Optimisation of the management of complicated UTI

K. D. Hendriks-Spoor

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PhD Thesis, Utrecht University, the Netherlands
ISBN: 978-94-6361-737-6
Author: Kelly Dalva Hendriks-Spoor
Cover: De Dokter by Gerard Dou from Rijksmuseum, Amsterdam
Layout and printing: Optima Grafische Communicatie (www.ogc.nl)

This thesis is printed with financial support from the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht.

Optimisation of the management of complicated UTI

Optimalisatie van de behandeling van de gecompliceerde urineweginfectie
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan
de Universiteit Utrecht op gezag van de
rector magnificus, prof.dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op

maandag 26 september 2022
des middags te 14.15 uur

door

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geboren op 25 september 1987
te Oosterhout

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Nobody said it was easy
No one ever said it would be this hard

Oh take me back to the start
I was just guessing at numbers and figures,
Pulling your puzzles apart
Questions of science, science and progress

Coldplay – The scientist

CONTENTS

1

GENERAL INTRODUCTION

GENERAL INTRODUCTION

Urinary tract infection (UTIs) is a collective name for several types of bacterial infections concerning the urinary tract. This includes infections of the lower urinary tract consisting of the bladder (cystitis), the urethra (urethritis), or the upper urinary tract consisting of the kidney (pyelonephritis) and the tissue surrounding the urinary tract (perinephric abscess). The burden for the patient caused by UTIs ranges from inconvenient complaints to life-threatening infections. The incidence of UTIs is high and 50% of women have experienced a UTI once in their lifetime[1]. Those with immunocompromised health due to comorbidities or age are even at a higher risk[2–4].

Cystitis or lower tract UTIs are divided between uncomplicated and complicated cystitis, which is based on the risk of complications, like febrile infection, abscesses or sepsis. Uncomplicated UTI occurs in non-pregnant women with a normal urinary tract, while a complicated UTI occurs in men and women with an increased risk of developing treatment failure. The complicated UTI group is a heterogeneous group consisting of patients with abnormalities of the urinary tract (e.g. polycystic renal disease of nephrolithiasis), but also patients with an increased risk of complications (e.g. immunosuppression or Diabetes Mellitus). Due to the higher risk of treatment failure, these patients are often treated longer or with different antibiotics.

Cystitis is diagnosed based on symptoms of infection, including burning pain on urination (dysuria), frequent voiding often of small amounts of urine (increased frequency), and the urge to void immediately (urgency), in combination with the presence of bacteria in the urine (bacteriuria). While most symptoms are a clear result of the bacterial infection of the tissue of the bladder and urethra, some are less specific like fever, delirium and/or chills.

Bacteriuria can be tested by urine culture, dipslide tests and leukocyte esterase and nitrite urine tests. But the possibility of false-positive results remains an important problem. While clean-catch urine samples are promoted, contamination of the sample with skin flora remains a possibility resulting in a false-positive result of bacteriuria. Additional, while previously the idea is that urine is sterile, more and more research has shown that especially in older adults urine is not sterile and often there is asymptomatic bacteriuria (ASB)[3].

Older adults

UTIs are the most common infections in long term care facilities, resulting in a significant burden for older residents[2,5,6]. Older adults are more prone to infections due to age and host-related risk factors such as declining physical functions (e.g. voiding function), immunosenescence, comorbidities and communication disorders (including dementia and stroke).

This has resulted in high antibiotic use in long-term care facilities and contributes to increased antibiotic resistance. Currently, the mean antibiotic use in long-term care facilities is 50.4 DDD/1,000 residents/day, though the use varied highly between facilities[5,7,8]. Additionally, broad-spectrum antibiotic use seems to increase.

Previous research has shown that a substantial proportion of antibiotic prescriptions in long-term care facilities are unnecessary or inappropriate and this is especially so in UTIs[9]. This is mainly due to the inappropriate treatment of asymptomatic bacteriuria (ASB). While it can be hard to uncover specific UTI-related comments in the resident of LTCF due to communication disorders, additional several non-specific complaints are attributed to UTIs, like delirium, feeling unwell and reduced intake. These non-specific complaints have been thought to be more frequent in older adults, presenting difficulties in correctly diagnosing UTIs. This results in the testing for UTI in asymptomatic older adults with urine culture and/or leukocyte esterase and nitrite urine tests.

Due to high levels of ASB in institutionalized older adults, current diagnostic methods for detecting UTIs are unreliable. The prevalence of asymptomatic bacteriuria ranges from 25-50% in institutionalized older women and from 15% to 40% in institutionalized older men[10]. Additional, asymptomatic bacteriuria is associated with a host response, like pyuria, resulting in a positive leukocyte esterase urine test[11–13].

In conclusion, the difficulties in diagnosing UTIs based on unreliable clinical symptoms and bacteriuria results in an untrustworthy diagnosis of UTI in a fragile population. Complications of a 'missed' UTI can result in significant comorbidities and even mortality[14]. These factors result in a low threshold for antibiotic treatment for UTIs and a significant proportion of unnecessary antibiotic prescriptions. Inappropriate antibiotic use affects both the individual and the community. On an individual level it can result in comorbidities as other illnesses can remain undertreated due to misdiagnosing UTI or due to side effects of antibiotics e.g. clostridium difficile infections[15,16]. The misuse of antibiotics on a larger scale can result in antibiotic resistance problems[17].

Starting the thesis, there were different ideas about which criteria were essential for the diagnosis of UTI in older adults residing in LTCFs[18–21]. In 2016, a Delphi procedure was performed by a Dutch research team to find consensus about which symptoms, commonly attributed to UTI should and should not lead to antibiotic prescriptions in fragile older adults[22]. This article and the Dutch Guideline that was developed from it were used as the base for the development of the new guideline for UTI in fragile older adults by the association of Elderly Care Physicians (Verenso) which was published during the control period of our first study[23].

Antibiotic stewardship programs

More and more bacteria are losing their susceptibility to commonly used antibiotics, resulting in untreatable bacterial infections. As few new antimicrobials and no new antibiotic classes are being developed, the problem of antimicrobial resistance is increasing. This has led to the introduction of interventions to improve responsible antibiotic use[24]. As one of the driving factors in antimicrobial resistance is the use of antimicrobials, several interventions have been developed to reduce unnecessary antimicrobial use. Various stewardship programs have been developed to improve the appropriateness of antimicrobial use. Antibiotic stewardship programs were first developed for hospitals and have been shown to reduce inappropriate antimicrobial use and decrease therapy days without being associated with increased mortality[25].

Many studies have described that antimicrobial overuse is a problem in long-term-care facilities[9]. This has resulted in the development of antimicrobial stewardship programs specific to long-term care facilities[26]. In 2015, Laura van Buul published her study on the effect of a tailored antibiotic stewardship intervention in patients with UTI[27]. In her study, the intervention as tested did not improve appropriate prescribing of antibiotics and more studies were deemed necessary to determine how prescription practices of elderly care physicians could be modulated successfully. Moreover, a systematic review on interventions to improve antibiotic prescribing in hospitals concluded that enabling interventions with feedback had probably the best effect in improving appropriate antibiotic use[24,25]. We, therefore, designed another antibiotic stewardship intervention study, but this time with specific emphasis on audit and feedback of prescriptions. The introduction of the intervention in the first organization coincides with the introduction of the new Dutch guideline on UTI in fragile older adults, which was used as the base for our intervention[23].

Diabetes mellitus

Like older adults, Diabetes Mellitus is associated with an increased risk of developing infections and therefore also an increased prevalence of UTI and therapy failure[4,28]. A number of systemic and local host factors probably contribute to this risk. Especially those with poor glycemic control have an increased risk of hyperglycemia-related impairment of the immune response, autonomic neuropathy and vascular insufficiency, which can lead to an increased prevalence of urinary tract infection.

While it is accepted that diabetics have an increased susceptibility to infection, it is still the question of what the impact of Diabetes Mellitus is on the severity of urinary tract infection and whether these patients should be treated more aggressively than women with uncomplicated UTI[29]. Without accounting for glycemic control or severity of the complaints, it is advised to treat DM patients with UTI with an extended antibiotic course[30]. It is however

still unclear whether this extended treatment is cost-effective, especially in a day and age in which antimicrobial resistance is becoming a serious problem.

AIM OF THESIS

This thesis aims to study several ways to improve appropriate antibiotic treatment of complicated lower tract UTIs. ABS remains important to improve appropriate antibiotic treatment. We hope that this thesis can help clinicians to choose an appropriate treatment for UTIs.

THESIS OUTLINE

In the first part of this thesis, we introduced an antibiotic stewardship intervention targeting UTI's in fragile older adults. Using the information from this first study, we continued our research on understanding and improving the diagnostic process in older adults living in long term care facilities. The last part of the thesis consisted of improving treatment of complicated cystitis in women with diabetes.

Previous studies have shown that almost one-fourth of antibiotic prescriptions in Dutch nursing homes are inappropriate, but in UTI it is almost one third. Earlier work of van Buul showed little effect of an antibiotic stewardship intervention using a participatory action research strategy (PAR)[31]. In which local stakeholders were selected to perform interventions in time period of 4 months. Both time restrictions and the absence of repeated PAR cycles were possible limitations of the study. We, therefore, designed an antibiotic stewardship intervention targeting specifically UTI and consisted of repeated educational meetings and additional audit and feedback on the results. The results of the implementation of this antibiotic stewardship can be found in **Chapter 2.** In this chapter, we describe the Antibiotic Stewardship on Urinary Tract Infection in Dutch long-term care facilities (ASUTID) study and the effect of antibiotic stewardship intervention on antibiotic consumption.

Using the data collected in the ASUTID study, we tried to understand the diagnostic determinants related to antibiotic use and guideline-discordant care in long-term care facilities. In **Chapter 3**, we described the effect of the intervention on guideline-concordant and guideline-discordant therapy. Additionally, we analyzed which resident determinants were associated with antibiotic use and guideline-discordant care.

There are no appropriate diagnostic tests for the diagnosis of UTI in long-term care facilities. Besides nitrite and leukocyte esterase tests, urine culture remains one of the few options

available. The use of urine cultures, though, is hampered by the difficulties in acquiring reliable samples in residents with urine incontinency, and logistic problems that result in long turnaround times between obtaining samples and reporting results. Reducing turnaround times might increase the appropriateness of therapy, especially in long-term care facilities with known resistance problems. In **Chapter 4,** I describe the accuracy of two rapid (overnight) antibiotic susceptibility tests for diagnosing UTI and generating antibiotic susceptibility of isolates in urine from long-term care residents suspected of UTI.

Several studies on antibiotic duration have shown that often antibiotic treatment duration can be reduced safely, but most studies on UTI treatment are performed in young women and not in high-risk populations like women with diabetes mellitus. Using available observational data from the Julius GP network, we analyzed the risk of recurrent UTI in women with diabetes treated with antibiotics for five or seven days in **Chapter 5**.

Finally, the interpretations of the main findings and implications of these results are discussed in **Chapter 6.**

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2

THE IMPACT OF ANTIBIOTIC STEWARDSHIP INTERVENTION TARGETING URINARY TRACT INFECTIONS IN DUTCH LONG-TERM CARE FACILITIES.

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P.D. van der Linden, J.W. Dorigo-Zetsma

ABSTRACT

Objective

To study the effect of an antibiotic stewardship intervention consisting of education and audit and feedback targeting UTI in Dutch long-term-care facilities.

Methods

A stepped wedged, cluster-randomized study in 13 Dutch LTCF took place between September 2017 and December 2019. Data on antibiotic prescriptions and UTI episodes were collected. Relative reductions of days of therapy (DOT) of UTI-related antibiotic (UTI-AB) and all antibiotics (all AB) was analyzed with a negative binomial regression, correcting for organization, location, seasonality, calendar time, influenza-like illness incidence, to assess the immediate effect and effect over time of the intervention. An unplanned analysis of the total number of prescriptions of UTI-AB and all-AB was performed. Safety outcomes were complete recovery, all-cause hospitalization, and all-cause mortality all within 10 days of a suspected UTI, and an unplanned analysis of overall all-cause mortality/1000 resident-days.

Results

2897 antibiotic prescriptions and 405 UTI episodes were studied. The average age of residents was 88 (IQR 83-91) and 73% were women. DOT for UTI-AB and all AB did not change significantly in the intervention period (DOT UTI-AB relative reduction 2%, 95% CI: -39% to 30%; DOT all AB relative reduction -10%, 95% CI -45% to 16%). The relative reduction of the absolute number of UTI-AB prescriptions was 22% (95% CI: 4% to 37%). Prescriptions for all AB did not change (Relative reduction 1%, 95% CI: -17% to 16%). We found no safety signals.

Conclusion

Antibiotic stewardship intervention targeting UTI antibiotic treatment in nursing homes does not decrease antibiotic DOT but may reduce the number of prescriptions for UTI-related antibiotics.

INTRODUCTION

Older adults in long-term care facilities (LTCF) have a higher risk of developing infections compared to their community-dwelling peers, but research has shown that they are also at risk for overtreatment with antibiotics[1,2]. Urinary tract infections (UTI) account for almost half of the healthcare-associated infections in this population and according to a Dutch study, 32% of the prescriptions might be inappropriate[3,4]. Reasons for this overprescription could be that diagnosing UTI in the LTCF residents is challenging due to communication problems and secondly the high prevalence of asymptomatic bacteriuria (ASB)[4,5].

The Dutch association of Elderly Care Physicians (Verenso) acknowledges the high prevalence of ASB in older adults and advises antibiotic treatment only in patients with specific complaints to discourage antibiotic treatment of ASB. But contrary to the guideline, a Dutch study still found 68.9% of patients with non-specific complaints received antibiotics[3,6].

Inappropriate antibiotic prescriptions for UTIs impact both the individual and society. On an individual level, other illnesses can be missed due to misdiagnosing UTI and the high incidence of side effects of antibiotics in older adults decreases their quality of life[7,8]. Additionally, the overuse of antibiotics can lead to an increased burden of multidrug-resistant bacteria, which can afflict both the individual and society[9].

We aimed to improve appropriate prescribing of antibiotics for urinary tract infections by introducing an antibiotic stewardship intervention. A Cochrane review on antibiotic stewardship in hospitals showed that education and feedback could increase the intervention effect, but a previous effort to improve the appropriateness of antibiotic prescriptions in nursing homes using a single educational intervention did not result in a significant improvement[10,11]. To increase the effectiveness of the intervention, we added repeated educational meetings and audit and feedback to the intervention. The aim of the study was to determine the impact of the intervention on antibiotic use and the clinical outcome of UTI in LTCF residents.

METHODS

Design and study setting

The study was set up as an unblinded, cluster-randomized step-wedged intervention study determining the impact on antibiotic consumption by introducing antibiotic stewardship focusing on UTIs. The trial was performed from September 2017 to December 2019 in three long-term care organizations in the region 'Gooi en Vechtstreek' in the Netherlands. The organizations provide care in 12 different locations with varying numbers of revalidation,

somatic and psychogeriatric wards. A total of 879 beds were included with an average of 73 beds per location (range 14 – 150). The wards are managed by specialized elderly care physicians. Switch from control to intervention was planned in blocks of 6 months with a total study duration of 24 months (figure 1).

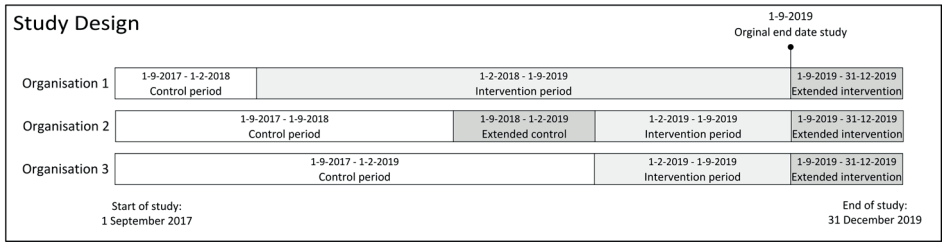

Figure 1: Timeline of the study. The study started in September 2017 and continued into December 2019. Due to a low inclusion rate, we continue the control period in one location and the intervention period in all three locations for 4 months.

Data collection

All three organizations started with a control period. Data collection consisted of two parts: 1) antibiotic prescription data and 2) anonymized clinical record forms (CRF) of UTI episodes. To assess the overall antibiotic use during the study period, data on antibiotic drug prescriptions were extracted from the electronic health record (EHR). Data included resident characteristics (birth year and sex), drug names, start and stop dates and dosing schedules. The LTCF provided information on the number of beds and all-cause mortality during the study. Bed occupancy was assumed to be 100% for all locations throughout the study. During the control- and intervention period, data on episodes of suspected UTI in residents were collected. Physicians completed an anonymized CRF per resident when they suspected a UTI based on their clinical judgment. The form contained information on resident characteristics (e.g. age, sex), medical history (e.g. immobilization, indwelling urinary catheter), signs and symptoms related to the suspected infection, diagnostic testing and treatment. Ten days after inclusion, physicians were asked to give an update on the complaints and results of the started treatment, as well as if residents were hospitalized or died. These data were used to assess the safety outcome of the intervention.

Outcomes

The primary outcome was antibiotic use for UTI based on days of therapy (DOT). Antibiotics related to UTI were selected based on ATC codes from prescription data. Based on the current local and national guidelines for UTI, we selected trimethoprim (ATC - J01EA01), nitrofurantoin (ATC - J01XE01), fosfomycin (ATC - J01XX01) and ciprofloxacin (ATC – J01MA02) as UTI related antibiotics. Secondary outcomes included overall antibiotic use measured in DOT. This endpoint was chosen to study if there was a shift from antibiotics commonly used for UTI to antibiotics with other indications. Additionally, the absolute

number of prescriptions for antibiotics related to UTI and overall antibiotics was studied in an unplanned analysis as, during the exploratory data analysis, we found that the number of antibiotic prescriptions decreased, while treatment duration increased. Safety outcomes consisted of complete recovery of complaints within ten days of suspected UTI, all-cause hospitalizations within ten days and all-cause mortality within ten days. We also included an unplanned analysis of mortality per 1000 resident days to further study mortality, as we found a protective trend of the intervention on mortality after UTI without reaching our targeted sample size.

Sample size

The sample size was determined to detect a reduction of 15% in antibiotics prescribed for urinary tract infections. We used the following assumptions in our calculation: type I error of 5% (2 sided), 80% power and an intracluster correlation of 0.03. This led to a required sample of 534 UTI episodes in total (267 episodes in each control and intervention period).

Intervention

The intervention was an antibiotic stewardship strategy focusing on the knowledge of the physicians on diagnosing UTI, e.g., discriminating UTI-related symptoms from non-specific symptoms and interpreting the available diagnostics correctly. We performed repeated audit and feedback to the healthcare personnel on adherence to the recently updated guideline UTI of Verenso[10]. Organizations were planned to start the intervention in a stepped wedged formation, in which the intervention would be introduced after 6, 12 and 18 months. After the control period, all physicians were invited for an educational presentation and e-learning based on the Verenso guideline of 2018[12]. During the presentation posters and pocket cards with a diagnostic flowchart (table 1 & 2) were distributed to all physicians. After the first presentation, educational presentations were repeated every 6 months and included audit and feedback on prescribing. Every two months, a newsletter with feedback on the performance per location was sent to the participating physicians. The results of performed urine cultures were discussed with the requesting physician during the intervention period. New physicians who started their employment during the intervention were contacted by email or telephone and received a personalized educational newsletter on the study and an invitation for the e-learning. Presentations to nursing staff were provided. Participation of medical staff was on a voluntary basis.

Data analysis

CRFs were entered in castor EDC forms, while the antibiotic prescription overviews were extracted from the electronic health record (EHR). Antibiotic overviews from the EHR were used to calculate the number of prescriptions and Days of Therapy (DOT) per 1000 resident care days per location per week. Prophylactic antibiotic prescriptions, antifungal prescrip-

Table 1: Diagnostic criteria for urinary tract infection in a resident without an indwelling urine catheter as based on Verenso guideline for UTI in frail older adults.

Residents without indwelling urine catheter	
1	One or more recent complaints of dysuria, frequency, urgency, urinary incontinence, (visible) urethral pus discharge or other UTI-related symptoms AND either fever, chills or a delirium
2	Two or more recent complaints of dysuria, frequency, urgency, urinary incontinence, (visible) urethral pus discharge or other UTI-related symptoms of which one is severe **AND** no other diagnoses are probable
3	Two or more recent complaints of dysuria, frequency, urgency, urinary incontinence, (visible) urethral pus discharge or other UTI-related symptoms AND either nephritic or suprapubic pain
4	Recent complaints of nephritic pain and one or more symptoms of fever, chills or delirium without other suspected infections

Table 2: Diagnostic criteria for urinary tract infection in residents with an indwelling urine catheter as based on Verenso guideline for UTI in frail older adults.

Residents with indwelling urine catheter	
1	One or more complaints of fever, chills, delirium after excluding urinary retention as a possible cause **AND** there is no other probable diagnosis to explain the complaints.

tions, and prescriptions for treatment duration over 14 days were excluded as they were assumed to represent prescriptions for complicated infections that are not subject to the stewardship intervention. Antibiotics related to UTI were selected based on ATC codes from prescription data. Based on the current local and national guidelines for UTI, we selected trimethoprim, nitrofurantoin, fosfomycin, and ciprofloxacin as UTI related antibiotics. These antibiotics are prescribed primarily for UTIs and are not used as first-line antibiotics for respiratory infections according to the Dutch GP and elderly care guidelines. Data cleaning was performed in R. Descriptive statistics were used to summarize the data. Chi-square, T-tests and Mann-Whitney U-tests were applied to analyze the group differences. A negative binomial regression was used to assess the immediate effect (step change) and time-effect (slope change) of the intervention corrected for the locations, organization, calendar time, and seasonality. The step-change was seen as the immediate effect of the intervention, starting at the first educational meeting. The slope change was the effect of the continued efforts to improve guideline compliant prescribing using i.e. audit and feedback. The step-change was reported as relative reduction, calculated as (1 – relative risk) * 100%; a positive relative reduction means a lower number of DOTs in the intervention period compared to the control period. Similarly, the time effect was reported as a relative reduction per 90 days since the start of the intervention. Robust confidence intervals were used to calculate 95% confidence intervals. Additionally, a negative binomial regression analysis on the number of prescriptions was added as we observed a slightly higher average therapy duration. This increased therapy duration was expected due to the advice that residents with cystitis should be treated with nitrofurantoin for the extended duration of seven days and men with complicated UTI with 14 days antibiotic regimens due to perceived increased risk of complications. The safety

outcome analysis consisted of a binomial regression to adjust for location, organization, calendar time, time since intervention and data from the national sentinel surveillance network monitoring Healthcare-Associated Infections (SNIV) on influenza-like illness (ILI) incidence in nursing homes. We performed an unplanned analysis of weekly all-cause mortality per 1000 resident days using a similar negative binomial regression as the primary endpoint with step and slope change. The analysis was corrected for location, calendar time, standardized mortality in Dutch older adults[13], ILI incidence and resident-days per location. R software version 3.5.1 was used for data analysis, with R package 'MASS' and 'GLMMadaptive' to perform the negative binomial regressions. The pre-specified two-sided significance level was set at $P<0.05$.

