care testing for novel urinary inflammatory markers is feasible. [25]

Alternatively, rather than replacing pyuria as the keystone of UTI diagnosis, these new biomarkers could also be utilised in conjunction with pyuria to improve diagnostic accuracy. For instance, in a post hoc analysis in **Chapter 5** we found that when comparing UTI and ASB subgroups, the combination of several urine biomarkers with pyuria had superior diagnostic accuracy to pyuria alone. This is due to the fact that patients with ASB showed a rather wide range of pyuria.

Regardless of which diagnostic strategy will prove to be best, both in terms of accuracy and feasibility, our findings on both pyuria quantification and novel biomarkers need to be externally validated in a broader population with various clinical presentations (including non-specific symptoms), comorbidities and levels of frailty. Our case-control design and our study population were chosen to prove a concept for which a clear definition and reliable assessment of UTI and ASB was necessary but may have contributed to overestimated diagnostic accuracy results. Furthermore, our population was rather young and did not have advanced cognitive impairment, raising the question of whether our results apply to a more frail population. Future studies should also evaluate the impact of improved diagnostic accuracy on prescribing rates, MDRO colonisation rates, and patient outcomes (i.e. symptom burden).

Something we did not address in this thesis, but that may become increasingly important in the near future is reducing the turnaround time of pathogen identification and antimicrobial susceptibility testing (AST). Increasing AMR rates underscore the necessity of rapid AST results, allowing for tailored antimicrobial therapy. This is especially relevant in populations with high a priori probabilities of AMR, such as patients in LTCFs and patients with recurrent UTI. However, fast pathogen identification and susceptibility results can potentially lower the threshold for clinicians to prescribe (reserve) antimicrobials. While fast culture

results offer advantages in timely antimicrobial treatment, the associated risks underscore the importance of diagnostic tools capable of effectively differentiating between ASB and UTI.

Part III: Alternative prophylactic and treatment strategies

We have seen how ambiguous definitions and imprecise diagnostics of UTI contribute to inappropriate prescribing of antimicrobials, and thus to unnecessary side effects, drug interactions, *Clostridioides difficile* infections, and AMR. Patients with recurrent UTI (rUTI), defined as at least three episodes per year or two episodes per six months, particularly contribute to AMR, both due to frequent courses of antimicrobials and the use of continuous oral antimicrobial prophylaxis. [26] At the same time, patients with rUTI are disproportionally affected by the negative effects of AMR, as it limits their treatment options, sometimes precluding any oral antimicrobials. In healthy individuals, the gut microbiota, consisting of diverse communities of bacteria and other microorganisms, prevents the overgrowth of potentially harmful pathogens, also known as colonisation resistance. Antimicrobial treatment leads to a perturbed gut microbiota with impaired colonisation resistance, increasing the risk of invasive infections. These infections then require antimicrobial treatment, promoting further gut dysbiosis and selection of resistant strains. [27, 28] Worby et al. [28] have shown decreased gut microbial richness in women with rUTI. **Chapter 6 and 7** of this thesis focus on breaking this vicious cycle, which is displayed in **Figure 1**.

The direct instillation of antimicrobials in the bladder may be an appealing 'gut-sparing' alternative to systemic antimicrobial prophylaxis and treatment. For instance, in bacterial conjunctivitis, antimicrobial eye-drop formulations ensure a directly delivery of the drug to the site where it is needed, minimising systemic effects. Adjuvant chemotherapy in non-muscle invasive bladder cancer showcases the usefulness of targeted bladder delivery. [29] Beyond preserving the gut microbiota, intravesical antimicrobial therapy offers an additional potential advantage, i.e. the delivery of high concentrations of antimicrobials directly into the bladder. This targeted approach ensures that even pathogens with higher minimum inhibitory concentrations can be effectively eradicated.