Ethics approval

In consultation with the Dutch Central Committee on Research Involving Human Subjects, the study was deemed not to be subject to the law on human research and informed consent was waived. Individuals are not traceable as all data were anonymized.

RESULTS

Antibiotic prescriptions

3167 antibiotic prescriptions were registered during the total study period: of these 270 prescriptions were excluded (Figure 2). Of the remaining 2897 prescriptions, 1441 (49.7%) were for antibiotics likely related to UTI based on ATC codes.

Baseline characteristics

There were few differences in the baseline characteristics of the residents between control and intervention (Table 3). Only treatment duration was significantly longer in the intervention group.

The three most prescribed antibiotic groups in the control period were nitrofurantoin, penicillin's with a β-lactamase inhibitor and quinolones The top three antibiotics remained the same in the intervention period.

Primary analysis

Both in the crude and the adjusted analysis, the immediate effect of the intervention on DOT of antibiotics related to UTI was not significant (Table 4). The time effect of the intervention was also not significant. When plotting crude DOTs over time, a decreasing trend of DOT over time in the intervention period seemed present, while the point estimates in the adjusted analysis suggested no immediate effect but a non-significant negative effect of the

intervention over time (Figure 3A). When studying the antibiotics separately, fosfomycin showed a significant immediate reduction in DOT, but no significant intervention effect over time. Nitrofurantoin did not show an immediate increase in DOT but did increase significantly during the intervention. All other antibiotics did not show a significant change in DOTs.

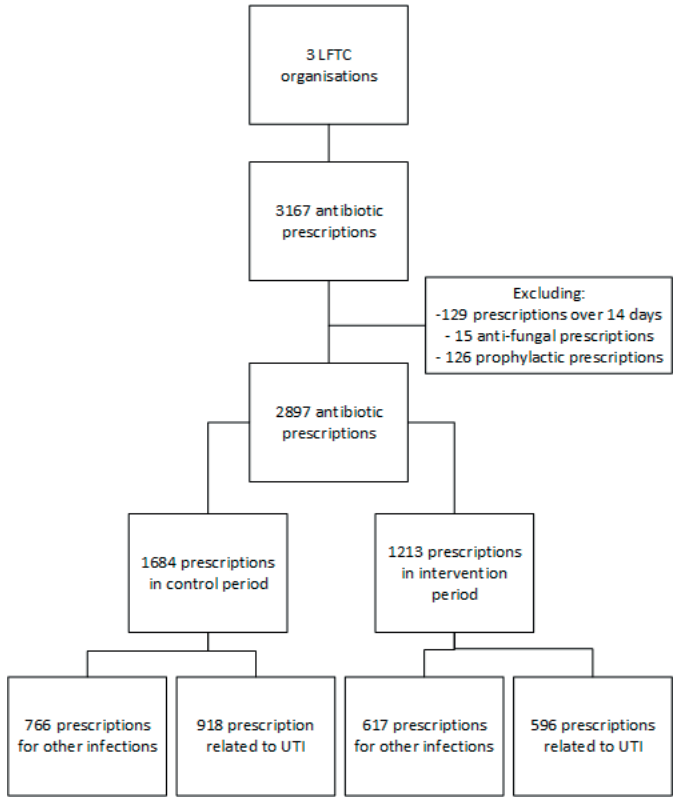

Figure 2: Flow chart of the study selection of antibiotic prescriptions.

Table 3: Characteristics of the residents with antibiotic prescriptions.

	Control	Intervention	P-test
Included prescriptions	1684	1213	
Female (%)	1246 (74.0)	884 (72.9)	0.53
Median age (IQR)	87 (81 – 93)	88 (81 – 92)	0.29
Mean duration (SD)	6.05 (2.87)	6.45 (2.85)	<0.01
Indication missing (%)	1122 (66.6)	626 (51.6)	<0.01
Indication provided (%):			<0.01
Respiratory	4 (0.7)	54 (9.2)	
Skin	2 (0.4)	48 (8.2)	
Urological	547 (97.3)	448 (76.3)	

Figure 3: Visualization of DOT and prescriptions of antibiotics related to UTI (A & B) and overall antibiotic use (C & D) over time. Control and intervention overlap due to the stepped wedge design.

Table 4: Analysis of UTI related antibiotic use measured in days of therapy (DOT). Adjusted relative reduction (RR) was calculated with a negative binomial model with correction for location, organization, calendar time and seasons. Step change represents the immediate effect of the intervention and slope change represents the effect of the intervention per 90 days. Positive numbers are in favour of the intervention (i.e. a reduction of DOT).

Antibiotic (ATC code)	DOT / 1000 resident days		Crude RR		Adjusted RR	
	Control	Intervention	Step change (95% CI)	Slope change (95% CI)	Step change (95% CI)	Slope change (95% CI)
Nitrofurantoin	6.09	4.66	27%	-3%	1%	-17%
(J01XE01)			(22% to 33%)	(-6% to -1%)	(-63% to 40%)	(-37% to 0%)
Trimethoprim	0.26	0.23	14%	7%	78%	-100%
(J01EA01)			(-30% to 45%)	(-7% to 19%)	(-537% to 99%)	(-527% to 36%)
Fosfomycin	0.46	0.29	31%	5%	56%	5%
(J01XX01)			(-28% to 62%)	(-16% to 21%)	(9% to 79%)	(-20% to 25%)
Ciprofloxacin	5.71	4.40	16%	2%	-9%	8%
(J01MA02)			(7% to 24%)	(-1% to 5%)	(-111% to 43%)	(-13% to 24%)
Total	12.52	9.57	24%	-1%	2%	-6%
			(-3% to 43%)	(-10% to 8%)	(-39% to 30%)	(-19% to 5%)

Secondary outcome

Both the crude and the adjusted analysis of overall antibiotic DOT did not show a significant reduction in DOT (Table 5). When visualizing the overall DOT over time, it seems to increase at the start of the intervention, but then plateau over the rest of the study period (Figure 3C). When studying the separate antibiotic groups, DOT of imidazole derivates and fluoroquinolones seemingly decrease in the crude analyses, while DOT of nitrofurantoin, penicillin's and sulfonamides & trimethoprim increased. In the adjusted analysis, only the increase of DOT of nitrofuran derivates remains significant

For the number of antibiotic prescriptions related to UTI, there was an immediate reduction of 22% (95% CI: 4% to 37%), but the reduction was non-significant (relative reduction 6%, 95% CI: -1% to 12%) per 90 days in the adjusted analysis (Table S2). Fosfomycin showed a immediate reduction of 62% (95% CI: 34% to 78%), though the time effect was non-significant (relative reduction 13%, 95% CI: -9% to 24%). When plotting this data, there was a clear visible decrease in UTI-related antibiotic prescriptions over time (Figure 3B).

The absolute number of overall antibiotic prescriptions did not show an immediate decrease (relative reduction 1%, 95% CI: -17% to 16%) in the adjusted analysis, but did decrease over time with 7% per 90 days (95% CI: 3% to 12%) (Table S3). When studying the antibiotic groups separately, only other antibiotics showed an immediate decrease of 60% (95% CI: 30% to 60%), while fluoroquinolone and penicillins with β-lactamase inhibitors decreased over time by, respectively 13% (95% CI: 3% to 22%) and 13% (95% CI 5% to 21%) per 90 days. The other groups did not show a significant change in the adjusted analyses.

Table 5: Analysis of overall antibiotic use, measured in Days of Therapy (DOT) per 1000 resident days. Relative reduction calculated by crude and adjusted negative binomial regression. The adjusted regression corrects for location, calender time, season, organisation and national ILI incidence. Outcome measured in immediate effect (step change) and time-effect (slope change).

Antibiotic (ATC code)	DOT / 1000 resident days		Crude RR		Adjusted RR	
	Control	Intervention	Step change (95% CI)	Slope change (95% CI)	Step change (95% CI)	Slope change (95% CI)
Penicillin with β-lactamase inhibitor (J01CR)	7.43	7.31	-1%	1%	5%	7%
		-9.63%	(-9% to 6%)	(-1% to 3%)	(-67% to 45%)	(-10% to 21%)
Imidazole derivatives (J01XD)	0.27	0.15	78%	-26%	95%	-51%
		-47.96%	(60% to 88%)	(-47% to -8%)	(-159% to 100%)	(-434% to 57%)
Macrolides & Lincosamides (J01F)	0.75	1.04	-39%	0%	-98%	-8%
		+26.71%	(-72% to 13%)	(-6% to 6%)	(-692% to 50%)	(-66% to 30%)
Nitrofuran derivatives (J01XE)	6.09	4.66	27%	-3%	-1%	-17%
		-29.78%	(20% to 33%)	(-6% to -1%)	(-67% to 39%)	(-37% to 0%)
Penicillin's (J01CA & J01CE)	4.59	4.62	-31%	9%	-36%	17%
		-7.41%	(-44% to -18%)	(7% to 12%)	(-179% to 34%)	(-3% to 34%)
Fluoroquinolones (J01MA)	5.95	4.43	19%	2%	-6%	7%
		-31.67%	(11% to 27%)	(-1% to 5%)	(-103% to 44%)	(-14% to 23%)
Sulfomanides & trimethoprim (J01E)	0.70	1.30	-101%	10%	-225%	-9%
		+70.16%	(-145% to 65%)	(4% to 15%)	(-1829% to 35%)	(-83% to 35%)
Tetracyclines (J01A)	0.97	0.28	47%	0%	Na[1]	Na[1]
		-73.60	(-100% to 83%)	(0% to 1%)		
Other (J01XX)	0.53	0.41	22%	1%	49%	4%
		-28.72	(-52% to 59%)	(-22% to 20%)	(-9% to 76%)	(-23% to 26%)
Total	27.27	24.19	6%	2%	-10%	-5%
		-11.29%	(-21% to 27%)	(-5% to 9%)	(-45% to 16%)	(-14% to 4%)

[1] *Due to the limited number of prescriptions the adjusted model could not be fitted*

[2] *The group of other antibiotics consists of fosfomycin and linezolid.*

Safety outcomes

Data for 408 episodes of UTI were collected during the study period. Both complete improvement, all-cause hospitalization and mortality did not significantly change during the intervention period. Due to the large though non-significant difference in mortality in the control versus the intervention group, we added a post hoc analysis to study all-cause mortality / 1000 resident days. In the control period 629 residents died, compared to 476 in the intervention period, resulting in crude all-cause mortality OR of 1.34 (95% CI: 1.06 – 1.69). Adjusted all-cause mortality / 1000 resident days showed a significant increase in the intervention period (OR 1.61, 95% CI: 1.27 to 2.04), but this seemed to be a temporary effect as the mortality decreased during the intervention (time effect OR 0.82, 95% CI:0.76 to 0.89) (Figure 4).

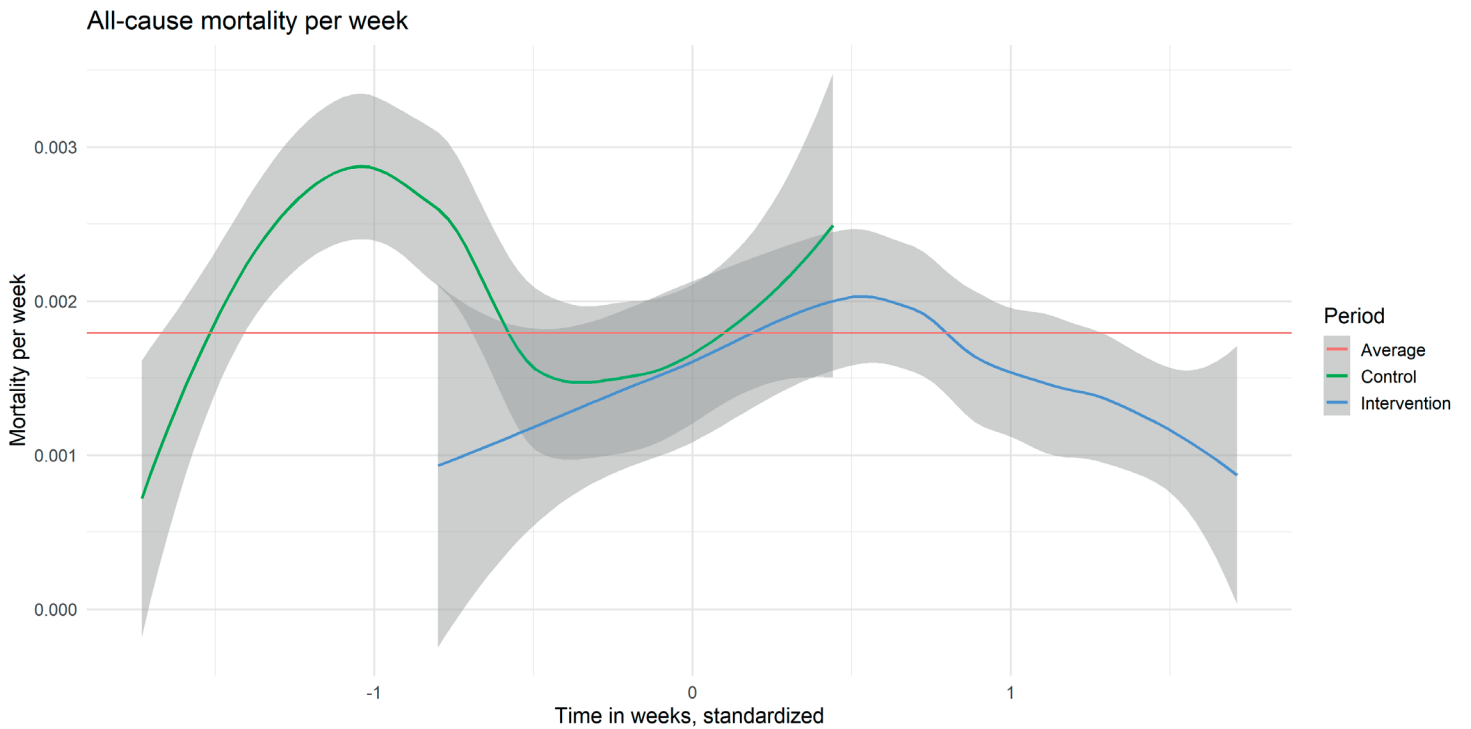

Figure 4: Visualization of all-cause mortality / 1000 resident days per week. Control and intervention overlap due to the stepped wedge design.

Table 6: Secondary safety outcomes in residents with a suspected UTI between September 1 2017 and December 31 2019.

	Control	Intervention	Crude OR (95% CI)		Adjusted OR (95% CI)	
UTI episode outcomes	N=201	N=204				
Complete improvement (%)	99 (55.6)	98 (52.4)	1.13		0.91	
			(0.66 – 1.95)		(0.56 – 1.40)	
All-cause hospitalization post UTI (%)	4 (2.3)	3 (1.7)	0.75		0.78	
			(0.14 – 3.62)		(0.14 – 4.35)	
All-cause mortality post UTI (%)	13 (7.4)	3 (1.7)	0.22 (0.05 – 0.72)		0.29 (0.06- 1.00)	
	Control	Intervention	Step change (95% CI)	Slope change (95% CI)	Step change (95% CI)	Slope change (95% CI)
All-cause mortality	367 707 resident days	337 762 resident days				
All-cause mortality (IR/1000 resident days)	629 (1.7)	476 (1.4)	1.34	0.79	1.61	0.82
			(1.06 – 1.69)	(0.73 – 0.86)	(1.27–2.04)	(0.76 – 0.89)

DISCUSSION

Our study demonstrated that an antibiotic stewardship intervention targeting UTI did not reduce antibiotic use related to UTI measured in DOT. Overall antibiotic use, either in the number of prescriptions or DOT also did not decrease significantly during the intervention. However, the absolute number of prescriptions for UTI-related antibiotics did decrease after the intervention.

This discrepancy between the effects on DOTs of UTI related therapy and the number of UTI related prescriptions could be due to an increase in the duration of antibiotic therapy during the intervention period. During the study, we noticed that residents were often treated for 5 days nitrofurantoin as uncomplicated cystitis, though guidelines advised treating older adults as complicated cystitis with an extended treatment duration of 7 days since older adults are a risk group for complications of UTIs. Stimulating appropriate antibiotic use could thus have resulted in fewer prescriptions but longer treatment duration. Another reason for the discrepancy between results in DOTs and UTI-related prescriptions could be due to the fact that the biggest reduction in DOT was found in fosfomycin, which is a single administration prescription. This would not affect the overall DOT as much as other antibiotics with multiple-day treatment durations.

The clinical improvement rate and the number of hospitalizations remained stable during the study. The all-cause mortality post-UTI rate remained stable during the intervention

period. However, the all-cause mortality/1000 resident days increased. at the start of the intervention followed by a decrease later on during the intervention. We assume that the increase in mortality at the start of the intervention was due to an external unmeasured factor. Nevertheless, we were unable to provide a full and unequivocal explanation of the observed overall increase in mortality.

One recent retrospective study containing 312 896 UTI episodes in older adults found that deferred or withholding antibiotics in residents with UTI was associated with a significant increase in all-cause mortality within 60 days of the UTI[14]. While their study focused on the effect of deferred antibiotic prescribing in the older adults presented to a general practitioner with UTI excluding ASB, our study focused on targeting inappropriate antibiotic prescriptions in LTCFs of which treatment of ASB is one of the biggest causes. Extensive studies of ASB have shown that untreated ASB does not affect morbidity or mortality[15]. Several other studies have also shown that antibiotic stewardship focusing on guideline-coherent treatment for UTIs is viable, safe and necessary in long-term care[16–18]. Important to notice is, that our study was not designed to show a difference in mortality after UTI infection and our sample size is too low to definite state that the intervention affects mortality related specifically to UTI.

As said before, two other Dutch studies have studied different antibiotic stewardship techniques for reducing inappropriate antibiotic prescriptions for UTIs in LTCF[11,19]. While Rutten *et al* focused on a record-integrated decision tool and Van Buul *et al* on the participation of prescribing physicians, both interventions did not result in a significant increase in appropriate antibiotic prescriptions. Even though previous studies suggest guideline-concordant prescribing can be increased, the possible gain might be marginal[3].

When assessing the results of our study, some possible limitations should be taken into account. Performance bias could have occurred as the organizations were not blinded to the intervention during the study and shifts were covered by a pooled team of physicians both from the control and intervention period. Also, the publication of new guidelines, advocating a more restrictive use of the diagnosis of urinary tract infection in older adults could have mitigated the contrast in outcome measurements between intervention and control centres. Additionally, we experienced problems with the inclusion rate and the participation rate of the educational meetings, due to high staff turnover and limited staffing, resulting in a sub-optimal recruitment rate of participants. Finally, to extend the intervention beyond elderly care physicians, an educational meeting for nursing personnel was offered in all locations but attendance was very low due to limited staffing. The meeting was only performed in a single location. Including more nursing personnel could have supported the antibiotic intervention

more as they often signal symptoms in residents. These three phenomena might have caused an underestimation of the effect of our intervention

A strength of the study was that the intervention was personalized per location and practical tools were designed especially for the facilities. A large part of the education consisted of passive methods and could be easily continued after this study or implemented in other LTCFs.

Our study intervention consisted of a bundle of interventions promoted by several studies as effective methods to reduce inappropriate antibiotic use in hospitals and general practitioners' offices. Our intervention did however not result in a significant reduction of antibiotic DOTs. For future studies in this field, we recommend finding a way to involve nursing staff more, and tailoring the intervention according to perceived local obstacles in implementing current guidelines.

CONCLUSION

Our findings suggest that an antibiotic stewardship intervention targeting UTIs in long-term care facilities does not decrease antibiotic DOTs but decreases the number of antibiotic prescriptions associated with UTIs. Antibiotic stewardship remains an important tool to prevent antibiotic overtreatment and further studies on the effects of antibiotic stewardship specific to LTCF are necessary.

FUNDING

This project received funding from the Science bureau of the Tergooi MC. The funder had no role in the study design and conduct of the study and decision to submit the manuscript for publication.

TRANSPARENCY DECLARATIONS

None to declare

ACKNOWLEDGEMENTS

We would like to thank the LTCFs for their participation in the study and in particular the physicians for their registration of the UTI consultations.

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SUPPLEMENTARY MATERIAL

Table S1: Indication provided per antibiotic group.

Antibiotic group	Indication			
	Missing, N (%)	UTI, N (%)	RTI, N (%)	Other, N (%)
Combination penicillines	740 (100%)	0 (0%)	0 (0%)	0 (0%)
Nitrofurantoin derivates	24 (4%)	647 (96%)	0 (0%)	0 (0%)
Others	13 (6%)	218 (94%)	0 (0%)	2(0%)
Penicillines	348 (81%)	18 (4%)	30 (7%)	36 (8%)
Fluoroquinolones	433 (83%)	63 (12%)	11 (2%)	16 (3%)
Sulfomanides & trimethoprim	47 (46%)	48 (47%)	1(1%)	6 (6%)

Table S2: Analysis of UTI related antibiotic use measured in the absolute number of prescriptions. Adjusted relative reduction (RR) was calculated with a negative binomial model with correction for location, organisation, calendar time and season. Measured both in immediate effect (step change) and time-effect (slope change).

	Prescriptions		Crude RR		Adjusted RR	
Antibiotic (ATC code)	Control	Intervention	Step change (95% CI)	Slope change (95% CI)	Step change (95% CI)	Slope change (95% CI)
Nitrofurantoin	404	267	29%	-3%	21%	-1%
(J01XE01)			(7% to 46%)	(-12% to 4%)	(-7% to 41%)	(-11% to 8%)
Trimethoprim	18	11	15%	11%	35%	-18%
(J01EA01)			(-158% to 76%)	(-28% to 43%)	(-253% to 88%)	(-118% to 36%)
Fosfomycin	150	72	33%	8%	62%	9%
(J01XX01)			(-5% to 58%)	(-6% to 22%)	(34% to 78%)	(-9% to 24%)
Ciprofloxacin	302	202	16%	3%	-8%	13%
(J01MA02)			(-15% to 39%)	(-7% to 12%)	(-54% to 24%)	(3% to 22%)
Total	874	552	25%	1%	22%	6%
			(7% to 39%)	(-10% to 11%)	(4% to 37%)	(-1% to 12%)

Table S3: Analysis of overall antibiotic use measured in the absolute number of prescriptions. Adjusted relative reduction (RR) was calculated with a negative binomial model with correction for location, organisation, calendar time and season. Measured both in immediate effect (step change) and time-effect (slope change).

Antibiotic group	*Prescriptions*		Crude RR		Adjusted RR	
	Control	Intervention	Instant change (95% CI)	Slope change (95% CI)	Instant change (95% CI)	Slope change (95% CI)
Penicillin's with β-lactamase inhibitor (J01CR)	398	342	-3%	1%	-19%	13%
		-14.07%	(-36% to 22%)	(-7% to 9%)	(-61% to 11%)	(5% to 21%)
Imidazole derivatives (J01XD)	14	6	80%	-25%	86%	-18%
		-57.14%	(1% to 97%)	(-95% to 23%)	(-37% to 98%)	(-126% to 39%)
Macrolides & Lincosamides (J01F)	**47**	**55**	-36%	1%	-155%	8%
		17.02%	(-137% to 24%)	(-16% to 16%)	(-460% to -16%)	(-17% to 28%)
Nitrofuran derivatives (J01XE)	404	267	29%	-3%	19%	-1%
		-33.91%	(7% to 46%)	(-12% to 4%)	(-9% to 41%)	(-10% to 8%)
Penicillin's (J01CA & J01CE)	240	192	-18%	6%	-72%	10%
		-20.00%	(-65% to 16%)	(-4% to 15%)	(-158% to -16%)	(-2% to 20%)
Fluoroquinolones (J01MA)	319	204	15%	3%	-11%	13%
		-36.05%	(-15% to 38%)	(-6% to 13%)	(-57% to 21%)	(3% to 22%)
Sulfomanides & trimethoprim (J01E)	47	55	-72%	13%	-114%	7%
		17.02%	(-209% to 5%)	(-5% to 29%)	(-405% to 9%)	(-24% to 30%)
Tetracyclines (J01A)	60	14	26%	49%	47%	15%
		-76.67%	(-19% to 81%)	(-5% to 52%)	(-53% to 82%)	(-27% to 43%)
Other[2] (J01XX)	155	78	30%	8%	60%	8%
		-49.68	(-9% to 56%)	(-7% to 21%)	(30% to 77%)	(-10% to 23%)
Total	1684	1213	12%	2%	1%	7%
		-27.97%	(-7% to 27%)	(-4% to 7%)	(-17% to 16%)	(3% to 12%)

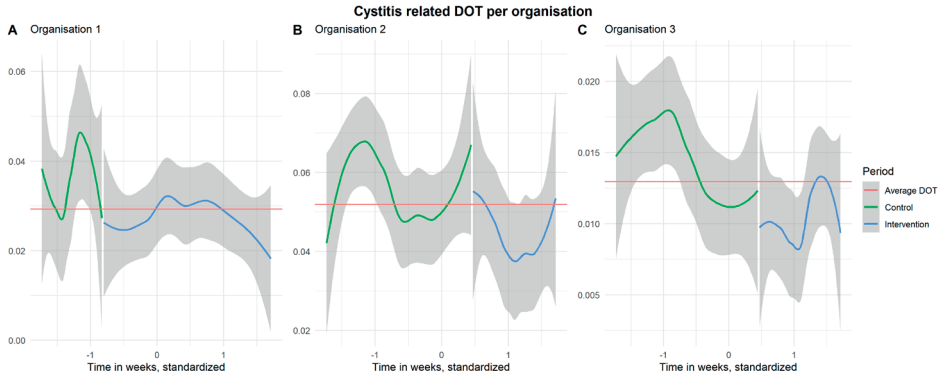

Figure S1: Cystitis related DOT per organization

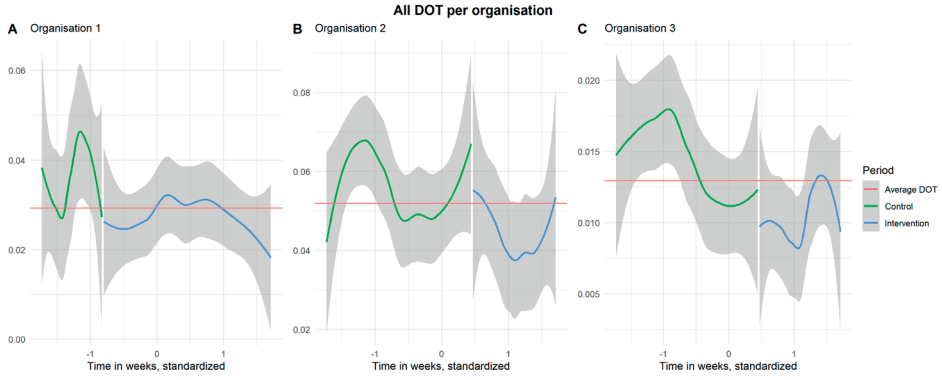

Figure S2: Overall DOT per organization

3

THE MANAGEMENT OF UTI IN OLDER PEOPLE: AN ANTIBIOTIC STEWARDSHIP INTERVENTION ON COMPLIANCE TO GUIDELINES.

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ABSTRACT

Background

Dutch elderly care physicians often prescribe antibiotics to treat urinary tract infections in their residents, but only a small proportion of these prescriptions are guideline compliant, due to the difficulty of diagnosing UTI, partly caused by communication problems and asymptomatic bacteriuria in this population. We introduced antibiotic stewardship (ABS) intervention in long term care facilities (LTCF) and aimed to study the effects of the intervention on guideline non-compliant care. In addition, we studied which determinants were related to guideline non-compliant care.

Methods

A stepped wedge, cluster-randomized study in 13 Dutch LTCF was performed between September 2017 to December 2019. Data on UTI episodes were collected. The primary outcome was the percentage of guideline non-compliant care for UTI based on the UTI guideline of the Dutch association of Elderly Care physicians and Social Geriatrics. Secondary outcomes consisted of the changes in the determinants related to guideline non-compliant care before and after implementation of the stewardship intervention.

Results

Introducing ABS did not significantly change guideline non-compliant care (OR 0.77, 95% CI: 0.52 – 1.15), overtreatment (OR 0.83, 95% CI 0.51-1.33), or undertreatment (OR 0.79, 95% CI 0.39 – 1.70). While delirium (OR_{adj} 4.13, 95% CI 1.56 – 11.58) and discomfort (OR_{adj} 18.30, 95% CI 1.51 – 896.82) were associated with overtreatment in the control period, this was not the case in the intervention period.

Conclusion

Multifaceted antibiotic stewardship targeting UTI did not reduce overtreatment but can change determinants correlated to antibiotic prescriptions. More studies to improve diagnosis and treatment of frail older people with presumed urinary tract infections are needed.

INTRODUCTION

Long term care facilities (LTCF) can be an important source of antimicrobial resistance, as there is a lot of overuse of antibiotics and has been for over 20 years[1–3]. This has resulted in the development of antibiotic stewardship (ABS) specifically targeting LTCFs.

The high use of antibiotics is explained by the residents in long term care facilities, which consist of mainly vulnerable older adults with an increased risk of developing infections and complications. This is due to their declining immunity, use of invasive devices (e.g. urinary catheters) and high risk of acquiring resistant bacteria due to frequent use of hospital care[4,5]. Additional, the number of institutionalized older people getting inappropriate antibiotic treatment is higher compared to community-dwelling older people[6,7].

The proportion of inappropriate antibiotic treatment is highest in urinary tract infections (UTI), due to difficulties in differentiating between UTI and asymptomatic bacteriuria in older people[8]. Guidelines advise treating only those with specific UTI-related complaints to avoid treatment of asymptomatic bacteriuria. Still, a recent Dutch study in ten nursing homes found that almost one-third of prescriptions for UTIs were inappropriate based on an algorithm using national and international guidelines[9].

So, management of older people in LTCF with urinary tract infections means balancing between under- and overtreatment and compliance to evidence-based guidelines seems pivotal. ABS is needed to improve guideline compliant prescribing, but where ABS in hospitals focuses on e.g. formulary restrictions, pre-authorization and audit and feedback, the barriers to implementing appropriate antibiotic prescribing in LTCF are expected to be different. For example, the lack of diagnostic resources and the influences of family and nursing staff play a bigger role[10]. Several Dutch studies have been studying the effect of various antibiotic stewardship interventions to increase appropriate antibiotic prescribing in LTCF, but they did not find a significant effect[11,12] Based on previous research, we expanded our intervention with repeated educational training and by performing audit and feedback on the performance of physicians[13].

In this paper, we aimed to study whether the introduction of an antibiotic stewardship intervention focusing on clinical symptoms and audit and feedback on diagnostics and antibiotic prescribing, decreased the percentage of guideline non-compliant care. Additional we studied how the determinants of residents related to guideline non-compliant care changed.

METHODS

Design and study setting

The study was set up as an unblinded cluster-randomized stepped-wedge intervention to determine the impact of an antibiotic stewardship intervention targeting LTC residents suspected of UTI. The trial was performed from September 2017 to December 2019 in three long-term care organizations situated in the 'Gooi' area in the Netherlands. In total 12 locations, consisting of 898 beds with varying numbers of revalidation, somatic and psychogeriatric wards were included. All the wards were managed by elderly care physicians. Switch from control to intervention was planned in blocks of 6 months with a total study duration of 28 months.

Data collection

All three organizations started in the control period. Data collection consisted of two parts: 1) antibiotic prescription data and 2) anonymized clinical record forms (CRF) of UTI episodes. This study focused on the CRF to assess guideline non-compliant care. Physicians were asked to complete an anonymized clinical record form (CRF) when they suspected a resident of having a UTI. Multiple episodes of the same resident were allowed. Collected data included resident characteristics (e.g. age and sex), medical history (e.g. indwelling urinary catheter, immobilization), signs and symptoms related to the UTI (e.g. dysuria) and details on diagnostics (e.g. urine dipstick for leucocytes and nitrite) and treatment. Ten days after the episode onset, the physicians were asked to fill in a follow-up questionnaire about possible persistent complaints, therapy results and hospital admissions or deaths. The complete questionnaire can be found in appendix 1 & 2.

Outcome

The primary outcome was the change in the percentage of guideline non-compliant care for UTIs before and after the antibiotic stewardship intervention.

Guideline non-compliant care was split up as (I) guideline non-compliant prescribing (e.g. overtreatment) and (II) guideline non-compliant non-prescribing (e.g. undertreatment). Guideline compliant care was split up as (I) prescribing according to the guideline (i.e. compliant prescribing), (II) non-prescribing when not indicated (i.e. compliant non-prescribing). To classify the prescribing decision as guideline compliant or non-compliant, an algorithm based on the Verenso guideline for UTI in vulnerable older adults was developed (Appendix 3)[14].

Second, we studied the use of diagnostic tests and determinants that were associated with guideline non-compliant care by calculating percentages and odds ratios.

Intervention

The intervention consisted of the implementation of an antibiotic stewardship strategy focusing on the knowledge of the physicians on diagnosing UTI, e.g. discriminating between non-specific and specific UTI complaints and interpreting the available diagnostics correctly. We performed repeated audits and feedback on the healthcare personnel on their compliance with the guideline. Organizations were planned to start the intervention in a stepped wedge formation, in which the intervention would be introduced after 6, 12 and 18 months. After the control period, all physicians were invited to an educational presentation and e-learning. During the presentation posters and pocket cards with a diagnostic flowchart (Appendix 4) were distributed to all physicians. After the first presentation, educational presentations were repeated every 6 months and included audit and feedback on prescribing. Every two months, a newsletter with feedback on the performance per location was sent to the participating physicians. During the intervention period, the results of performed urine cultures were discussed with the requesting physician. New physicians who started their employment during the intervention were contacted by email or telephone and received a personalized educational newsletter on the study. Additionally, educational presentations and pocket cards with instructions for diagnostic tests, specific to nursing staff were offered to all long-term care facilities. Participation was voluntary.

The guidelines

The national guidelines on urinary tract infections in LTCF differentiates between cystitis, complicated UTI and catheter-related UTI. Symptoms considered UTI-specific are increased urgency, increased frequency of urination, dysuria and new or worsened incontinence for urine. Non-specific complaints are flank pain, fever or chills, delirium or worsened activities of daily living (ADL). Suprapubic pain, cloudy or smelly urine, hematuria and other complaints are classified as nonspecific complaints unrelated to UTI in patients without a urinary catheter and were excluded from the algorithm (Table S1). Physicians are advised to diagnose the UTI based on clinical symptoms instead of possible diagnostic tests. Physicians are advised to only use a dipstick with nitrite and leukocyte esterase to rule out UTI in symptomatic residents. A negative nitrite in combination with a negative leukocyte esterase makes the possibility of UTI very unlikely and physicians are advised to check for other illnesses. Other uses of dipsticks than ruling out UTI, were considered to be guideline non-compliant. Also, the use of urine culture to diagnose a UTI was considered guideline-non compliant due to the high levels of asymptomatic bacteriuria. Guideline compliant reasons to perform urine cultures were to identify the causative pathogen and its resistance pattern to optimize antibiotic treatment in cases of complicated UTI with signs of tissue invasion, male patients, failure of antibiotic treatment, expected resistance problems and/or recurrent infections.

Data analysis

All CRFs were received on paper and entered manually in Castor EDC, an online data management system. Descriptive statistics were used to summarize the data. Chi-square, T-tests and Mann-Whitney U-tests were applied to analyze the group differences. Additionally, we used a multivariable logistic regression analysis to find the resident determinants associated with both antibiotic prescriptions and guideline non-compliant prescribing. For the model, we select determinants with a P-value of <0.2 using the chi-square test. Using backwards-stepwise selecting, we used a cut-off value of 0.05 for expulsion from the model. R-studio software version 3.5.1 was used for data analysis. Packages including lme4 were used to perform regression analysis

Ethics approval

In consultation with the Central Committee on Research Involving Human Subjects (CCMO), the study was deemed not to be WMO obligatory and informed consent was waived. Individuals were not traceable as all data were anonymized.

RESULTS

Baseline characteristics

In total 405 episodes were included: 201 in the control- and 204 in the intervention period. Overall, the residents in the control and intervention period were similar in age, sex and type of care provided (Table 1). In the intervention period, the number of episodes with a noticeable change in incontinence for urine and flank pain increased (Table 1). There was a slight decrease in the number of episodes with increased frequency.

Guideline non-compliant care

In the control period, 102 (50.7%) of the 201 episodes were considered to be guideline non-compliant compared to 91 (44.6%) of the 204 episodes in the intervention period (figure 1). Guideline non-compliant care decreased non-significantly with an OR of 0.77 (95% CI: 0.52 – 1.15). The percentage of overtreatment decreased in the intervention period by 4.7 % (OR 0.83, 95% CI 0.51 – 1.33) and undertreatment by 4.9% (OR 0.79, 95% CI 0.39 – 1.70) but the changes were also statistically non-significant.

Resident determinants associated with guideline non-compliant care

In the control period, guideline non-compliant care (either overtreatment or undertreatment) was associated with a lower age (OR_{adj} 0.94, 95% CI 0.89 – 0.98) and a general feeling of discomfort (OR_{adj} 8.16, 95% CI 1.00 – 204.40) (Appendix 5, Table S3). Residents with complaints of increased frequency of urination (OR_{adj} 0.14, 95% CI 0.05 – 0.35), dysuria (OR_{adj}

Table 1: Baseline resident characteristics

Characteristic	Control (n = 201)	Intervention (n= 204)
Sociodemographics		
Females, n/N (%)	166 (82.6%)	154 (75.5%)
Age (years), mean (range)	84.5 (80 – 90)	84.3 (80 – 89)
Type of unit, n/N (%)		
Somatic	24 (11.9%)	21 (10.3%)
Psychogeriatric	116 (57.7%)	138 (67.6%)
Rehabilitation	41 (20.4%)	29 (14.2%)
Other	18 (9.0%)	11 (5.4%)
Unknown	2 (1.0%)	5 (2.5%)
Functioning, n/N (%)		
Immobile	59 (29.4%)	60 (29.4%)
Urinary catheter	17 (8.5%)	35 (17.2%)
Urinary incontinence	43 (21.4%)	25 (12.3%)
Co-morbidities, n/N (%)		
Diabetes Mellitus	23 (11.4%)	32 (15.7%)
Dementia	127 (63.2%)	133 (65.2%)
Immunocompromised	5 (2.5%)	4 (2.0%)
Reduced eGFR	27 (13.4%)	11 (5.4%)
Severity illness, n (%)		
Severe systemic illness	8 (4.1%)	8 (4.0%)
Mild systemic illness	61 (31.4%)	46 (22.9%)
No systemic illness	125 (64.4%)	147(73.1%)
Specific complaints, n (%)		
Urgency	30 (14.9%)	28 (13.7%)
Increased frequency of urination	59 (29.4%)	37 (18.1%)
Dysuria	45 (22.4%)	243 (21.1%)
New/worsened incontinence	12 (6.0%)	23 (11.3%)
Non-specific complaints, n (%)		
Flank pain	1 (0.5%)	11 (5.4%)
Fever	19 (9.5%)	19 (9.3%)
Delirium	88 (43.8%)	96 (47.1%)
UTI unrelated complaints, n (%)		
Suprapubic pain	36 (17.9%)	36 (17.6%)
Unusual urine	21 (10.4%)	24 (11.8%)
Hematuria	27 (13.4%)	14 (6.9%)
Other	67 (33.3%)	73 (35.8%)
Duration complaints, mean (range)	3.5 (1 – 4)	4.2 (2 – 5)
Previous treatment with AB, n (%)	22 (10.9%)	12 (5.9%)
Urine culture prior to inclusion (<6 months), n (%)	59 (29.4%)	54 (26.5%)

0.13, 95% CI 0.04 – 0.37), changes in the color or smell of urine (OR_{adj} 0.24, 95% CI 0.06 – 0.78) were less likely to receive guideline non-compliant care. In the intervention period, residents with dysuria (OR_{adj} 0.24, 95% CI 0.09 – 0.60) and new or worsened urine incontinency (OR_{adj} 0.22, 95% CI 0.06 - 0.69) were less likely to receive guideline non-compliant care. There were no determinants associated with increased risk of guideline non-compliant care.

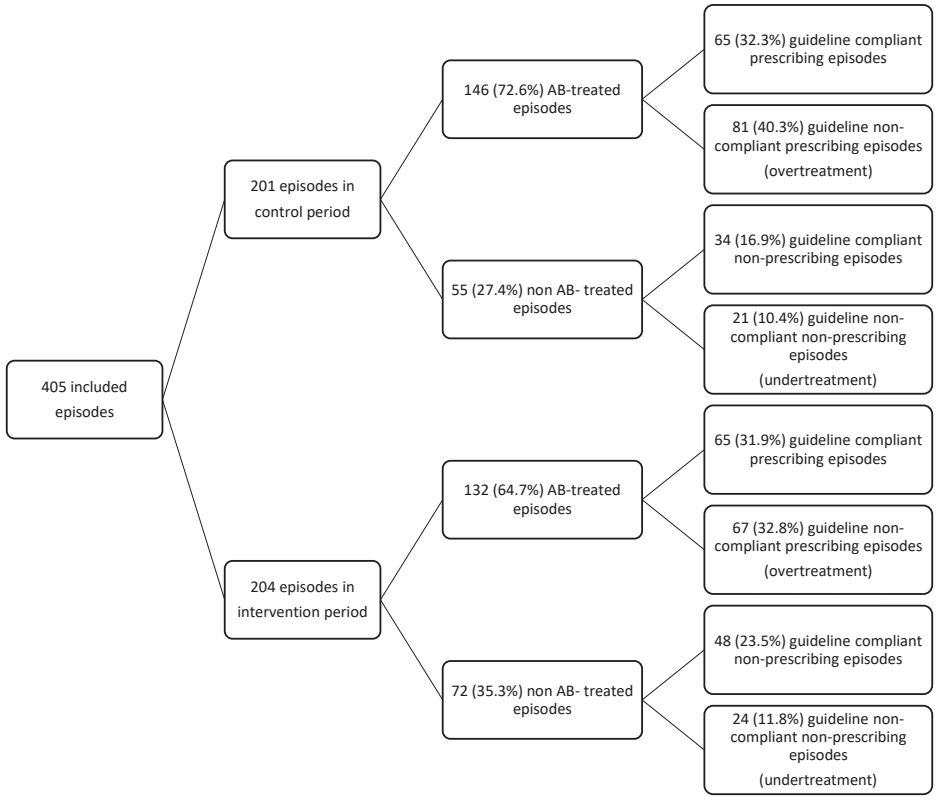

Figure 1:Treatment of UTI in included UTI episodes.

Additionally, overtreatment was studied. In the control period, male residents (OR_{adj} 7.70, 95% CI 1.37 – 75.15), residents with delirium (OR_{adj} 4.13, 95% CI 1.56 – 11.58) and those with a general feeling of discomfort (OR_{adj} 18.30, 95% CI 1.51 – 896.82) had a greater risk of overtreatment (Appendix 5, Table S4). The risk of overtreatment was lower in those with increased frequency of urination (OR_{adj} 0.01, 95% CI 0.00 – 0.05) or new or worsened incontinence (OR_{adj} 0.08, 95% CI 0.00 – 0.57).

Table 2: Diagnostic test table

	Control period (n=201)	Intervention period (n=204)	OR (95% CI)
Dipstick performed, n/N (%)	178/201 (89.0%)	151/204 (74.8%)	0.36 (0.21 – 0.63)
Nitrite positive	129/178 (72.5%)	116/151 (77.9%)	1.33 (0.80 – 2.23)
Leucocytes positive	167/178 (93.8%)	145/151 (96.0%)	0.76 (0.31 – 1.90)
Samples nitrite and leucocytes positive, n/N (%)	125/178 (70.2%)	112/151 (80.8%)	0.81 (0.49 – 1.33)
Samples nitrite and leucocytes negative, n/N (%)	5/178 (2.1%)	2/151 (1.3%)	2.06 (0.42 – 16.16)
Cultures performed, n/N (%)*	110/201 (55.6%)	161/204 (79.7%)	3.14 (2.02 – 4.89)
Negative results	25/110 (22.7%)	22/161 (13.7%)	0.57 (0.30 – 1.08)
Cultures with growth	66/110 (60.0%)	127/161 (78.9%)	2.18 (1.15 – 4.17)
Cultured episodes with AB, n/N (%) (guideline compliant)	65/201 (32.3%)	91/204 (44.6%)	2.82 (1.72 – 4.68)
Cultured episodes without AB, n/N (%) (guideline non-compliant)	44/201 (21.9%)	70/204 (34.3%)	6.68 (1.59 – 49.83)

** There were 19 missing samples in the control period and 12 missing samples in the intervention period*

In the intervention period, residents with fever (OR_{adj} 6.64, 95% CI 1.31 – 58.66) were more likely to receive overtreatment, while patients in revalidation wards (OR_{adj} 0.03, 95% CI 0.00 – 0.36), or residents with dysuria (OR_{adj} 0.13, 95% CI 0.03 – 0.41) were less likely to receive overtreatment.

Diagnostic tests

In total, 329 (81.8%) dipsticks for leukocyte esterase and nitrite were performed of which 178 (88.6%) were in the control and 151 (74.0%) in the intervention period (Table 3). Even though, the chance of UTI with a negative dipstick for both nitrite and leucocytes is very small, in the control period, 1 of 5 episodes and in the intervention period, 1 of 2 episodes residents with a negative dipstick were prescribed antibiotics due to UTI-specific complaints.

During the study 271 (66.9%) urine cultures were performed, 110 in the control period and 161 in the intervention period. The number of cultures taken significantly increased in the intervention period as did the rate of cultures with growth. Additional, the number of urine cultures performed in residents without antibiotic treatment, which was deemed guideline non-compliant, also increased during the intervention period.

DISCUSSION

Our study showed that a multifaceted educational antibiotic stewardship intervention did not result in significantly decreased guideline non-compliant care, either overtreatment or undertreatment, for UTI in long-term care residents.