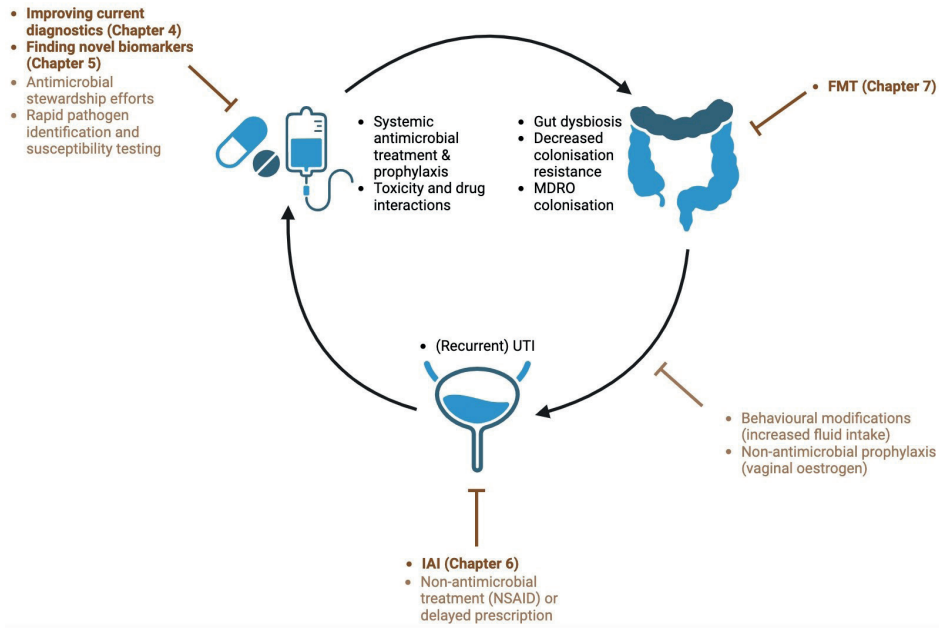

Figure 1: Vicious cycle of antimicrobial treatment and resistance. FMT = faecal microbiota transplantation, MDRO = multidrug resistant organism, IAI = intravesical aminoglycoside instillations, NSAID = non-steroidal anti-inflammatory drug, UTI = urinary tract infection

In **Chapter 6**, we describe the results of a cohort study including 44 patients who were treated with intravesical aminoglycoside instillations (IAI) in our institution. This study expands upon a prior study demonstrating efficacy of IAI in patients with rUTI, after which IAI was applied in a growing number of patients for longer durations. [30] Patients with multiple treatment cycles (on and off IAI) acted as their own controls. We found that IAI increased the time to the first recurrence and reduced the number of recurrences. This, together with the fact that one in four recurrences could be treated with daily instillations, reduced the number of oral and intravenous antimicrobial prescriptions. Moreover, serum aminoglycoside levels were undetectable in all but one patient, confirming the non-systemic potential of intravesical administration.

Furthermore, we found that the rate of UTI being caused by MDROs did not increase over the study period (18 and 14% off and on IAI respectively). We did see some instances of UTI due to aminoglycoside resistant Enterobacterales, but these

could be treated by oral antimicrobials and did not recur despite continuation of the same aminoglycoside. These aminoglycoside resistant strains are probably not the result of induced resistance, as IAI is gut-sparing, but rather the results of previous systemic antimicrobial treatment. In the previous study by Stalenhoef et al. [30] the rate of UTI being caused by MDRO dropped from 78 to 23%. We did not routinely perform faecal swabs in our patients, yet Stalenhoef et al. [30] found that intestinal colonisation remained relatively low at approximately 15%. Both Stalenhoef et al. and we did not investigate gut microbial richness, so whether IAI can alleviate gut dysbiosis remains an open question.

No malignancies were found on follow-up cystoscopy. While our data cannot definitively exclude the carcinogenic potential of long-term IAI, our relatively long follow-up period (more than 3.5 years for 25% of study participants) does diminish prior concerns.

Future studies should focus on the development of different antimicrobials for IAI. For instance, we observed more enterococcal infections in patients on IAI, which is likely explained by the fact that enterococci are frequently intrinsically resistant to high levels of aminoglycosides. Leaving aside the question of whether enterococcal infections should be treated at all, intravesical instillations with a vancomycin-containing regimen could address this matter. However, vancomycin does not have appropriate pharmacokinetic properties for intravesical installation as its efficacy is time-dependent rather than peak concentration-dependent, and intravesical antimicrobial concentrations rapidly decline due to urinary dilution and frequent voiding. In contrast with aminoglycosides, glycopeptides such as vancomycin do not exhibit a significant post-antibiotic effect.