When studying guideline non-compliant episodes, overtreatment was seen more often than undertreatment both in the control and the intervention period. Determinants related to overtreatment changed during the study. While in the control period delirium and general feelings of discomfort were associated with overtreatment, this was not seen in the intervention period, in line with the current guideline. In both periods, residents with specific complaints (e.g. dysuria) were less likely to receive inappropriate antibiotic prescriptions. In the intervention period, only fever was associated with overtreatment. Fever in itself is not an indication for antibiotic treatment in the guidelines, but it should be noted, however, that in frail older people with fever treatment with antibiotics is most likely correct for other reasons than an assumed UTI.

There has been extensive literature on the effects of antibiotic stewardship intervention in LTCF to improve prescribing of antibiotics for UTIs. Several studies showed a significant improvement in guideline compliant antibiotic prescribing for uncomplicated UTI, two Dutch studies failed to show a relevant increase in appropriate antibiotic prescribing through antibiotic stewardship intervention in LTCF[11,12,15–17].

Most of the studies that have studied ABS used decision tools to improve UTI diagnosis and subsequent treatment. Our study showed that adding feedback on prescription rates to the stewardship program did not have the anticipated effects. Current guidelines use specific UTI-related symptoms to distinguish between UTI and asymptomatic bacteriuria (ASB) and rely heavily on the symptomology of the patient[18]. In Dutch nursing homes, a majority of residents have however difficulty with communication, due to reasons like neurodegenerative diseases or hearing problems. Physicians are afraid to miss specific symptoms in this vulnerable population, resulting in starting antibiotics in order to be ‘better safe than sorry’.

The high rate of cultures in our study is in contrast with a large study from Canada that showed that the introduction of antibiotic stewardship resulted in a reduction in the number of UTI diagnoses and number of urine cultures performed[17]. In agreement with a previous Dutch study, we found that a number of cultures were performed in episodes without antibiotic prescriptions[19]. The indications of these cultures are unknown, but in general urine cultures in untreated older people should be avoided, as the value of positive urine culture

is limited to gathering information on the causative pathogen and optimizing antibiotic treatment.

Our trial had several potential limitations. First, the introduction of the intervention in the first organization coincides with the introduction of the new guideline for UTIs in vulnerable older people. It introduced a more stringent way of diagnosing and treating UTIs than the previous Dutch guideline. We used the updated guideline as part of our intervention. While publication of this new guideline of course affected both the intervention and the control periods, it still could have mitigated the contrast between control and intervention measurements. Second, the study was extended to a total of 28 months due to a low inclusion rate. Still, we did not reach the previously calculated sample size. Elderly care physicians reported that they struggled with documenting UTI episodes due to high work pressure and limiting staffing. The high staff turnover might be related to the low inclusion rate, but may also underestimate the effect of the trial. Third, to extend the intervention beyond elderly care physicians, an educational meeting for nursing personnel was offered in all locations but attendance was very low due to limited staffing. The meeting was only performed in a single location. Including more nursing personnel could have supported the antibiotic intervention as they often signal symptoms in residents.

The strength of the study was that the intervention was standardized but small details could be personalized per location. For example, the standard pocket card contained first and second choice antibiotics for cystitis and complicated UTIs based on local resistance patterns.

CONCLUSION

Our study suggests that a multifaceted stewardship intervention targeting UTI in LTCF does not significantly improve appropriate antibiotic prescribing, though it seems that physicians based their choice to start antibiotic treatment less on non-specific complaints. More studies on effective interventions to reduce guideline non-compliant care for UTI in long term care residents are still necessary.

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SUPPLEMENTARY MATERIAL

A. Example of inclusion form

Patient characteristics:

- Age in years
- Gender
- Type of care:
  - o Revalidation
  - o Psycho-geriatric
  - o Somatic
  - o Other

Medical history:

- Comorbidities (Y/N)
  - o Dementia
  - o Immobilization / Wheelchair-bound
  - o Immunocompromised*
  - o Kidney failure **
    - If yes: date of the last measurement
  - o Diabetes
  - o Incontinence for urine
  - o Urinary catheter ***
- Recent use of antibiotics (<7 days) (Y/N)

Symptoms

- Is the patient unwell
  - o No
  - o Yes, slightly unwell
  - o Yes, very ill
- Which symptoms are the patient experiencing that makes you think of UTI (Y/N)
  - o Fever (>37.9°C) or chills
  - o Delirium or worsening general daily activities
  - o Increased frequency of urination
  - o Dysuria
  - o Increased urgency of urination
  - o Incontinence for urine
  - o Hematuria
  - o Suprapubic pain

  - Costovertebral angle tenderness
  - Cloudy or smelly urine
  - Other, not mentioned complaints
- Duration of the complaints in days

Diagnostics

- Is a urine dipstick performed (Y/N)
  - If yes: nitrite positive (Y/N)
  - If yes: leucocytes
    - 0
    - +
    - ++
    - +++
- Is there a recent urine culture available (<6 months) (Y/N)
  - If yes: what was the result of the culture
- Did you perform a new urine culture? (Y/N)

Treatment

- Did you start antibiotics (Y/N)
  - If yes: what antibiotic
  - If yes: which dose
  - If yes: how many days
- Did you advise any additional therapy (pain medication, rehydration, etc.)

*: residents are immunocompromised if:

- active HIV infection with CD4 count <300/μL
- cytotoxic chemotherapy and/or radiotherapy within the last 3 months
- Chronic hemodialysis longer than 3 months
- Residents that underwent organ or stemcell transplantation
- Use of immunosuppressive therapy (e.g. corticosteroids >0,5mg/kg/day prednisolone for >2 weeks)

**: residents with an eGFR <30ml/min are considered to have kidney failure

***: residents with a nephrostomy drain, suprapubic and transurethral urine catheter are all accepted

B. Example of follow-up form

Symptoms

- Did the complaints improve since inclusion?
  - o No
  - o Yes, partly
  - o Yes, completely
- If no: which symptoms does the patient experience (Y/N)
  - o Fever (>37.9°C) or chills
  - o Delirium or worsening general daily activities
  - o Increased frequency of urination
  - o Dysuria
  - o Increased urgency of urination
  - o Incontinence for urine
  - o Hematuria
  - o Suprapubic pain
  - o Costovertebral angle tenderness
  - o Other, not mentioned complaints

Medical microbiology

- Did you have contact with the researcher / medical microbiologist about this case? (Y/N)

Conclusion

- If a urine culture was performed, was it positive? (Y/N)
  - o If yes: what bacteria was found
- Are there additional antibiotics prescribed?
  - o If yes: what antibiotic
  - o If yes: which dose
  - o If yes: how many days

If the patient was admitted to the hospital or passed away during the last 10 days, please note the date.

C. Algorithm for UTI

Table S1: Algorithm for UTI based on Verenso guideline (10)

Cystitis	One or more specific complaint(s)
	No urinary catheter in medical history
	Duration complaints <8 days
	Only women
Complicated UTI	One or more specific complaint(s)
	Any non-specific complaints
	No urinary catheter in medical history
	Duration complaints <8 days
	No cystitis
Catheter-related UTI	One or more non-specific complaint(s)
	Urinary catheter in medical history

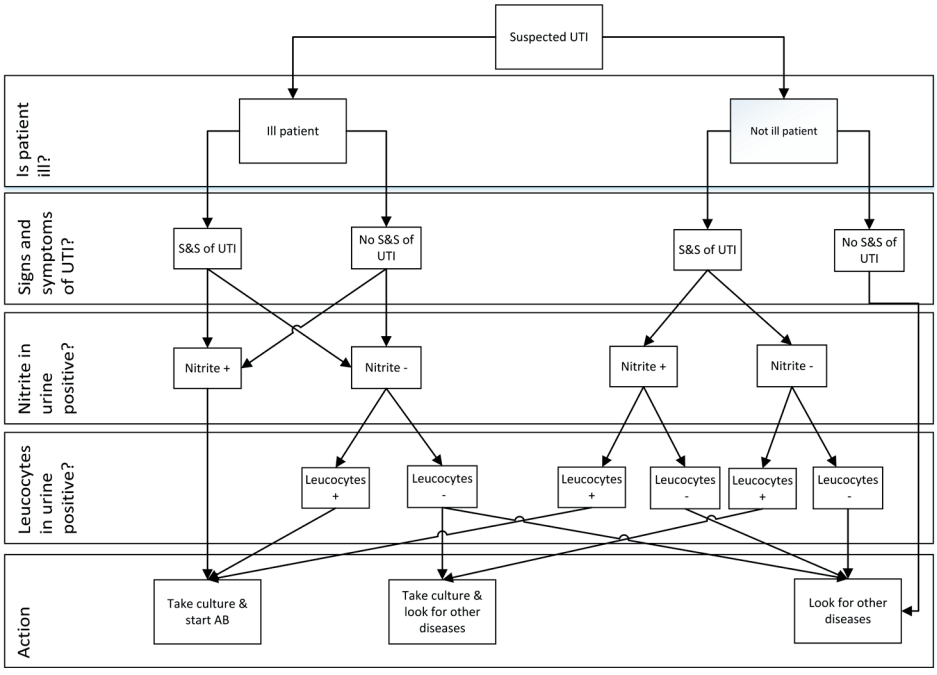

Figure S1: example of pocket card (Dutch)

Table S2: Significant determinants associated with guideline non-compliant prescribing during the control and intervention period.

Determinants – full model	Control		Intervention	
	OR	aOR	OR	aOR
Age	0.96 (0.92 – 1.00)	0.94 (0.89 – 0.98)	0.98 (0.93 – 1.02)	
Male	2.98 (1.06 – 9.71)		1.19 (0.42 – 3.56)	
History of dementia	1.23 (0.63 – 2.39)		1.78 (0.84 – 3.83)	
History of diabetes mellitus	3.26 (1.17 – 10.56)		0.46 (0.17 – 1.15)	
Fever	2.77 (0.88 -10.49)		2.62 (0.72 – 12.42)	
Increased frequency	0.14 (0.06 – 0.30)	0.14 (0.05 – 0.35)	0.44 (0.17 – 1.06)	0.64 (0.23 – 1.81)
Urgency	0.28 (0.10 – 0.72)		0.32 (0.08 – 1.03)	
Dysuria	0.10 (0.03 – 0.27)	0.13 (0.04 – 0.37)	0.22 (0.09 – 0.52)	0.24 (0.09 – 0.60)
Delirium	2.21 (1.15 – 4.31)		1.87 (0.93 – 3.80)	
Incontinency	0.83 (0.23 – 2.89)		0.26 (0.07 – 0.80)	0.22 (0.06 – 0.69)
Stomache pain	0.40 (0.17 – 0.91)		0.81 (0.35 – 1.86)	
Abnormal urine	0.29 (0.09 – 0.80)	0.24 (0.06 – 0.78)	0.45 (0.15 -1.26)	
General discomfort	10.23 (1.85 – 191.10)	8.16 (1.00 – 204.40)	1.23 (0.26 – 6.45)	
Unexplained symptoms	7.72 (1.33 – 146.25)		2.26 (0.60 – 10.85)	
Other	3.62 (1.84 – 7.33)		1.79 (0.87 – 3.74)	
Positive leukocyte esterase (+1)	0.64(0.07 – 4.37)		1.50 (0.13 – 17.42)	
Positive leukocyte esterase (+2)	0.24 (0.03 – 1.12)		0.67 (0.07 – 6.31)	
Positive leukocyte esterase (+3)	0.24 (0.03 – 1.07)		1.23 (0.14 – 10.58)	

Table S3: Significant determinants associated with overtreatment during the control and intervention period.

Determinants – full model	Control		Intervention	
	OR	aOR	OR	aOR
Psychogeriatric ward	0.88 (0.28 – 2.64)		1.64 (0.46 – 6.61)	0.70 (0.14 -3.62)
Revalidation ward	0.15 (0.03 – 0.56)		0.10 (0.00 – 0.85)	0.03 (0.00 – 0.36)
Other wards	0.26 (0.41 – 3.26)		1.75 (0.16 – 20.03)	0.60 (0.21 – 5.05)
Age	0.99 (0.95 – 1.03)		0.99 (0.94 – 1.03)	
Male	2.69 (0.99 – 7.75)	7.70 (1.37 – 75.15)	0.43 (0.11 – 1.32)	
History of incontinency	1.47 (0.68 – 3.19)		0.29 (0.07 – 0.95)	
History of dementia	2.46 (1.22 – 5.14)		3.44 (1.52 – 8.46)	
Previous treatment with AB	0.16 (0.02 – 0.60)	0.54 (0.07 – 2.78)	7.71 (1.20 – 150.11)	
Fever	2.18 (0.72 – 6.96)		4.27 (1.17 – 20.25)	6.64 (1.31 – 58.66)
Increased frequency	0.02 (0.00 – 0.08)	0.01 (0.00 -0.05)	0.14 (0.03 – 0.45)	
Urgency	Na[1]		0.21 (0.03 -0.80)	
Dysuria	$7.93e^{-9}$ ($2.03e^{-155}$ – $5.10e^{13}$)		0.12 (0.03 – 0.34)	0.13 (0.03 – 0.41)
Delirium	3.38 (1.72 – 6.76)	4.13 (1.56 – 11.58)	2.61 (1.27 – 5.50)	
Incontinency	0.14 (0.01 – 0.75)	0.08 (0.00 – 0.57)	Na[1]	
Urinary retention	Na[1]		Na[1]	
Stomach ache	0.45 (0.18 – 1.06)		1.00 (0.42 – 2.30)	
General discomfort	15.88 (2.87 – 297.09)	18.30 (1.51 – 896.82)	1.96 (0.41 – 10.31)	
Abnormal labresults	6.43 (0.92 – 127.48)		0.46 (0.02 – 3.72)	
Unexplained symptoms	11.89 (2.04 – 225.38)	32.14 (1.54 – 3.31e+3)	2.27 (0.61 – 9.27)	
Other	7.10 (3.48 – 15.07)	3.19 (1.09 -9.80)	1.90 (0.92 – 3.95)	
Duration complaints (days)	0.96 (0.86 – 1.04)		1.06 (1.01 – 1.14)	1.09 (1.01 – 1.19)
Positive nitrite	1.88 (0.87 – 4.29)		1.78 (0.73 – 4.67)	
Positive leukocyte esterase (+1)	6.86 (0.87 – 146.94)		1.29 (0.10 – 32.06)	
Positive leukocyte esterase (+2)	5.54 (0.9 – 107.39)		2.00 (0.22 – 43.68)	
Positive leukocyte esterase (+3)	5.6 (0.96 – 106.27)		(2.34 0.29 – 48.31)	

1.There were not enough data points to fit the model

4

FIVE VERSUS SEVEN DAYS OF NITROFURANTOIN FOR URINARY TRACT INFECTIONS IN WOMEN WITH DIABETES: A RETROSPECTIVE COHORT STUDY.

K.D. Hendriks-Spoor, F.L. Wille, T. ten Doesschate, J.W. Dorigo-Zetsma, T.J.M. Verheij, C.H. van Werkhoven

ABSTRACT

Objective

To compare the effectiveness of five versus seven days of nitrofurantoin treatment for cystitis in diabetic women.

Methods

Data were collected retrospectively from Dutch general practitioners between 2013 and 2020. Nitrofurantoin prescriptions with a duration of five (5DN) or seven days (7DN) in women with diabetes were included. Inverse propensity weighting (IPW) was performed to calculate adjusted risk differences (RD) for treatment failure within 28 days. Secondary outcomes were 14-day treatment failure, severe treatment failure, and 28-day treatment failure in defined risk groups.

Results

Nitrofurantoin was prescribed in 6866 episodes, 3247 (47,3%) episodes with 5DN and 3619 (52,7%) episodes with 7DN. Patients in the 7DN group had more co-morbidities, more diabetes-related complications and were more insulin-dependent. There were 517/3247 (15.9%) failures in the 5DN group versus 520/3619 (14.4%) in the 7DN group. The adjusted RD for failure within 28 days was 1.4% (95% CI -0.6 to 3.4).

Conclusion

We found no clinically-significant difference in treatment failure in diabetic women with cystitis treated either five or seven days with nitrofurantoin within 28 days. A 5-day treatment should be considered to reduce cumulative nitrofurantoin exposure in DM patients.

INTRODUCTION

Urinary tract infections (UTI) are the most common infections in patients with diabetes mellitus (DM)[1]. An epidemiological study showed an adjusted incidence for UTI per 1000 person-years in women with Type 2 DM of 102.9 (95% CI 100.5 to 105.4) versus 76.2 (95% CI 74.2 to 78.2) in patients without DM[2]. There is little research on the optimal treatment duration of cystitis in DM patients. Some guidelines suggest that patients with well-controlled diabetes may be considered to have uncomplicated cystitis[3]. This hypothesis is supported by an observational study in 259 women with DM that found no benefit of longer treatment duration (≥5 days of treatment) on the recurrence of UTI within 30 days to one year of follow-up[4]. While this study stratified for the Charlson comorbidity index, it did not correct for potential risk factors for clinical failure like age, glycemic control and insulin use. Despite this current guideline recommendations are still largely based on the expert opinion that UTI in DM-patients should be treated as a complicated UTI. For example, the Dutch College of General Practitioners recommends treating UTI in diabetic patients with seven days nitrofurantoin, instead of five days as recommended for cystitis in healthy women, because of the supposed higher risk on recurrent UTI and complications[5].

Five instead of seven days of nitrofurantoin might reduce cumulative use by 28% in a patient population already consuming large amounts of antibiotics due to a high incidence of infections[1]. Shorter duration might decrease the number of days with side-effects due to nitrofurantoin, such as abdominal complaints (nausea or abdominal discomfort) and headaches, while increasing patient satisfaction, improving therapeutic compliance and cost-effectiveness[6–8]. Therefore, additional studies are necessary to address this problem.This study aimed to determine the effectiviness of 5 days nitrofurantoin (5DN) compared to 7 days nitrofurantoin (7DN) for cystitis in women with DM.

METHODS

Data collection

Data were collected from the Julius General Practitioners' Network (JGPN), containing information from 84 different primary care practices in the province of Utrecht in the Netherlands from January 2013 until September 2020 (Figure 1). The database contains information on patient characteristics, diagnoses, prescriptions and laboratory results. Episodes of cystitis were selected based on Anatomical Therapeutic Chemical (ATC) codes for nitrofurantoin and were additionally linked to International Classification of Primary Care (ICPC) codes for UTI.

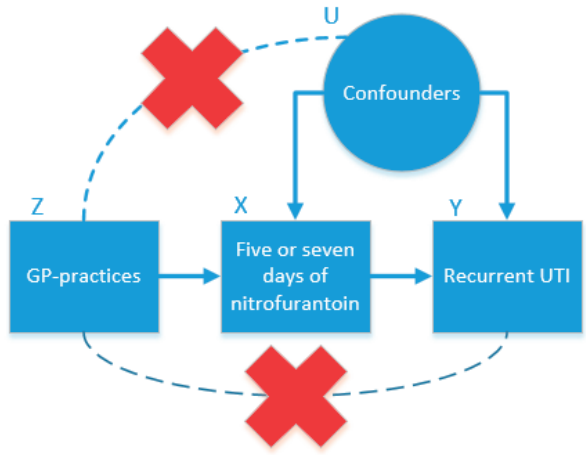

Figure 1: Graphical representation of the model and the assumption for instrumental variable analysis. Assumption 1 – Relevance. The instrumental variable Z has an effect on the exposure X. Assumption 2 - Exclusion restriction. The instrumental variable Z does not affect the outcome Y. Assumption 3 – exchangeability. The confounders (U) are independent of the instrumental variable Z. IV-analysis is assumed to be unbiased if GP practice preference only affects clinical failure only through prescription of 5DN or 7DN (X) and they have no direct effect on the outcome of clinical failure (Y) and do not differ in the type of patients (U) for whom they prescribe either 5DN or 7DN.

Study population

Index UTI episodes were selected from women ≥12 year of age with DM, either Type 1 or Type 2, based on ICPC code or the ATC code for DM-medication, who received a nitrofurantoin prescription for 5 or 7 days in combination with an ICPC code for a UTI or UTI-related symptom. The duration of the prescription was calculated with the number and dosages of the nitrofurantoin tablets prescriped. The ICPC and ATC codes are provided in table S1. Multiple episodes per patient were allowed in the analysis. Episodes with a presumed UTI 28 days prior to the index UTI episode were excluded from the analysis to distinguish between treatment failure and a new index UTI. Episodes from patients with a complicated UTI based on risk factors other than DM were excluded from the database, e.g. pregnancy, use of immunosuppressive drugs, kidney or bladder disease, an estimated glomerular filtration rate (eGFR) below 30 ml/min or three or more recurrent UTI's in the last 6 months or prophylactic treatment in the last 6 months. Episodes with less than 28 days of follow-up due to missing information of the GP were excluded.

Endpoints

The primary outcome measure of treatment failure was defined as a new prescription of nitrofurantoin, fosfomycin, trimethoprim, ciprofloxacin, trimethoprim-sulfamethoxazole or amoxicillin-clavulanic acid combined with an ICPC code for UTI or any symptom or sign correlated to UTI occurring within 28 days of the initial prescription. Secondary outcomes were 14-day treatment failure, severe treatment failure, defined as a new prescription for ciprofloxacin, trimethoprim-sulfamethoxazole or amoxicilline-clavulanic acid combined with

an ICPC code for pyelonephritis, and 28-day treatment failure in defined risk groups. Studied risk groups were increased HbA1c, age and use of insulin.

Statistical analysis

Inverse propensity weighting (IPW) with clustering per patients to adjust for patients with repeated episodes, was used to estimate risk differences (RD) with a 95% confidence intervals (95% CI). IPW analysis redistributes patient groups based on available variables to form a standardized pseudo-population. There are three assumptions for IPW: consistency, exchangeability, and positivity[9–11]. The consistency assumption suggests that the individual's potential outcome under the observed exposure is the actual outcome. This is deemed plausible as the treatment for UTI is fairly standardized in the Netherlands. The assumption of exchangeability assumes that there is no unmeasured confounding. By using a database with a broad selection of variables, we aimed to reduce unmeasured confounding. The positivity assumption suggests that all patients have the chance of getting the exposure of interest, e.g. 5 or 7 days of nitrofurantoin, even those with uncommon co-variates. Based on the variation in the baseline table and the distribution of the 5DN and 7DN per primary care practice (Supplement 2), we do not expect the positivity assumption to be a problem.

IPW score was calculated to predict the probability of receiving 5DN or 7DN by using the following variables: age, antidiabetic medication, extended or normal release nitrofurantoin, eGFR (continuously from >30 ml/min and above), diabetic complications, urinary incontinence, urolithiasis, neuropsychiatric disorders, sexually transmitted disease, HbA1c values (≤3 months), glucose values (≤7 days), cardiovascular disease and related medication, antibiotic prescriptions for UTI in the previous 6 months (0, 1 or 2 previous prescriptions) and GP practice (Supplement 1). Weights derived from the IPW score were trimmed at the first and 99th percentile to enhance the precision of the analysis[11].

We recoded eGFR, glucose values and HbA1c values, to account for missing values. The eGFR was calculated with the Chronic Kidney Disease Epidemiology (CKDepi) formula using age, gender, and the most recent plasma creatinine. Missing eGFR values were set to 60 mL/min, reflecting a normal eGFR. Glucose was recoded into four groups (<6 mmol/L, 6-11 mmol/L, >11 mmol/L, missing value) and HbA1c in three groups (<53 mmol/mol, >53 mmol/mol, missing value), reflecting clinically relevant thresholds. Missing information on duration or dosage of prescribed nitrofurantoin was collected from the free text when possible.

We included a modified intention-to-treat (m-ITT) analysis, excluding treatment failure within 6 days, since the intervention is identical during the first five days. We conducted a post-hoc analysis of stratifying for groups with higher risk of UTI: suboptimal glycemic control (based on HbA1c levels), patients over 65 years of age and insulin use as a proxy for more severe DM.

Instrumental variable (IV) analysis was performed as a sensitivity analysis as an alternative to control for unobserved confounding. By using the GP practices as an instrumental variable, we were able to provide an estimation of the failure rates. There are three assumptions to perform a valid instrumental variable analysis (Figure 2). The relevance assumption was that the GP preference had an effect on treatment duration and would vary between practices. The exclusion restriction suggests that outcome is not affected by the instrumental variable other than through treatment. The last and third assumption is the exchangeability assumption. It assumes that GP practices were independent of patients characteristics. Both age and outcome were independent of GP practice as visible in figures S1 and S2. If possible these assumptions were checked by using F-statistics.

R software version Version 1.1.456 was used for data analysis, with R package 'ipw' to perform IPW and "ivpack" to perform the IV analysis.

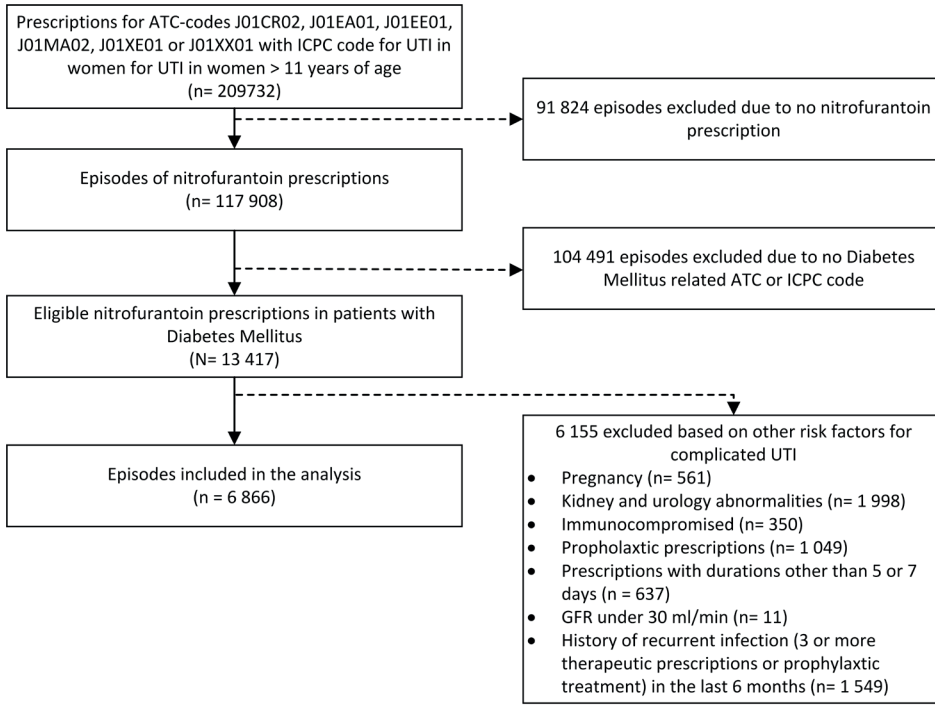

Figure 2: Flow chart of the study selection of nitrofurantoin prescriptions with a duration of five or seven days from 84 Dutch GP practices between January 2013 and September 2020

Ethics

Ethical approval was obtained from the medical ethical committee of the University Medical Center Utrecht, the Netherlands, with a waiver for informed consent. Individuals are not traceable as all data were anonymized.

RESULTS

Patient selection

A total of 14352 nitrofurantoin prescriptions in DM-patients were found during the study period. After the exclusion of 6527 episodes, we analyzed 6866 episodes in 3681 unique patients, consisting of 3247 (47.3%) episodes in 5DN and 3619 (52.7%) in 7DN (Figure 1).

Baseline Characteristics

The 7DN group had more comorbidities, received more often insulin treatment or a combination of insulin and oral medication, though were comparable in age with 5DN (Table 1). While the HbA1c levels were higher in the 7DN group, the average glucose levels were similar. The 7DN group had been treated for UTI more frequently in the previous six months.

Assumptions instrumental variable

The preference for treatment duration was highly variable between GP-practices (figure S1), while population age and outcome between the practices did not differ (Figure S2). Using the GP practice to predict the treatment duration gave an F-statistic of 1.77 e^{+27}, which confirms the appropriateness of the instrumental variable.

Primary analysis

Of the 3247 patients that were treated with 5DN, 15.9% patients received a new prescription within 28 days, while in the 7DN, 14.4% of the 3619 received a new prescription (table 2). Using the IPW analysis, the adjusted RD was 1.4% (95% CI:-0.6–3.4). Similarly, the sensitivity IV analysis yielded an RD of 1.6% (95% CI:-2.6–5.8).

Secondary analyses

While the crude failure rate of recurrence of UTI within 14 days was higher in the 5DN group (11.0% versus 9.3%), 5DN was not associated with an increased RD in the crude RD, adjusted RD (1.5%, 95% CI:0.0–1.5)., or in the sensitivity analysis (2.0, 95% CI:-2.6–5.8). Both the m-ITT change (aRD 0.9%, 95% CI:-0.9–2.7, sensitivity RD 1.8%, 95% CI:-2.0–5.7) and the severe failure endpoint (aRD -0.3% 95% CI:-0.8–0.2, sensitivity RD 0.2% 95% CI:-1.0–1.3) did not results in a signicant difference between the groups.

Table 1: Baseline characteristics in the study population that received either nitrofurantoin for five days or seven days to treat cystitis in women with diabetes.

	5DN	*7DN*	*P-value*
N	3247	3619	
Age (mean(SD))	66.81 (15.54)	67.86 (14.17)	0.003
Use of insulin, n (%)	760 (23.4)	1162 (32.1)	<0.001
Use of oral antidiabetic medication, n (%)	2337 (72.0)	2864 (79.1)	<0.001
Biguanides (A10BA)	2211 (68.1)	2709 (74.9)	
Sulfonylureas (A10BB)	1097 (33.8)	1470 (40.6)	
Combinations (A10BD)	13 (0.4)	16 (0.4)	
Alpha-glucosidase inhibitors (A10BF)	24 (0.7)	12 (0.3)	
Thiazolidinediones (A10BG)	17 (0.5)	41 (0.4)	
DPP-4 inhibitors (A10BH)	116 (3.6)	200 (5.5)	
GLP-1 analogues(A10BJ)	72 (2.2)	122 (3.4)	
SGLT2 inhibitors (A10BK)	20 (0.6)	35 (1.0)	
Other blood glucose lowering drugs (A10BX)	26 (0.8)	35 (1.0)	
Combination insulin and oral antidiabetic medication, n(%)	546 (16.8)	872 (24.1)	<0.001
Glucose level (median(IQR)) *	7.7 (6.3 – 9.0)	7.7 (6.8 – 8.9)	0.407
Glucose categorical, n (%)			<0.001
Hyperglycemic (>11.9 mmol/L)	82 (2.5)	139 (3.8)	
Hypoglycemic (<6.0 mmol/L)	338 (10.4)	314 (8.7)	
Normal (>5.9 - <12.0 mmol/L)	1136 (35.0)	1515 (41.9)	
Missing	1691 (52.1)	1651 (45.6)	
HbA1c in mmol/mol (median(IQR)) **	53 (47 - 61)	54 (49 - 63)	<0.001
Hb1Ac categorical, n (%)			<0.001
High(>53.0 mmol/mol)	347 (10.7)	589 (16.3)	
Normal (<53.1 mmol/mol)	356 (11.0)	491 (13.6)	
Missing	2544 (78.3)	2539 (70.2)	
Diabetic complications, n (%)	195 (6.0)	426 (11.8)	<0.001
Retinopathy	98 (3.0)	274 (7.6)	
Glomerulopathy	5 (0.2)	5 (0.1)	
Neuropathy	100 (3.1)	183 (5.1)	
GFR in ml/min (mean (SD)) ***	101 (24)	102 (20)	0.291
Missing, n(%)	600 (18.5)	507 (14.0)	
Received antibiotics for UTI in the last 6 months, n (%)	650 (20.0)	822 (22.7)	<0.001
Use of hormones[a], n (%)	221 (6.8)	170 (4.8)	<0.001
History of neuropsychiatric diseases[b], n (%)	625 (19.2)	687 (19.0)	0.804
History of cardiovascular risk factors[c], n (%)	2638 (81.2)	3172 (87.6)	<0.001
History of cardiovascular disease,[d] n (%)	179 (5.5)	302 (8.3)	<0.001

* *Most recent level* within 7 days prior to UTI episode

** *Most recent level within 30 days prior to UTI episode*

*** *Most recent measurement within 365 days to UTI episode*

[a] *This category includes GP prescriptions for oral contraception, estrogen and progesterone.*

[b] *This category includes ICPC codes for cognitive impairment, dementia and depressions as*

[c] *This category includes GP prescriptions of medication for hypercholesterolemia, antihypertensive and anti-thrombotic medication.*

[d] *This category includes ICPC codes for previous acute myocardial infarction and ischemic heart disease*

Table 2: Endpoint for primary and secondary outcomes in the population that were prescribed either five or seven days of nitrofurantoin as treatment for cystitis in women with diabetes. A risk difference (RD) >0 is in favour of seven days of nitrofurantoin treatment.

		Follow-up duration	5DN	Failure rate (n)	7DN	Failure rate (n)	Crude RD (95% CI)	IPW RD (95% CI)	IV RD (95% CI)
Primary outcome	Overall failure	Day 0-28	3247	15.9% (517)	3619	14.4% (520)	1.6 (-0.1 – 3.3)	1.4 (-0.6 – 3.4)	1.6 (-2.6 – 5.8)
Secondary outcome	Overall failure	Day 0-14	3338	11.0% (368)	3749	9.3% (348)	1.7 (0.3 – 3.1)	1.5 (0.0 – 3.1)	2.0 (-1.5– 5.5)
	m-ITT	Day 6-28	3247	12.8% (416)	3619	11.8% (426)	0.9 (-1.0– 2.7)	0.9 (-0.9 – 2.7)	1.8 (-2.0 – 5.7)
	Severe failure	Day 0-28	3247	0.9% (28)	3619	1.0% (36)	-0.3 (-0.8 – 0.2)	-0.3 (-0.8 – 0.2)	0.2 (-1.0 – 1.3)

Subgroup analysis

Patients with an HbA1c >53mmol/ml have an increased failure risk compared to those with HbA1C <53mmol/ml (table 3). The IPW showed 5DN non-significantly decreased RD in the HbA1c >53mmol/ml group (-1.8, 95% CI:-6.8-3.4), while increasing the RD in those with HbA1c <53mmol/ml (1.1%, 95% CI:-4.2-6.4). Patients >65 years have an increased failure risk compared to those younger, though 5DN or 7DN did not effect the failure rate in the adjusted RD (>65: 1.5, 95% CI: -1.4–4.4 versus <65: 1.5 95% CI:-1.4–4.3). 5DN in the insuline group decreased the failure rate while adjusted RD remained stabile (-0.7 95% CI:-4.5–3.1), while those in the non-insuline group had an increased failure rate and non-signifcant increased adjusted RD (2.4%, 95% CI:0.0–4.8).

Table 3: Endpoints for the subgroup analysis in which the population is stratified for three risk groups: increased HbA1c as a proxy for glycemic dysregulation, increased age and insulin use as a proxy for severity of diabetes. A risk difference (RD) >0 is in favour of seven days of nitrofurantoin treatment. The endpoint was measured at 0-28 days of post-index prescription.

Subgroup	5DN	Failure rate (n)	7DN	Failure rate (n)	Crude RD (95% CI)	IPW RD (95% CI)	IV RD (95% CI)
HbA1c > 53 mmol/ml	374	14.1% (49)	589	14.3% (84)	-0.1 (-4.8 – 4.5)	-1.8 (-6.8 – 3.4)	0.7 (-7.9 – 9.4)
HbA1c < 53 mmol/ml	356	12.9% (46)	491	12.8% (63)	0.1 (-4.5 – 4.7)	1.1 (-4.2 – 6.4)	-4.4 (-13.4 – 4.6)
Patients >65 years	1908	14.5% (276)	2310	13.2% (305)	1.3 (-0.8 – 3.5)	1.5 (-1.4 – 4.4)	0.0 (-4.5 – 4.4)
Patients < 65 years	1339	10.5% (140)	1309	9.2% (121)	1.2 (-1.1 – 3.5)	1.5 (-1.4 – 4.3)	3.8 (-2.7 – 10.2)
Insulin using patients	760	13.9% (106)	1162	15.0% (174)	-1.0 (-4.0 – 2.0)	-0.7 (-4.5 – 3.1)	- 2.3 (-8.7 – 4.2)
Non-insulin using patients	2487	16.5% (411)	2457	14.1% (346)	1.8 (-0.1 – 3.6)	2.4 (0.0 – 4.8)	2.3 (-2.2 – 6.8)

DISCUSSION

Our study demonstrates that 5DN to treat cystitis in women with DM does not lead to a significant increased risk of treatment failure compared to the guideline-advised seven days of nitrofurantoin. This was found in both the IPW and the sensitivity analyses of the primary outcome as well as in the subgroups and secondary outcomes.

According to our main analysis, a risk difference of over 3.4% in favour of 7 days is unlikely. There is no consensus with respect to a clinically relevant risk difference that would justify an additional two days of nitrofurantoin treatment. E.g. if the true risk difference were 5%, we could prevent one antibiotic prescription for recurrent UTI by treating 20 patients for an extra 2 days (i.e. 40 treatment-days to prevent one antibiotic prescription of 5-10 days). Hence we conclude that our study is sufficiently powered to exclude a clinically relevant risk difference.

The high percentage of GP practices that prescribed five days of nitrofurantoin in women with DM was an unexpected finding and illustrates the need for studies on this subject. This is in contrast with earlier research showing that compliance to the UTI-guideline had increased over the years[12].

The crude failure rate of cystitis treatment for DM-patients remains high. Earlier research has shown that antimicrobial resistance is not higher in patients with DM, so this is not likely to play a role in treatment failure, but is probably due to an impaired immune response, though studies have been contradictory on the subject[13-14]. Risk factors for recurrent cystitis in women with diabetes are often related to worse glycemic control and diabetic complications. However, we did not find that 7DN reduces treatment failure in patients with a high HbA1c. Similarly, stratifying for age >65 years or insulin use, neither resulted in a relevant difference between 5DN and 7DN outcomes.

Two observational studies have shown that the number of new UTI infections within 30 days was not effected by treatment duration, though they did not correct for common risk factors as medication or glycemic control[5,14]. To our knowledge, this study is the first to find a lack of effect of longer treatment for uncomplicated UTI in women with DM, while correcting for bias by using an IPW analyse.

Antimicrobial therapy duration should always be shortened if deemed safe. While only 2% of patients discontinue the treatment due to side-effects, 28-49% of women experience common side-effects during their treatment, like nausea and headaches[8,15]. We presume that shorter treatment duration could also shorten the duration of side effects, although there

is no literature to support this. Second, longer treatments decrease cost-effectiveness and therapeutic compliance[16]. Third, while it is unproven that a reduction of two days would cause less selective pressure on the microbiome and reduce antimicrobial resistance, nitrofurantoin prescription independent of the dosage has been associated with antibiotic resistant infections and a shorter duration, if safe, is generally recommended to reduce antibiotic resistance development[17-19].

There are several limitations to the study. First, as we do not have information on severity of the complaints, residual confounding by indication is still a possibility. Non-adherence to the cystitis guidelines of Dutch GPs could be associated with non-adherence to guidelines in general, such as lifestyle advice preventing UTI, and might result in a higher rate of recurrence.

Second, our outcomes have been based on using retrospective prescription data, and lacks data on microbiology cultures, which can lead to misclassification. However, GP's included in this database spend extra care in providing correct information and the database has been studied before and appears to provide reliable data[20].

Third, the endpoint of clinical failure has been based on a new prescription for UTI. Failures could have been missed due to out-of-office prescriptions or patients admitted to the hospital. This group is expected to be small and unlikely to be different in the short versus longer treatment group.

Based on this study and possible persistent residual confounding, we think a clinical trial on this topic is needed. While outside of our study domain, it could also be interesting to study different antimicrobial options, as treatment failure in women with DM is still far higher than in healthy women (15.9% versus 4.1%)[21].

In conclusion, there was no significant difference in treatment failure between 5DN and 7DN for uncomplicated cystitis in patients with DM after 28 days, as we do not think a difference of a few percent to be clinical relevant. Furthermore switching standard therapy to 5DN could reduce the number of antibiotic days in patients with DM.

FUNDING

No funding was received for this research.

TRANSPARENCY DECLARATIONS

None to declare

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SUPPLEMENTARY MATERIAL

Table S1 - Inclusion and endpoint criteria based on ICPC and ATC codes as used in the study population.

	Diagnosis	Code	Explanation code
Inclusion criteria	Diabetes Mellitus	ICPC: T90, T90.1, T90.2	Defined from diagnose of Diabetes Mellitus, both type 1 and 2.
		ATC: A10A, A10AB, A10AC, A10AD, A10AE, A10AF, A10B, A10BA, A10BB, A10BC, A10BD, A10BF, A10BG, A10BH, A10BJ, A10BK, A10BX.	Includes use of insulin, biguanides, sulfonylureas, sulfonamides, alpha-glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase-4 (DDP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues, sodium-glucose transporter-2 (SGLT-2) inhibitors, other blood-glucose-lowering drugs, and combinations of oral blood glucose-lowering drugs.
	Index episode	ICPC: U01 (stranguria), U02 (pollakisuria), U05 (other miction problems), U70 (pyelonephritis), U71 (urinary tract infection), U71.1 (cystitis), U72 (non-specific urethritis)	Complaints of cystitis or symptoms related to cystitis.
		ATC: J01XE01 (nitrofurantoin) for 5 or 7 days of therapy	Antibiotic advised for the treatment of UTI by the guideline of the Dutch College of General Practitioners.
Endpoint	UTI	ICPC: U01 (stranguria), U02 (pollakisuria), U05 (other miction problems), U70 (pyelonephritis), U71 (urinary tract infection), U71.1 (cystitis), U72 (non-specific urethritis)	Complaints of cystitis or symptoms related to cystitis.
		ATC: J01CR02 (amoxicillin-clavulanic acid), J01EA01 (trimethoprim), J01EE01 (trimethoprim-sulfamethoxazole), J01MA05 (ciprofloxacin), J01XE01 (nitrofurantoin), J01XX01 (fosfomycine)	Antibiotic advised for the treatment of UTI by the guideline of the Dutch College of General Practitioners.
	Pyelonephritis	ICPC: U70	ICPC code for pyelonephritis
		ATC: J01CR02 (amoxicillin-clavulanic acid), J01EE01 (trimethoprim-sulfamethoxazole), J01MA05 (ciprofloxacin)	Antibiotic advised for complicated UTI by the guideline of the Dutch College of General Practitioners.

Table S1 - Inclusion and endpoint criteria based on ICPC and ATC codes as used in the study population. (continued)

	Diagnosis	Code	Explanation code
Exclusion criteria	Pregnancy	ICPC codes starting with W, excluding W01, W02, W10, W10.01, W10.02, W11, W12, W13, W14, W14.01, W14.02, W14.03, W15, W19, W19.01, W19.02, W30, W31, W33, W34, W35, W38, W40, W41, W42, W43, W45, W46, W47, W48, W49, W50, W51, W52, W54, W56, W58, W59, W60, W67, W73.01, W94, W95.01, W99.03, W99.04, W99.05	ICPC code for pregnancy and or related codes starting with W 9 months before index case
	Use of immunosuppressive drugs	ATC: H02AB06, H02AB07, H02AB02, H02AB04, H02BX01, all medications with an ATC code starting with L01 and L04	Immunosuppressive drugs 6 months before index case
		ICPC: A87.02	ICPC code for organ transplant 6 months before index case
	Kidney or bladder disease	ICPC: U76, U99.04 U99.05, U99.06, U75, U99.02, U85, U79, U77, U85.01, U80.02	Urological anatomical abnormalities, excluding kidney stone
	Estimated glomerular filtration rate (eGFR) below 30 ml/min	Chronic Kidney Disease Epidemiology (CKDepi) calculated with most recent creatinine within 6 months of the index UTI episode, gender and age. The 'nephro' package in R was used to calculate the CKDepi.	