Currently, methods to extend bladder incubation time of antimicrobials are being developed, for instance by means of nanoparticles. [31] These particles have been shown to promote endocytosis of antimicrobials into the urothelium in *in vitro* bladder models. Other non-antibiotic formulations are being investigated as well. The antiseptic cetylpyridinium chloride, which is a quaternary ammonium salt already being used in mouthwashes and eye drop formulations, was studied in three women with rUTI caused by extensively resistant uropathogens, with moderate success. [32] Other groups are exploring the potential of trimeric thiomannoside clusters, which prevent adherence of *E. coli* to the urothelium by inhibition of FimH adhesin. [31]

These new developments suggest that intravesical therapies are a promising modality for rUTI. However, the inconvenience of intravesical instillations will likely preclude its becoming a first-line modality. In our cohort, we found high treatment satisfaction scores. However, our population mainly consisted of postmenopausal women who had already failed continuous oral antimicrobial prophylaxis or who were immunocompromised due to kidney transplantation. As such, this group was highly motivated to try new therapies. For patients with a lower disease burden, intravesical installation, which requires clean intermittent catheterisation, might prove to be too invasive.

Another avenue to break the vicious cycle of gut dysbiosis and AMR, is by therapy directly targeting the gut. The most well-known example of effective gut restorative therapy is faecal microbiota transplantation (FMT) in patients with recurrent *Clostridioides difficile* infection (rCDI), a condition also characterised by gut dysbiosis. FMT involves introducing processed stool bacteria obtained from a healthy donor into the intestinal tract of a patient. In patients with rCDI, FMT has been shown to increase microbiota diversity and decrease the number of antibiotic resistance genes. [33, 34] Multiple studies have shown high cure rates in patients with rCDI, and FMT has become a widely used treatment modality for rCDI in clinical practice. [35]

In **Chapter 7**, we describe the results of a systematic review including recent studies that had investigated the efficacy of FMT for intestinal MDRO decolonisation. We found considerable heterogeneity between studies regarding the population, type of MDRO (mostly carbapenem-resistant Enterobacterales or vancomycin-resistant *Enterococcus*), route of administration, post-FMT antimicrobial use, and duration of follow-up. Although decolonisation rates varied greatly, the largest study showed significantly higher decolonisation rates in the FMT group compared with controls (66% versus 25% at 6 months, respectively). [36] Intriguingly, in two studies in the review, FMT showed a robust reduction in the number of MDRO infections (including UTI) even though the decolonisation rates were modest. [37, 38] A similar effect was seen in two other studies that were not included in the review. One study investigated the use of FMT in rCDI, and coincidentally found a reduced number of UTI recurrences (median 4 to 1 infections per year pre- and post-FMT, respectively). [39] While this finding might be explained by resolution of diarrhoea (thereby decreasing the risk of periurethral colonisation and exogeneous infection), it might also be explained by restoration of gut microbial richness and thus colonisation resistance. Recently, a small study showed FMT to be highly

effective in eradicating intestinal extended-spectrum beta-lactamase producing *E. coli* in kidney transplant recipients with rUTI. [40] In our tertiary care hospital, we are currently conducting a randomised clinical trial comparing FMT and oral decontamination with polymyxin and neomycin to oral decontamination only in the same target population, although its primary aim is to assess the safety of FMT in this population. Future studies should focus on the question whether FMT can not only reduce intestinal MDRO colonisation but also prevent recurrent infection in patients with rUTI.

The widespread application of FMT is impeded by the drawbacks inherent to this therapy: it is costly and invasive, and imposes a burden not only on the recipients but on donors as well. Alternatively, one could only administer selected components of the intestinal microbiota. For instance, a recent study showed that oral capsules composed of purified Firmicutes were highly effective in preventing a recurrent episode in patients with rCDI. [41]

Conclusion

Tackling the patient burden of UTI against the backdrop of increasing AMR will require a multifaceted approach, addressing both diagnostic and therapeutic knowledge gaps. To that end, this thesis underscores the importance of uniform research definitions and proposes a new reference standard. Furthermore, it shows the potential of both existing and new diagnostics for UTI in older patients, allowing for a more judicious use of antimicrobials. Finally, it highlights two alternative modalities for the management of patients with rUTI and MDRO colonisation. Follow up studies, building upon the work presented in this thesis, are already underway. As astutely put by Angela Huttner, UTI research is not an intellectual dead end, yet an exciting new frontier. [42]

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