Table S1 - Inclusion and endpoint criteria based on ICPC and ATC codes as used in the study population. (continued)

	Diagnosis	Code	Explanation code
Confounders	Antidiabetic medication	ATC: A10A, A10AB, A10AC, A10AD, A10AE, A10AF, A10B, A10BA, A10BB, A10BC, A10BD, A10BF, A10BG, A10BH, A10BJ, A10BK, A10BX.	Includes use of insulin, biguanides, sulfonylureas, sulfonamides, alpha-glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase-4 (DDP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues, sodium-glucose transporter-2 (SGLT-2) inhibitors, other blood-glucose-lowering drugs, and combinations of oral blood glucose-lowering drugs.
	Estimated glomerular filtration rate (eGFR) below 30 ml/min	Chronic Kidney Disease Epidemiology (CKDepi) calculated with most recent creatinine within 6 months of the index UTI episode, gender and age. The 'nephro' package in R was used to calculate the CKDepi.	
	Urine incontinence	ICPC: U04	Diagnoses for incontinence within one year of the index UTI episode
	Urolithiasis	ICPC: U95	Diagnoses for urolithiasis
	Diabetic complications	ICPC: F83.01, N94.02, U88	Diagnoses diabetic retinopathy, diabetic neuropathy and glomerulonephritis.
	Neuropsychiatric disorders:	ICPC: P70, P85	Diagnosis of dementia and cognitive impairment
		ATC code starting with N06A	ATC code for anti-depressiva
	Sexually transmitted disease: ICPC codes including	ICPC: X99, X74, X91, X90, X71, X70, Y70, Y71, Y72, Y76, Y99.07.	STD diagnoses within 6 months of the index case.
	Use of anti-conceptive agents and/or hormones	ATC codes starting with G03A, G03C, G03D	Use of hormones within 6 months of index UTI episode
	Cardiovascular disease	ATC codes: B10A, C02	Use of antithrombic medication and antihypertensive medication
		ICPC codes: K75, K76.	Diagnoses of (chronic) heart ischemia

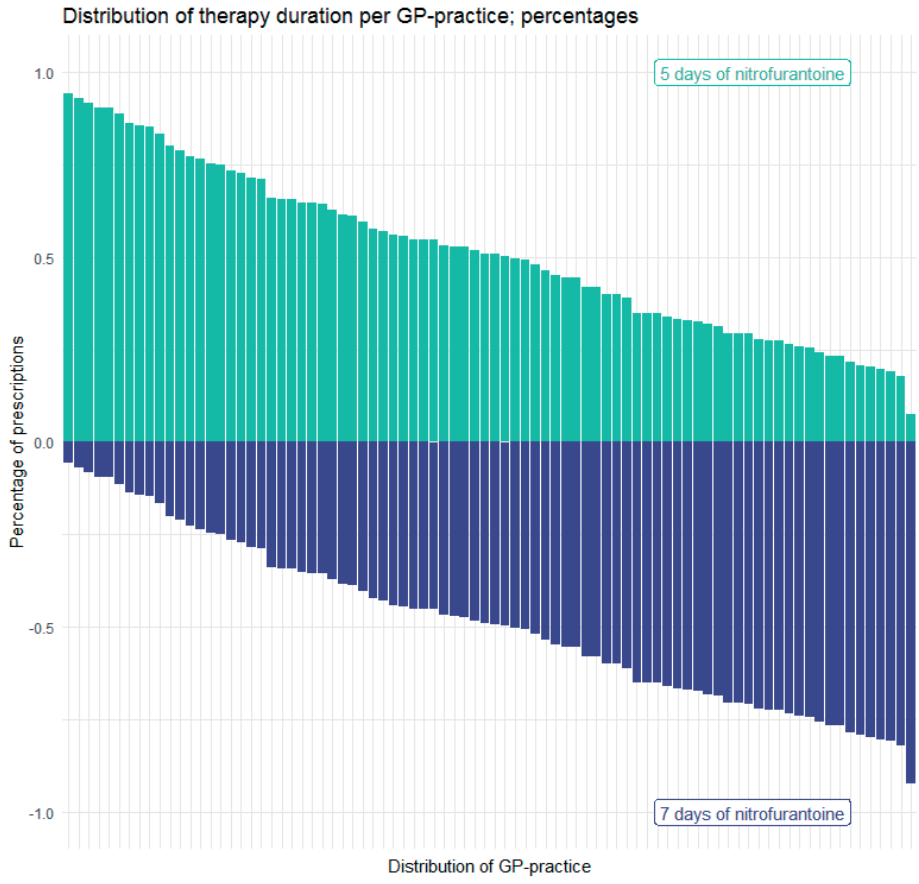


Figure S1 – Crude distribution plot of 5DN and 7DN per GP-practice in percentages of the total number of nitrofurantoin prescriptions

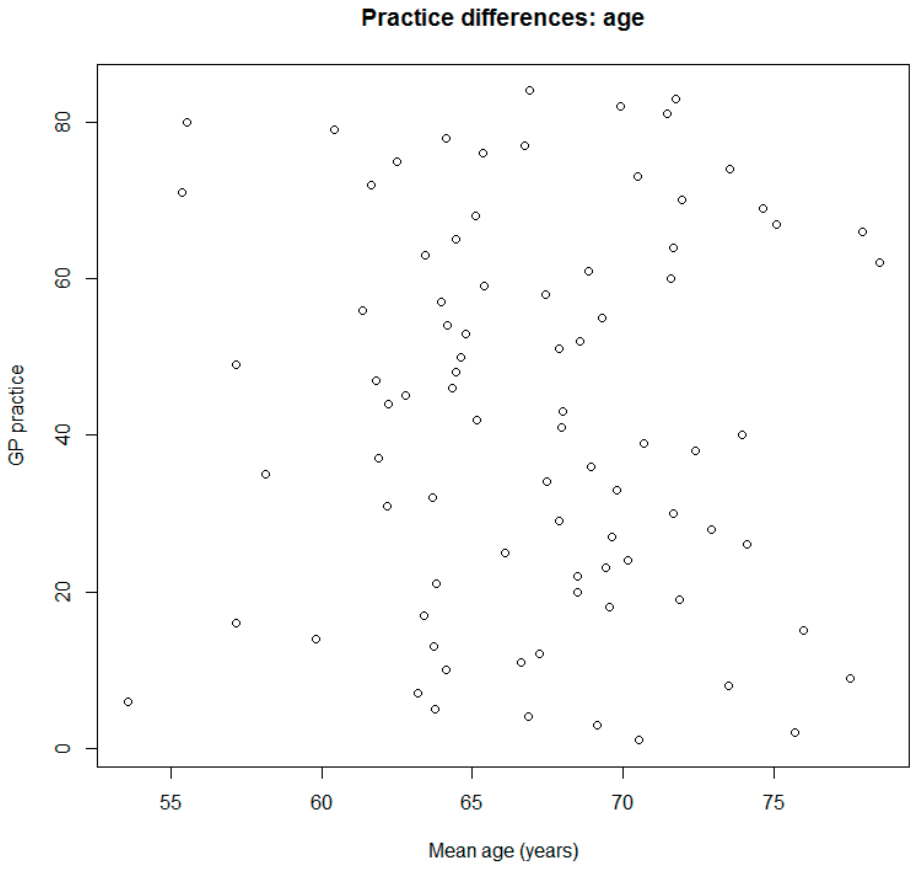


Figure S2: Crude plot of the mean age per GP-practice. Average age per practice is 67.08 (SD 5.30).

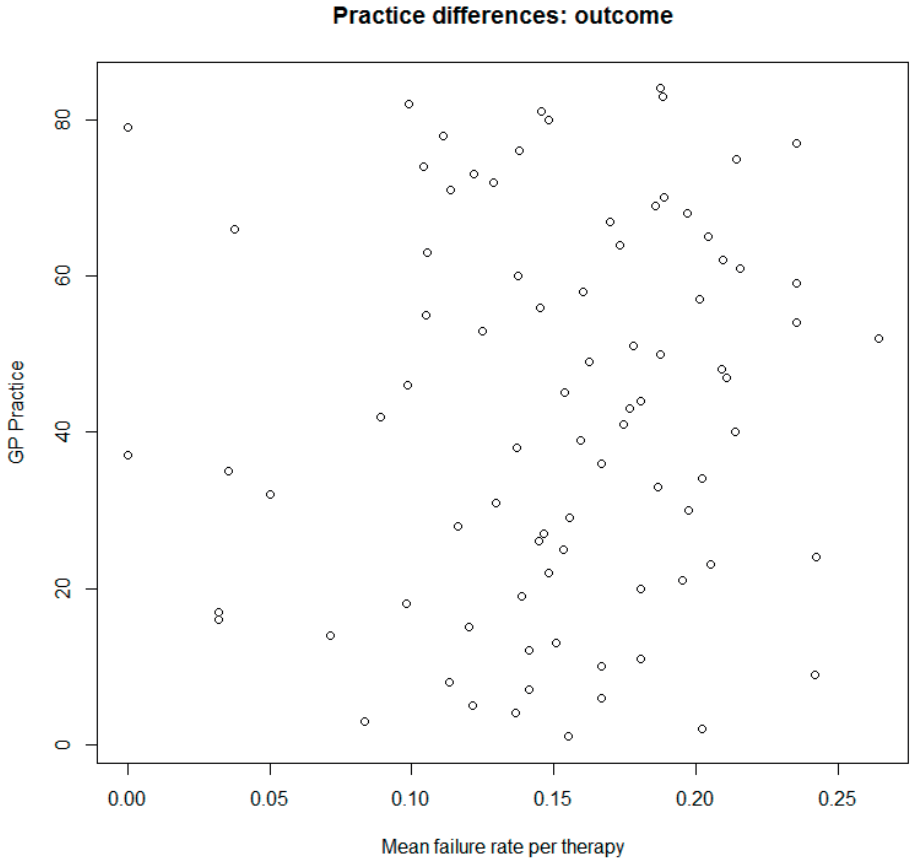


Figure S3: Crude plot of outcome per practice. Mean failure rate is 15.1% (SD 5.58)

5

DIAGNOSTIC ACCURACY OF DIRECT SUSCEPTIBILITY TESTING AND FLEXICULT™ FOR URINARY TRACT INFECTIONS IN LONG-TERM CARE RESIDENTS.

K.D. Hendriks-Spoor, C.H. van Werkhoven, T.J.M. Verheij, P.D. van der Linden, J.W. Dorigo-Zetsma

ABSTRACT

Introduction

Bedside resistance tests might improve appropriate prescribing for urinary tract infections (UTI) in residents of long-term care facilities (LTCF) by decreasing the turnaround time. The accuracy of these tests in this population is still unknown.

Objective

To compare the accuracy of the Flexicult™ (FC) and the Direct susceptibility test (DST) with standard urine culture in recognizing UTI and antibiotic resistance of nitrofurantoin, fosfomycin, trimethoprim and ciprofloxacin.

Methods

Both tests were performed in samples from LTCF residents with suspected UTI. Results were compared to standard urine culture (SC), which was performed using MaldiTOF and VITEK2. Identification of UTI was based on England's Public Health Guideline.

Results

118 urine samples were included. Population consisted of 67% female with median age of 87.5 (IQR 81-91.75) years. Overall antibiotic resistance in SC ranged from 25.0% for fosfomycin to 46.7% for amoxicillin-clavulanic acid. FC generally performed better in identifying UTI (concordance FC 67.8% (95% CI: 59.3% - 76.2%) vs DST 61.9% (95% CI: 53.1% - 70.6%)). Resistance testing was superior in DST (concordance DST 82.4% (95% CI: 76.9% – 87.8%) vs FC 55.6% (95% CI: 48.5% – 62.7%)). In practice, using FC to determine treatment would result into more overtreatment (FC 32.2% vs DST 25.4% of all patients) while fewer patients would be undertreated (FC 11.0% vs DST 21.2% of all patients).

Conclusion

Both FC and DST result in a high rate of misclassifications potentially leading to both over- and undertreatment. Currently, we do not advise using these tests in LTCF residents.

INTRODUCTION

Urinary tract infections (UTI) are the most commonly seen infections in Dutch long-term care facilities (LTCFs) and the treatment of these infections is getting increasingly difficult due to increasing antimicrobial resistance worldwide[1-3]. The Dutch Association of Elderly Care Physicians and Social geriatricians advises evaluating UTI treatment with a urine culture (UC) to collect information on the causative microorganism and its resistance pattern. However, most UTIs in residents of Dutch LTCFs are treated empirically[4]. While an Australian study showed that the number of UCs per 10 000 resident days was 14.39 compared to 18.37 UTI diagnoses per 10 000 resident days[5], a Dutch study found that cultures were ordered in only 8% of the patients who started with empiric antibiotic treatment for UTI[6]. In only a quarter of these patients, in whom the culture results showed resistance to the prescribed antibiotic, therapy was adapted. Shortening the turnaround time of UCs might increase both the use of UCs and the subsequently appropriate prescribing of antibiotics[7].

Several new bedside tests have been developed for urinary cultures which can perform antibiotic susceptibility within 24 hours. The Flexicult™ (FC) and direct susceptibility test (DST) are two tests that could be used on location (figure S1)[8–11]. The FC is a near-patient overnight UC designed by the Statens Serum Institut in Denmark to quantify, identify and test susceptibility of bacteria in the urine. It is extensively used by Danish general practitioners and kits for the UK, Spain and Germany have been developed that differ in the selection of antibiotics for susceptibility testing. A study in general practitioners found an overall agreement of 0.76 (CI 0.71-0.80) compared to UC to identify UTI in the general population[12]. The DST is mostly used in a laboratory setting to test susceptibility of microorganisms directly from urine[13]. One study tested this on location in Dutch nursing homes and found an overall agreement of 89.8% when compared with UC[11]. Both tests could decrease the turnaround time of UCs. While the DST has been tested in a nursing home, the Flexicult™ is not yet tested in LTCFs. Therefore, we studied the diagnostic accuracy of both tests compared to the UC in LTCF-residents.

MATERIALS & METHODS

Study population

The study took place in a microbiology laboratory between June and August of 2020. Study samples were selected from surplus urine samples from routine UC from LTCF-residents with suspected UTI. The samples came from four LTCFs with several locations in the vicinity of the microbiology laboratory. The lab receives about 60 UCs per week from these facilities. Samples are transported refrigerated and processed on the day of collection. The UTI

suspicion was made by the elderly care specialists. Urine samples under 15 ml of volume or samples received on Fridays or during the weekend were excluded for logistical reasons.

Data collection

Data on patient age, gender, UTI-related symptoms as assessed by the elderly care specialist and previous antibiotic use were collected by a short questionnaire added to the standard laboratory form to be filled in by the LTCF personnel.

While the UCs were carried out by the laboratory technicians, the bedside tests were carried out in the laboratory by the researcher (KDH). This researcher had no previous laboratory training but received written and in-practice instructions to mimic application by nursing home personnel. The results of the standard urine culture (SC), FC and DST were registered into an electronic database. For the SC and the FC, identification and quantification of the microorganism and the resistance per microorganism were registered. For the DST test, only quantification and resistance data were collected as the test cannot differentiate between different bacterial species. Testing procedures can be found in table S1.

Outcomes

The primary outcome was defined as the presence or absence of UTI infection with the SC as reference test. Based on Public Health England (PHE) criteria, we interpreted SC and FC with (1) pure growth in $\geq 10^4$ CFU/ml, or (2) mixed growth with one predominant microorganism in $\geq 10^5$ CFU/ml or (3) *E. coli* or *S. saprophyticus* in $\geq 10^3$ CFU/ml as indicative of UTI [14,15]. In the DST, samples were indicative of UTI if there was (1) pure growth $\geq 10^4$ CFU/ml or (2) mixed growth with one predominant microorganism in $\geq 10^5$ CFU/ml. The third criterion was not applicable as the DST cannot differentiate between microorganism species. Samples with more than two species of microorganisms were discarded as contamination and samples without growth or less than 10^3CFU/ml were deemed negative.

The secondary outcome was the presence or absence of resistance against selected antibiotics in samples indicative of UTI. Resistance was based on either growth in the FC in the respective antibiotic-impregnated compartment or based on the diameter of the inhibitory zone in the DST.

Statistical analysis

Using the results of the quantification of colonies, purity of growth and identification of microorganisms, we assessed if samples were indicative of UTI. The diagnostic accuracy of identifying UTI was determined by calculating concordance, sensitivity, specificity, positive predicting value (PPV), and negative predicting value (NPV). The samples indicative of UTI were selected to compare resistance. Due to the limits of the DST to differentiate

between different microorganisms, resistance for all three diagnostic tests was determined per culture (1 or 2 microorganisms) instead of per microorganism. Resistance to at least one microorganism was considered as overall resistance, in line with selection of the appropriate antibiotic to treat the UTI.

We compared the theoretical treatment recommendation following DST and FC with that from SC. For this, we ranked patients according to the different tests as 1) no UTI (no treatment needed), or treatment indicated with 2) nitrofurantoin, 3) fosfomycin, 4) trimethoprim, 5) ciprofloxacin, or 6) requirement of additional susceptibility testing. The order of antibiotics was chosen according to the Dutch College of General Practitioners (NHG) guideline[16]. Patients with a lower rank in the DST or FC compared to SC were classified as undertreatment and thus a very major error (VME) while those with a higher rank compared to SC were classified as overtreatment and thus a major error (ME)[17,18]. The VME rate was calculated by the number of patients with undertreatment / total number of patients * 100% with an acceptable threshold as defined by the FDA of 1.5%[18]. Similarly, the ME rate was calculated by the number of patients with overtreatment / total number of patients * 100%. An acceptable major error rate as set by the FDA is 3%.

R software version 4.0.3 was used for data analysis.

Ethics

The research ethics board of the University Medical Centre Utrecht, the Netherlands declared that this study was not subject to the Medical Research Involving Human Subjects Act. Informed consent was not obtained based on the 'Code of conduct for health research'.

RESULTS

118 urine samples from 110 unique patients were collected between 19 June and 19 August 2020. 79 (67%) patients were female and the median age was 87.5 years (IQR 81-91.75). The most common complaint mentioned in 13 patients (11.0%) was dysuria.

The SC identified 86 (72.8%) samples with growth, 5 (4.2%) negative cultures and 27 (22.9%) contaminated cultures. Only 26 (22.0%) of the SC were a monoculture and 60 samples (50.8%) contained mixed growth. Of the cultures with growth, 60 cultures were considered indicative of UTI (Figure 1).

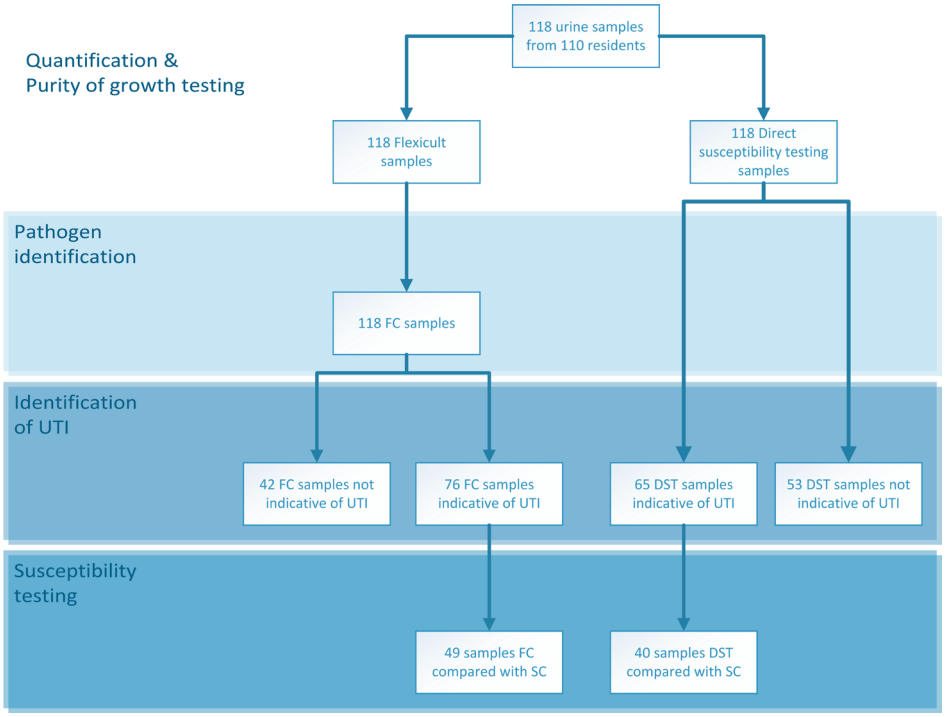


Figure 1: Flowchart of the urine samples in the Standard Culture (SC), Flexicult™ (FC) and Direct Susceptibility Test (DST). Samples indicative of UTI were selected to assess susceptibility. Additional, FC samples identified as mixed growth or pure samples were selected to calculate the diagnostic accuracy of microorganism identification by the Flexicult™.

Table 1: Predictive values for identifying cultures indicative of a UTI by the Flexicult™ and Direct Susceptibility test compared to standard cultures.

	Standard	Flexicult	DST
PHE positive (%)	60 (50.8%)	76 (64.4%)	65 (55.1%)
Concordance PHE positivity % (95% CI)	[ref]	67.8% (59.3 – 76.2)	61.9% (53.1 – 70.6)
Sensitivity % (95% CI)	[ref]	81.7% (70.1 – 89.4)	66.7% (54.1 – 77.3)
Specificity % (95% CI)	[ref]	53.4% (40.8 – 65.7)	56.9% (44.1 – 68.8)
Positive predictive value % (95% CI)	[ref]	64.5% (53.3 – 74.3)	61.5% (49.4 – 72.4)
Negative predictive value % (95% CI)	[ref]	73.8% (58.9 – 84.7)	62.3% (48.8 – 74.1)

** The 2x2 cross tables are provided in table S7. CI: confidence interval. DST: Direct susceptibility test. PHE: Public Health England criteria.*

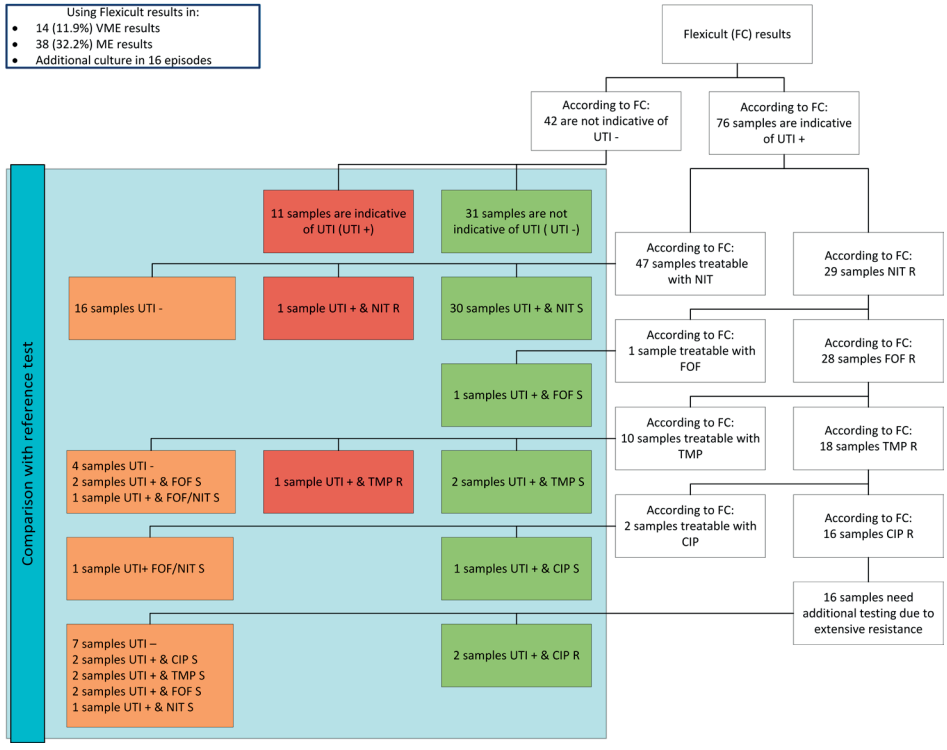
The diagnostic performance of the FC and DST on purity of growth, quantification of colonies, and identification of microorganisms can be found in tables S4–S6. The FC generally performed better than the DST in identifying cultures indicative of UTI (Table 1 & S7).

From the 60 samples considered indicative of UTI according to SC, a total of 76 microorganisms were tested for resistance. The overall resistance rate per culture was 25.0% for fosfomycin, 30.0% for ciprofloxacin and nitrofurantoin, 40.0% for trimethoprim, and 46.7%

Table 2: Predictive value for overall resistance in urine cultures indicative of UTI. N= total number of samples available for comparison, n= number of samples tested for a specific antibiotic, TR= true resistant, FS= false susceptible, TS= true susceptible, FR= false resistant.

		n	TR	FS	TS	FR	Concordance (95%CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Flexicult N = 49	Ciprofloxacin	47	10	1	16	20	55.3% (41.1-70.0)	90.9% (62.3-98.4)	44.4% (29.5-60.4)	33.3% (19.2-51.2)	94.1% (73.0-99.0)
	Fosfomycine	46	12	0	5	29	37.0% (23.0-50.9)	29.3% (16.1-45.5)	100% (47.8-100)	100% (47.8-100)	14.7% (12.4-17.4)
	Trimethoprim	46	10	4	18	14	60.9% (46.8-75.0)	71.4% (45.4-88.3)	56.2% (39.3-71.8)	41.7% (24.5-61.2)	81.8% (61.5-92.7)
	Nitrofurantoin	48	13	1	30	4	89.6% (80.9-98.2)	92.9% (68.5-98.7)	88.2% (73.4-95.3)	76.5% (52.7-90.4)	96.8% (83.8-99.4)
Direct Susceptiblity testing N = 40	Ciprofloxacin	36	5	5	21	5	72.2% (57.6 -86.9)	50.0% (23.7-76.3)	80.8% (62.1-91.5)	50.0% (23.7-76.3)	80.8% (62.1-91.5)
	Fosfomycin	38	8	1	22	7	79.0% (66.0-91.9)	88.9% (56.5-98.0)	75.9% (57.9-87.8)	53.3% (30.1-75.2)	95.7% (79.0-99.2)
	Trimethoprim	36	13	1	19	3	88.9% (78.6 – 99.2)	92.9% (68.5-98.7)	86.4% (66.7-95.3)	81.2% (57.0-93.4)	95.0% (76.4-99.1)
	Nitrofurantoin	40	8	3	28	1	90.0% (80.7-99.3)	72.7% (43.4–90.3)	96.6% (82.8-99.4)	88.9% (56.6-98.0)	90.3% (75.1-96.7)
	Amoxicillin-clavulanic acid	37	15	2	15	5	81.1% (68.5-93.7)	88.2% (65.7-96.7)	75.0% (53.1-88.8)	75.0% (53.1-88.8)	88.2% (65.7-96.7)

Figure 2: Flow chart of the treatment based on the performance of the Flexicult™ (A) and direct susceptibility test (B) versus the performance of the standard culture in urine cultures indicative of UTI. NIT: nitrofurantoin, FOF: fosfomycin, TMP: trimethoprim, CIP: ciprofloxacin, VME: very major error, ME: major error.

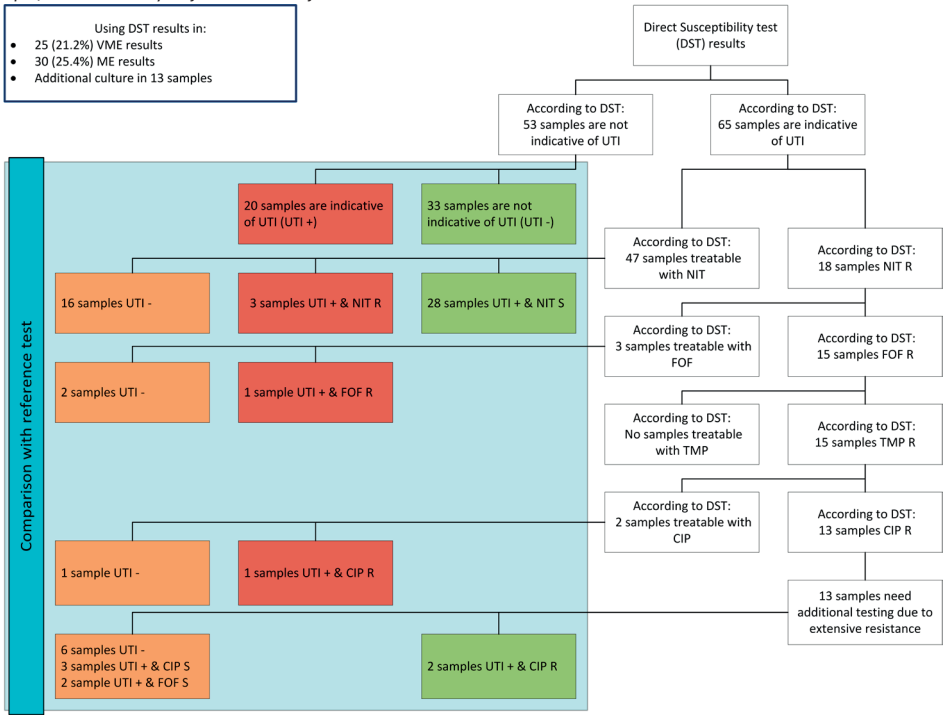


A: Flexicult™

for amoxicillin-clavulanic acid. For FC 49 of 118 samples were available and in the DST 40 of 118 samples (Table 2). According to FC, resistance rate was 36.7% for nitrofurantoin, 53.1% for trimethoprim, 55.1% for pivmecillinam, 65.3% for ciprofloxacin and 81.6% for fosfomycin. According to DST, resistance rate was 22.5% for nitrofurantoin, 27,5% for ciprofloxacin, 42.5% for fosfomycin, 45.0% for trimethoprim, and 57.5% for amoxicillin-clavulanic acid. The overall resistance was higher in the Flexicult™ than in the DST and the SC. Both tests performed generally well in correctly identifying nitrofurantoin- and trimethoprim resistance (Table 2). Both tests showed relatively large discordance with the SC for fosfomycin and ciprofloxacin resistance.

To illustrate how the FC and DST would perform in practice, we compared the treatments based on the results of the bedside tests with that of the reference test, using the Dutch guideline to determine the preferred treatment. Assuming that cultures were only performed in patients with suspected UTI and that all patients were eligible for empirical treatment awaiting culture results, FC would have resulted in 26% withheld or early stopped prescrip-

Figure 2: Flow chart of the treatment based on the performance of the Flexicult™ (A) and direct susceptibility test (B) versus the performance of the standard culture in urine cultures indicative of UTI. NIT: nitrofurantoin, FOF: fosfomycin, TMP: trimethoprim, CIP: ciprofloxacin, VME: very major error, ME: major error.



B: Direct susceptibility test

tions due to correct classification of no UTI but would have led to more overtreatment (ME) than DST. The DST would have resulted in 28% withheld or early stopped prescriptions but would have resulted in more undertreatment (VME) than FC (Figure 2).

DISCUSSION

In our study, both the FC and DST could not identify samples indicative of UTI with high accuracy. Both tests used as stand-alone tests would lead to 26-28% correctly withheld or early stopped prescriptions within 24 hours of the UTI diagnosis. However, the FC would additionally result in the undertreatment of 1 in 10 UTI episodes, while the DST would result in undertreatment in 1 in 6 episodes. While both tests can prevent overtreatment of UTI, which might have a positive effect on antibiotic resistance, it is important to consider whether the associated rate of undertreatment is acceptable[19].

We encounter several problems. The accuracy of identifying samples indicative of UTI was an expected problem in the DST as it cannot differentiate between microorganisms, but the accuracy of the FC was also low. The FC had trouble distinguishing mixed growth and *Enterococcus* spp, which might be caused by the average higher CFU/ml in the FC compared to SC. Higher CFU/ml hinders identifying a predominant microorganism in mixed growth samples and might lead the sample to be misidentified as contamination. The resistance rates showed large discrepancies, especially in fosfomycin resistance. This could partly be explained by the high number of mixed growth samples, which complicates the correct interpretation of the test. Additionally, performance of fosfomycin susceptibility testing using agar dilution methods is difficult, especially in *Enterococcus* spp., which were highly prevalent in our samples[20]. To improve the accuracy of the tests patients with urinary catheters could be excluded as this will probably reduce the number of mixed growth samples.

The strength of the tests is that both can be interpreted within 24 hours, which reduces the turnaround time significantly. Although both tests are easy to perform, the FC is easier to interpret. The downside of the FC is that material costs are higher (~12.50 euro versus ~1.00 euro material costs; personnel costs not included). Second, the FC has a limited shelf-life of 6 weeks, which can be problematic in case of limited use in LTCF sites. The DST can easily be made in small numbers with readily available products in a microbiology lab. Additionally, it can easily be adjusted to the local resistance patterns by changing the antibiotic disks. The downside of the DST is that it can be difficult to interpret the inhibitory zone, especially in mixed growth samples which might make it unreliable to be used by clinicians with less laboratory experience.

Other studies on FC and the DST found a higher accuracy of the tests, but these studies have been performed in a different population. Only one study has been performed on long-term-care residents. In a Dutch study of 49 samples from an LTCF, consisting of 73.5% pure cultures and 26.5% of mixed growth, DST had a concordance of the susceptibility of 89.8% with a VME rate of 0.9% and a ME rate of 9.4%[11]. While the population was comparable to our study, the percentage of mixed growth samples in this study was much lower. Another study on DST of 321 urine samples with *Enterobacteriaceae* from a tertiary hospital found an agreement rate of 97.9% with few VMEs (0.3%) and MEs (0.3%). They only included monomicrobial samples with leukocyturia >5x10^4/ml and gram-negative bacteria on microscopic examination, which lead to exclusion of almost 25% of the samples[21]. When using similar criteria in our study, this would lead to the exclusion of at least 50% of the samples. A study found that interpretation of the Flexicult™ by primary care physicians resulted in an overestimation of positive tests in women with uncomplicated UTI of 69.9% in the FC vs 47.4% in the SC, similarly to our study[22,23]. Unlike our study, this study found a high percentage of *E. coli* in the cultures of 75.8% with an average higher test accuracy for resistance measurement. The difference in

test accuracy might be related to the smaller proportion of mixed growth cultures and a high percentage of *E. coli*.

In our study, we compared the bedside resistance tests to the SC. To our best knowledge, there are no other head-to-head comparisons of FC, DST and SC available. While SC is often used as the reference standard, a positive UC only implies the presence of bacteria. Differentiation between UTI and asymptomatic bacteriuria is challenging, especially in LTCF-residents as asymptomatic bacteriuria can be as high as 50%[24,25].We instructed the elderly care physicians to only perform cultures in patients with UTI-related complaints, but we cannot exclude the possibility that asymptomatic bacteriuria samples were included and classified as UTI according to our reference test and/or bedside resistance tests. While we realise that the UC is not an optimal diagnostic test for UTI in older adults, it is recognised as the most reliable diagnostic test to gather information on causative microorganisms and resistance to UTI.

All FC and DST tests were performed and interpreted by the first author, who had no prior laboratory training, to best reflect testing by inexperienced personnel. Though we could not take into account the impact of testing in LTCF and possible inter-observer variability, these aspects are expected to further reduce test accuracy.

Additional studies are necessary to determine how the accuracy of the tests can be improved. To improve the high CFU/ml in the studied tests, a shorter incubation might be beneficial. Also introducing standardizing the turbidity of the samples, as performed in standard anti-microbial susceptibility testing, could lead to a more standardized quantification of CFU/ml and resistance[26].

In conclusion, while FC and DST can reduce the turnaround time, the use of these tests is likely to lead to a high rate of inappropriate treatment. Therefore, we do not advise the use of these diagnostic tests in LTCF. Studies on how to improve the accuracy of the tests in the LTCF population are warranted.

ACKNOWLEDGEMENTS

This work was supported by a research grant from the Tergooi MC

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SUPPLEMENTARY MATERIAL

Table S1: Testing procedures per test method.

Testing procedures	Standard culture (SC)	Flexicult (FC)	Direct susceptibility testing (DC)
Plating urine	Automatically plated by use of WASP (COPAN, Murrieta, U.S.) on - Sheep blood agar - McConkey - UTI specific chromoagar plate (all from Becton & Dickinson, Franklin Lakes, U.S.).	Vortexed and undiluted urine was distributed on the plate with a pipette. Excess urine was removed from the plate by pouring the excess liquid off.	Plating by streaking cotton swab dipped into a vortexed and undiluted urine specimen. Excess fluid was expressed before streaking for confluent growth onto a standard Mueller-Hinton agar plate (Becton & Dickinson, Franklin Lakes, U.S.). After streaking, commercial antibiotic disks (Thermofischer Oxoid, Waltham, U.S.) were distributed onto the agar surface using forceps.
Incubation	Plates were incubated for 18-24 h at 37 degrees Celsius before identifying bacteria.	After a 15 minute rest period, plates were incubated at 37 degrees Celsius for 16-24h.	The DST plates were incubated for 16-24 h at 37 degrees Celsius.
Identifying bacteria	Using the Malditof (Bruker, Billerica, U.S.) according to the manufacturer's instructions.	Plates were then read in accordance with the manufacturer's instructions (Table S2).	Results were interpreted as found in table S2.
Susceptibility testing and interpretation	According to VITEK 2 (Biomerieux, Marcy-l'Étoile, France). If there was 10^4 – 10^5 CFU/ml growth of a single microorganism or >10^5 CFU/ml from maximal 3 microorganisms based on the McConkey plate susceptibility testing was performed. Susceptibility interpretation was based on the criteria from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (27).	Susceptibility testing was performed for ciprofloxacin, fosfomycin, nitrofurantoin, pivmecillinam and trimethoprim. Plates were then read in accordance with the manufacturer's instructions (Table S2).	Susceptibility testing was performed by measuring inhibitory zones of the antibiotic disks of nitrofurantoin, trimethoprim, fosfomycin, ciprofloxacin and amoxicillin-clavulanic acid. Susceptibility interpretation was based on the criteria from the European Committee on Antimicrobial Susceptibility Testing ((EUCAST)[27].

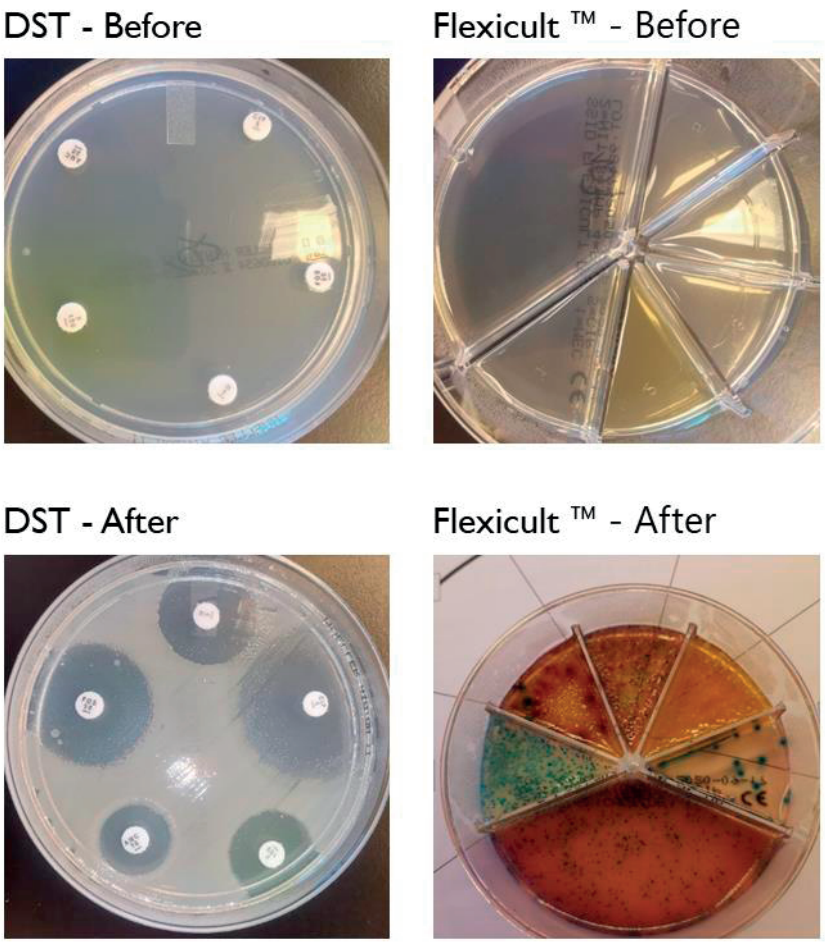

Figure S1: the Direct Susceptibility test (left) and the Flexicult™ (right) before and after culturing.

Table S2: Interpretation of Flexicult™ and Direct susceptibility testing results compared to standard culture

	Standard Culture	Flexicult™	Direct susceptibility testing	
Quantification of colonies	≤10^3 CFU/ml	<15 colonies	<15 colonies	
	10^4 - 10^5 CFU/ml	≥15 colonies	≥15 colonies	
	≥10^5 CFU/ml	(Semi-) confluent growth	(Semi-) confluent growth	
Purity of growth	no growth	No growth	No growth	
	pure growth	1 microorganism	1 microorganism	
	mixed growth	<3 microorganisms (with or without a predominant microorganism)	<3 microorganisms (with or without a predominant microorganism)	
	contamination	≥3 microorganisms	≥3 microorganisms	
Resistance microorganism	S	No or less growth in antibiotic compartment compared to identification compartment	Amoxi-clav[1]	≥16mm
			Ciprofloxacin	≥25mm
			Fosfomycin	≥24mm
			Nitrofurantoin	≥11mm
			Trimethoprim	≥15mm
	I	Na[2]	Amoxi-clav[1]	Na[2]
			Ciprofloxacin	22-24mm
			Fosfomycin	Na[2]
			Nitrofurantoin	Na[2]
			Trimethoprim	Na[2]
	R	Growth similar to identification compartment	Amoxi-clav[1]	<16mm
			Ciprofloxacin	<22mm
			Fosfomycin	<24mm
			Nitrofurantoin	<11mm
			Trimethoprim	<15mm
Identification bacteria	*E. coli*	Large red colonies	Na[2]	
	Klebsiella sp.	Large, fatty, dark blue/purple		
	Enterobacter sp	Large, dark blue/purple		
	Proteus sp.	Large, light brown with brown discolouration agar		
	P. vulgaris	Large (swarm), green/brown with brown discolouration agar		
	P. aeruginosa	Large, grey-white/green with green discolouration agar		
	E. fecalis	Small, green / greenish blue		
	E. faecium	Small, greenish/grey colonies		
	S. saprophyticus	Small, white/reddish colonies		
	Candida sp.	Large/minor white colonies		

[1] Amoxicillin-clavulanic acid
[2] Not applicable

Table S3A: Cross-tabulation of interpretation of Flexicult™ and DST versus standard culture in respect of purity of growth, divided into 4 categories: no growth, mixed growth with or without predominant microorganism and pure growth.

Tested samples n=118		Standard Culture				
		No growth	Mixed (n=2)	Contamination (n>2)	Pure growth	Total
Flexicult	No growth	3	2	3	0	8
	Mixed growth (n=2)	2	37	11	13	63
	Contamination (n>2)	0	13	10	1	24
	Pure growth	0	8	3	12	23
DST	No growth	5	3	9	1	18
	Mixed growth (n=2)	0	15	6	6	27
	Contamination(n>2)	0	8	3	0	11
	Pure growth	0	34	9	19	62

Table S3B:The predictive values of identification of pure growth and mixed growth in the Flexicult™.

	Standard	Flexicult	DST
% pure growth	22.0%	19.3%	52.5%
Concordance % (95% CI)		79.7% (72.3 – 86.9)	46.6 (37.6 – 55.6)
Sensitivity % (95% CI)		46.2% (28.8 – 64.5)	95.0% (76.4 – 99.1)
Specificity % (95% CI)		89.1% (81.1 – 94.0)	36.7% (27.9 – 46.6)
Positive predictive value % (95% CI)		54.5% (34.7 – 73.1)	23.5% (15.6 – 33.8)
Negative predictive value % (95% CI)		85.4% (77.0 – 91.1)	97.3% (86.2 – 99.5)
% mixed growth (> 1 microorganism)	73.7%	73.7%	32.2%
Concordance % (95% CI)		73.7% (65.8 – 81.7)	48.3% (39.3 – 57.3)
Sensitivity % (95% CI)		82.6% (73.2 – 89.1)	36.8% (27.4 – 47.3)
Specificity % (95% CI)		50.0% (33.6 – 66.4)	80.6% (63.7 – 90.8)
Positive predictive value % (95% CI)		81.6% (72.2 – 88.4)	84.2% (69.6 – 92.6)
Negative predictive value % (95% CI)		51.6% (34.8 – 68.0)	31.2% (22.2 – 42.1)
% negative[1]	4.2%	6.8%	15.3%
Concordance		91.5%	89.0% (83.3 – 94.6)
Sensitivity % (95% CI)		37.5% (13.7 – 96.4)	100% (56.6 – 100.0)
Specificity % (95% CI)		95.5% (89.8 - 98.0)	88.5% (81.3 – 93.2)
Positive predictive value % (95% CI)		37.5% (13.7 – 69.4)	27.8% (12.5 – 50.9)
Negative predictive value % (95% CI)		95.5% (89.8 – 98.0)	100% (96.3 - 100.0)
Overall concordance		76.3% (68.6 – 83.9)	65.0% (60.1 – 70.0)
Overall sensitivity % (95% CI)		53.9% (44.8 – 62.7)	31.3% (24.1 – 39.6)
Overall specificity % (95% CI)		83.5% (79.3 – 87.0)	78.4% (73.7 – 82.5)
Overall positive predictive value % (95% CI)		51.2% (42.4 – 60.0)	36.5% (28.3 – 45.6)
Overall negative predictive value % (95% CI)		84.9% (80.8 – 88.3)	74.2% (69.5 – 78.5)

Table S4A: Cross-tabulation of interpretation of the Flexicult™ and DST versus laboratory culture in respect of quantification of growth, divided into three groups: ≤10^3, 10^4-10^5 and >10^5 CFU/ml growth per culture.

		Laboratory			
		≤10^3	10^4 – 10^5	>10^5	Total
Flexicult	≤10^3	6	4	8	18
	10^4 -10^5	8	12	15	35
	>10^5	3	20	80	103
	Total	17	36	103	156
DST	≤10^3	6	13	3	22
	10^4 – 10^5	0	2	7	9
	>10^5	0	17	85	102
	Total	6	32	95	133

Table S4B: Predictive values of interpretation of the Flexicult™ and DST versus laboratory culture in respect of quantification of growth, divided into three groups: ≤10^3, 10^4-10^5 and >10^5 CFU/ml growth per culture.

	Standard	Flexicult	DST
%≤10^3 CFU/ml	10.6%	15.9%	17.2%
Concordance % (95% CI)		85.3% (79.7 – 90.8)	88.0% (82.4 – 93.5)
Sensitivity % (95% CI)		35.3% (17.3 – 58.7)	100% (61.0 – 100)
Specificity % (95% CI)		91.4% (85.5 – 95.0)	87.4% (80.5 – 92.1)
Positive predictive value % (95% CI)		33.3% (16.3 – 56.3)	27.3% (13.2 – 48.2)
Negative predictive value % (95% CI)		92.0% (86.3 – 95.5)	100% (96.7 – 100)
10^4 – 10^5 CFU/ml	21.8%	26.4%	6.2%
Concordance % (95% CI)		69.9% (62.7 – 77.1)	72.2% (64.6 – 79.8)
Sensitivity % (95% CI)		33.3% (20.2 – 49.7)	6.2% (1.7 – 20.1)
Specificity % (95% CI)		80.8% (72.9 – 86.9)	93.1% (86.4 – 96.6)
Positive predictive value % (95% CI)		34.3% (20.8 – 50.8)	22.2% (6.3 – 54.7)
Negative predictive value % (95% CI)		80.2% (72.2 – 86.3)	75.8% (67.6 – 82.5)
>10^5 CFU/ml	67.6%	57.7%	76.6%
Concordance		70.5% (63.4 – 77.7%)	80.5% (73.7 – 87.2)
Sensitivity % (95% CI)		77.7% (68.7 – 84.6)	89.5% (81.7 – 94.2)
Specificity % (95% CI)		56.6% (43.3 – 69.0)	55.3% (39.7 – 69.9)
Positive predictive value % (95% CI)		77.7% (68.7 – 84.6)	83.3% (74.9 – 89.3)
Negative predictive value % (95% CI)		56.6% (43.3 – 69.0)	67.7% (50.1 – 81.4)
Overall concordance		75.2% (68.4 – 82.0)	80.0% (74.9 – 85.0)
Overall sensitivity % (95% CI)		62.8% (55.0 – 70.0)	59.6% (51.8 – 67.0)
Overall specificity % (95% CI)		81.4% (76.7 – 85.3)	93.0% (89.1 – 95.6)
Overall positive predictive value % (95% CI)		62.8% (55.0 – 70.0)	84.5% (76.6 – 90.1)
Overall negative predictive value % (95% CI)		81.4% (76.7 – 85.3)	78.2% (73.1 – 82.6)

Table S5: Table of the microorganisms identified in the standard cultures and the Flexicult™. The DST results are not included as this test cannot identify species, only resistance.

Microorganisms	Standard		Flexicult	
	Absolute	Percentage	Absolute	Percentage
E coli	44	30%	41	27%
Mixed growth	30	20%	14	9%
Enterococcus sp	14	10%	41	28%
E fecalis	13	9%	11	7%
E. faecium	1	1%	31	21%
Proteus mirabilis	10	7%	13	9%
Klebsiella sp	10	7%	5	.83%
K. pneumoniae	7	5%	-[1]	-[1]
K. Oxytoca	2	1%	-[1]	-[1]
Klebsiella spp	1	1%	-[1]	-[1]
Staphylococcus sp	8	5%	7	5%
S aureus	5	3%	-[1]	-[1]
S. saphrophyticus	0	0%	7	5%
Staphylococcus sp	3	2%	-[1]	-[1]
P. aeruginosa	7	5%	7	5%
Enterobacter	3	2%	8	5%
E. aerogenes	2	1%	-[1]	-[1]
E. cloaca	1	1%	-[1]	-[1]
Candida sp	2	1%	5	3%
Unknown	Na[2]	Na[2]	10	7%
A. Urinae	8	5%	-[1]	-[1]
Oligella urethralis	1	1%	-[1]	-[1]
Streptococcus sp	3	2%	-[1]	-[1]
A. schaalli	1	1%	-[1]	-[1]
A. sanguinicola	2	1%	-[1]	-[1]
Corynebacterium sp	2	1%	-[1]	-[1]
C. koseri	2	1%	-[1]	-[1]
C. freundii	1	1%	-[1]	-[1]
Lactobacillus sp	1	1%	-[1]	-[1]
Total number	148	100%	151	100%

1 The Flexicult™ cannot differentiate or identify these species of bacteria.

2 The standard cultures were able to identify all species of bacteria.

Table S6A: Cross-tabulation of the interpretation of the Flexicult™ versus laboratory culture in respect of the identification of the microorganism.

Flexicult Identified microorganisms													
No growth	Unknown	Staphylococcus	Pseudomonas	Proteus	Mixed growth	Klebsiella	Enterobacter	E. fecalis	E. faecium	E. coli	Candida		
(n=38)	(n=9)	(n=7)	(n=7)	(n=13)	(n=14)	(n=5)	(n=8)	(n=10)	(n=31)	(n=21)	(n=5)		
0	0	0	0	0	1	0	0	0	0	0	1	(n=2)	Candida
9	0	0	0	0	0	0	1	0	2	32	0	(n=44)	E. coli
0	0	0	0	0	0	0	0	0	1	0	0	(n=1)	E. faecium
3	0	0	0	0	0	0	0	3	7	0	0	(n=13)	E. fecalis
0	0	0	0	0	0	0	2	0	0	1	0	(n=3)	Enterobacter
4	0	0	0	0	0	4	1	0	1	0	0	(n=10)	Klebsiella
9	1	1	1	1	4	0	2	2	8	1	0	(n=29)	Mixed growth
2	0	0	0	7	1	0	0	0	0	0	0	(n=10)	Proteus
0	0	0	6	1	0	0	0	0	0	0	0	(n=7)	Pseudomonas
3	2	1	0	1	1	0	0	0	0	0	0	(n=8)	Staphylococcus
8	4	0	0	1	0	1	1	2	2	2	0	(n=21)	Unknown
0	2	5	0	2	7	0	1	3	10	5	4	(n=39)	No growth

Laboratory identified microorganisms

Table S6B: Predictive value of identification of most common UTI related microorganisms by Flexicult™ as compared to the standard urine culture.

Microorganism	Concordance (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
E. coli	88.8	72.7	93.8	78.0	91.8
	(83.8 – 93.9)	(58.2 – 83.7)	(83.8 – 93.9)	(63.3 – 88.0)	(86.3 – 95.3)
Proteus sp	95.2	70.0	96.6	53.8	98.3
	(91.8 – 98.6)	(39.7 – 89.2)	(92.8 – 98.4)	(29.1 – 76.8)	(95.1 – 99.4)
Enterococcus sp	82.4	78.6	83.2	27.5	98.0
	(76.3 – 88.6)	(52.4 – 92.4)	(77.0 – 88.1)	(16.1 – 42.8)	(94.2 – 99.3)
Klebsiella sp	96.3	40.0	99.4	80	96.7
	(93.6 – 99.0)	(16.8 – 68.7)	(96.9 – 99.9)	(37.6 – 96.4)	(93.0 – 98.5)
P. aeruginosa	98.6	85.7	99.4	85.7	99.4
	(97.5 – 99.9)	(48.7 – 97.4)	(96.9 – 99.9)	(48.7 – 97.4)	(96.9 – 99.9)
Mixed growth	80.9	13.3	93.7	28.6	85.1
	(75.2 – 86.5)	(5.3- 29.7)	(88.7 – 96.5)	(11.7 – 54.6)	(79.0 – 89.6)
Overall	86.5	60.1	94.4	58.9	94.9
	(80.2 – 92.7)	(53.0 – 67.1)	(91.0 – 97.7)	(52.0 – 65.9)	(91.7 – 98.0)

Table S7: Cross-tabulation of interpretation of Flexicult™ and DST versus laboratory culture in respect of UTI indicative of UTI as based on England's Public Health guideline, including on the bottom of the table a list of discrepancies.

		Laboratory		
		PHE +	PHE -	Total
Flexicult	PHE +	46	30	76
	PHE -	10	32	42
DST	PHE+	40	25	65
	PHE -	20	33	53

6

GENERAL DISCUSSION

GENERAL DISCUSSION

As explained in the introduction, overuse of antibiotics is an important problem, in hospital care, but also in long-term care and primary care. In this thesis, we focused on issues related to diagnosis and antibiotic treatment of urinary tract infections in two high-risk groups, frail older adults and patients with diabetes mellitus. On the one hand, these two groups of patients have a higher risk for complications from urinary tract infections. Therefore, appropriate and timely antibiotic treatment is pivotal when an infection is diagnosed. Yet, overtreatment in these high-risk patients may be harmful, because of side effects and the development of antimicrobial resistance.

PART 1: ANTIBIOTIC STEWARDSHIP INTERVENTIONS IN LONG-TERM CARE FACILITIES

In the Antibiotic Stewardship Targeting Urinary Tract Infection in Dutch long-term care facilities (ASUTID) trial, we introduced antibiotic stewardship (ABS) in three local long-term care organisations. The trial aimed to promote guideline compliance and reduce days of therapy using active and passive education, including i.e. audit & feedback. The intervention did not result in a decrease in days of therapy or a decrease in overtreatment. Yet, it did result in a decrease in the number of prescriptions for antibiotics commonly prescribed for UTIs. Also, nonspecific complaints like suspected delirium and a general feeling of discomfort that were associated with overtreatment in the control period occurred less frequently in the intervention period.

Reflection on findings

Inappropriate antibiotic treatment for UTIs remains a problem due to the difficulties in recognizing signs and symptoms of UTI in older adults and the lack of a reliable diagnostic test. In the ASUTID trial, we evaluated the effects of introducing an antibiotic stewardship intervention based on the guideline of the Dutch association of Elderly Care Physicians (Verenso) on the frequency of inappropriate antibiotic prescriptions for presumed UTI. We encountered a lack of agreement in regard to the national guidelines. During the educational meeting, we learned that there was no consensus among elderly care physicians about the choice and duration of antibiotic treatment for UTI. The two most used guidelines concerning UTI in long-term care facilities are the Verenso guideline and the Dutch College of General Practitioners (NHG) guideline, as both elderly care physicians and general practitioners treat residents residing in LTCFs. Physicians tend to treat cystitis in residents with either five days or seven days of nitrofurantoin as both durations are supported by Dutch guidelines. The Verenso guideline recommends five days nitrofurantoin in cystitis, whereas the Dutch Gen-

eral Practitioners (NHG) guideline recommends seven days in patients other than healthy women[1,2]. Another difference is that the NHG guideline also recommends seven days of ciprofloxacin in women with complicated UTIs, whereas the Verenso guideline recommends 10 days in older women with complicated UTIs[1-3]. Most of the recommended durations of antibiotic treatment in these (and other) guidelines are based on expert opinion rather than randomized controlled trials in older adults.

The lack of agreement between national and international guidelines on antibiotic treatment of residents with cystitis can lead to confusion on what is the correct advice and then indirectly to inappropriate antibiotic use. A single national guideline with comparable advice on antibiotic treatment should be helpful, especially when it also correlates with international guidelines. Randomized controlled studies on the subject of antibiotic duration for UTI, especially in risk groups like older adults or subjects with diabetes mellitus could be very helpful. Yet, currently, such studies are lacking in older adults. Instead of relying solely on expert opinion, we can use observational data with novel statistical analyses to gather higher-quality evidence-based advice. An example of this can be found in Chapter 4 of this thesis.

In the previous Verenso guideline on UTI, there was no distinction between non-specific symptoms of UTI[4]. This resulted in a recommendation to start antibiotics in a resident, who was not ill, had no specific symptoms of UTI, but had nitrite and leukocyte esterase detected in urine. The update of the Verenso guideline in 2018 resulted in a considerable change for physicians[1,5]. Currently, antibiotic treatment is recommended only for those with specific complaints. This resulted in more guidance for elderly care specialists on starting antibiotics, yet also resulted in diagnostic uncertainty for residents with communication problems e.g. due to dementia or CVA. Complaints of dysuria and frequency are difficult to recognise in residents with dementia and urine incontinence. In these residents, the diagnosis of UTI is often based on nonspecific symptoms and leukocyte esterase and nitrite tests. Elderly care physicians expressed worry about missing specific signs and symptoms, especially as the current guideline correctly decreases the importance of a positive dipstick and focussed on the presence of a negative dipstick to rule out UTI. As these residents are considered the most fragile of their population, the perceived risk of a missed UTI was high. This might have resulted in the deviation from the guideline by physicians to start guideline non-compliant antibiotics.

The most helpful addition to diagnosing UTI in older adults would be a diagnostic test with high specificity and sensitivity. Nitrite, leukocyte esterase, CRP, pro-calcitonin and many more biomarkers have been tested, but none seem reliable enough to accurately diagnose UTI[6-9]. So, as there are no reliable diagnostic tests, it might be advantageous to add additional guidance on this specific subgroup of patients. While these residents might not communicate

symptoms, structural observations of vital signs and signs of pain or discomfort throughout the day by nursing personnel might be helpful in recognizing 'true' UTIs.

Nursing personnel has an important role in the care of residents and the recognition of signs and symptoms related to UTI, but also the decision to perform diagnostic tests, e.g. dipstick test[10]. We tried to target this by offering educational meetings for nursing personnel and pocket cards with instructions on when to use the dipsticks and cultures. Sadly, during the intervention the response of the nursing personnel in educational meetings was minimal which might be due to understaffing. Even though during the intervention period, personnel were made aware of the diagnostic uncertainty of dipstick tests, dipstick tests were still performed frequently in residents with non-specific complaints without prior consultation of the physicians[11,12]. Yet, a positive dipstick test might result in the expectation of antibiotic treatment for UTI and physicians might feel obliged to start antibiotics in these situations.

As nursing personnel plays a large role in the recognition of UTI[11]. LTCFs should stimulate the education of personnel on UTIs and facilitate time for these meetings, perhaps even making them mandatory. The education should focus on the importance of differentiating between specific and non-specific complaints and indications for additional testing. Additional, systematic daily recording of signs and symptoms might improve appropriate antibiotic prescribing.

To promote the independence of nursing personnel while stimulating appropriate use of the diagnostic test, local agreements on the indication for performing dipsticks and urine cultures should be made. Also, the communication between physicians and nursing personnel is important to facilitate the understanding of nurses, especially when antibiotics are not prescribed.

While the ASUTID trial did not yield a statistically significant decrease in days of therapy with antibiotics related to UTI, there was a significant reduction in fosfomycin use, both for days of therapy and for the number of prescriptions. Fosfomycin treatment for cystitis consists of a single administration[13]. This antibiotic was found especially popular in residents with dysphagia or problems with medication adherence. But while *E. coli* remains sensitive to fosfomycin, other common uropathogens like *Klebsiella* sp., *Proteus* sp. and Enterococci seem to develop resistance against the antibiotic[13]. These uropathogens are more frequently seen in UTIs in older adults residing in LTCFs[14]. While, the decrease seen in fosfomycin prescription is important, as overuse of fosfomycin can increase antimicrobial resistance and might make one of the few available oral therapies for UTIs unavailable, it seems that physicians are still unsure to reduce antibiotic use[15,16]. Additional, safety studies on no or deferred antibiotic treatment in this population might help to stimulate a wait-and-see approach. Several studies have been performed in younger women but none have been performed in older adults[17–19]. In

a Swedish study, a multifaceted educational intervention resulted in an increased use of 'wait and see' approaches, though this study did not report any safety outcomes[20].

Finally, something important to consider when implementing antibiotic stewardship interventions is the expected decrease in inappropriate treatment. It seems obvious that 100% guideline adherence is impossible to reach, but there are no data on what is an acceptable target, which most likely will be setting-dependent. In our sample size calculation, we chose a threshold of 15% reduction of DOTs, which seems acceptable but we had no definitive evidence of what would be an attainable target. More information on the attainability of the threshold of appropriate prescribing should be collected.

Implications for future research

Even though the ASUTID trial intervention was based on a previously successful antibiotic stewardship intervention, the results were unsatisfactory. Additional efforts should be made to study which behaviour change interventions are most effective to stimulate guideline-adherent therapy. Other than the difference between hospitals and LTCF, there might also be different barriers to effective intervention between different facilities. Based on unpublished results, the effect of the intervention was heterogeneous between long-term care organizations. This suggests that tailoring interventions to specific locations could result in more effective results. Therefore, a recommendation for future studies is to study local barriers and facilitators for the implementation of antibiotic stewardship. Currently, such a study exploring factors contributing to antibiotic prescribing for UTIs is ongoing[21].

During the study, it became clear that even though physicians were aware of guideline recommendations, they frequently decided to deviate from those guideline recommendations. Physicians mentioned that they missed guidance, especially in those residents with communication problems due to dementia. The perceived risk to miss a potential severe UTI was high and could very well result in guideline non-compliant treatment. Instead of focusing on signs and symptoms that are dependent on the resident's ability to communicate, Future studies targeting this subpopulation of older adults with communication problems could focus on which observational signs and symptoms are related to UTI, i.e. vital signs (fever, tachycardia), urine incontinence, decreased urine output, etc.

Previously, elderly care physicians have relied on diagnostic tests like the dipstick to diagnose UTI, but due to asymptomatic bacteriuria, these tests are only useful to rule out UTI[22]. At the moment there are no reliable tests to diagnose UTI in older adults and, in fact, it is unlikely that such tests may become available shortly. Still, while the dipstick is notoriously unreliable, it is used very frequently in Dutch long-term care facilities and could result in the overuse of antibiotics[23,24] In our intervention, we tried to educate physicians about the pitfalls of dipstick

tests but only result in a marginal decreased use of dipsticks. Instead of trying to improve the use of dipsticks to only rule out UTI, a new antibiotic stewardship study could try removing dipsticks completely from long-term care facilities. A similar project by the NHS in England called 'To Dip or Not to Dip' has shown promising results on antibiotic prescriptions[25,26].

PART 2: TREATMENT OF CYSTITIS IN DIABETES MELLITUS

We used observational data to compare the frequency of treatment failures after five days or seven days of nitrofurantoin treatment in women with diabetes and UTI. In **Chapter 4**, observational data were used from the Julius GP network, a database that consists of routine care data from participation GPs from Utrecht and its vicinity to study treatment failure in women with diabetes mellitus with suspected cystitis[27]. Using inverse propensity weighting, there was no clinically significant difference in treatment failure within 28 days for five days of nitrofurantoin, compared to those treated for seven days. Additional subgroup analysis on risk factors like increased HbA1c, age and insulin use did not reveal statistically significant differences in treatment failure between five or seven days of therapy. Five days of nitrofurantoin for cystitis in women with diabetes can, therefore, be considered equally safe with regard to the risk of treatment failure and could reduce cumulative nitrofurantoin exposure in diabetes patients.

Reflection on findings

Due to the lack of RCTs on this subject, we designed a retrospective cohort study aimed to provide information on the optimal treatment duration of cystitis in women with diabetes. With statistical analyses, we attempted to minimize effects of confounding, a common problem in observational data. We used inverse propensity weighting as the primary analysis and instrumental variable analysis as a sensitivity analysis.

Our primary expectation was that general practitioners in the Netherlands would adhere to current guidelines, especially as the Netherlands has been seen as a low-prescribing country[28]. To our surprise, we found that many GPs in the study did not adhere to the NHG guideline and prescribed five days of nitrofurantoin in women with diabetes. This could be due to following a daily routine they follow for healthy young women or perhaps because of the experience of GPs that 5 days of therapy is also sufficient in women with diabetes. This illustrates the need for evidence as the clinical practices already deviated from the current guideline.

The recently revised NHG UTI guideline recommends a seven-day course of antibiotics for women with diabetes and cystitis. This advice is based on expert opinion, as there are no recent trials on the optimal treatment duration of cystitis in women with diabetes and because the risk of recurrent UTI in this patient group is higher compared to healthy women without diabetes. Based on our research, this duration could be reduced to five days and even a shorter duration might be possible. Based on several studies, the NHS in England recommends that three days antibiotic regimens in non-pregnant women with UTI are effective[29-32]. While the NHS makes exceptions for males, pregnant patients and patients with severe symptoms, they do not exclude women with diabetes from this short treatment duration.

We hypothesized that patients with more severe diabetes, reflected by the use of insulin, or those with poorly controlled diabetes, reflected by elevated HbA1c levels, would respond better to a longer course of antibiotics. This was however not the case according to our subanalyses. While these patients did have an increased risk of recurrent infection, they did not have a significantly increased risk of treatment failure when treated for five days instead of seven days. While additional research should be performed on the matter, perhaps patients with diabetes should not be treated differently from healthy women for cystitis.

Implications for future research

With our study, we showed that shortened treatment duration with nitrofurantoin for cystitis in women with diabetes was not associated with treatment failure. The suggestion that cystitis in women with diabetes can be treated in a similar way as in healthy women without comorbidities could be extended to other antibiotic durations, i.e. trimethoprim for three days or seven days, or even shorter, as suggested in the NICE guideline[32]. Still, additional studies are needed to answer these questions.

Even if treatment failure did not differ between five or seven days of nitrofurantoin, our analysis revealed that the risk of treatment failure in women with diabetes was far higher than in healthy women. Studies on other treatment options besides empiric treatment of UTI with nitrofurantoin and other first-line antibiotics should be considered to reduce recurrent infections in patients with diabetes. Prophylactic treatment could reduce the number of reinfections in patients, but comparative evidence is lacking, especially for patients with diabetes[33–35]. Currently, *E. coli* vaccine studies are being performed that might result in new prophylactic treatment options, although these vaccines can only include some pathogenic serotypes of the more than 700 existing serotypes[36,37].

In the subgroup analysis, there was no evidence of differences in treatment failure between five days and seven days of treatment, but we cannot rule out that some risk groups do have a need for an extended course of antibiotics. Research aimed at the identification of

subgroups of patients with diabetes that respond better to seven days of nitrofurantoin could be informative. Using this information, a clinical prediction rule could be developed to select those subgroups that would benefit from extended treatment.

Randomized controlled trials (RCT) are considered evidence of the highest quality, setting up a randomized controlled trial requires a lot of hard work, time and money[38]. Therefore many RCTs are funded by pharmaceutical manufacturers to demonstrate their new products against the currently used product. An RCT to show non-inferiority between five days of nitrofurantoin and seven days of nitrofurantoin in the treatment of cystitis in women with diabetes would need a sample size of approximately 1500-3500 patients in total, depending on the non-inferiority margin of choice. It is unlikely that a study like this would be funded due to little commercial interest in testing widely used antibiotics. This is demonstrated by the lack of RCTs on the subject of optimal antibiotic duration in cystitis. Using observational data from an existing database can provide real-world answers to clinical problems concerning therapy[39]. Reliable observational studies are necessary, as, in my opinion, evidence-based medicine cannot possibly rely only on RCTs. Still, special care should be provided to the study design of the observational studies as they are more at risk for i.e. confounding even when using appropriate statistical methods[40,41].

PART 3: DIAGNOSIS OF UTI IN OLDER ADULTS

Current guidelines advise the use of cultures to streamline antibiotic treatment in residents in LTCF suspected of UTI with bacterial invasion of surrounding tissue, in men, and those with failure of previous antibiotic treatment and recurrent infections. At the moment, the turnaround time, the time between taking a urine sample and receiving culture results, ranges from three to seven days[42]. This can result in the overuse of antibiotics in case of negative culture results when antibiotics could have been discontinued earlier or could have been omitted completely. In addition, more rapid testing could inform antibiotic choices in case of uropathogens being resistant to empirically started antibiotics. Bedside tests hold the promise to provide susceptibility results of uropathogens within 24 hours.

In **Chapter 5**, we present the results of the COMPARE-POCT study which was designed as a pilot study aimed to determine the performance of bedside susceptibility tests in LTCFs. We studied two different bedside tests: the Flexicult™, a test designed by Staten Institute in Denmark and the homemade Direct Susceptibility test. While a version of the Direct Susceptibility Test was tested in nursing homes, the Flexicult™ was used primarily in general practitioners' practices in some countries[43,44]. The two bedside susceptibility tests were compared with standard urine culture in urine samples of LTCF-residents and were found to

reduce the turnaround time, but also resulted in an increased risk of inappropriate treatment of UTI due to the low accuracy of the susceptibility tests. Especially susceptibility test results for fosfomycin differed from those based on standard culture and testing practice. Comparing both bedside tests with each other, The Flexicult™ performed only slightly better than a homemade direct susceptibility test and was more expensive. In conclusion, bedside tests reduced turnaround times, but with a higher risk for inappropriate treatment.

Reflection on findings

Using the Flexicult or the direct susceptibility tests in practice can lead to more overtreatment and undertreatment compared to the results of standard urine culture. Important to note is that the bedside tests were performed in the laboratory by a researcher without prior laboratory education to partly simulate the situation in which these tests would be used in primary or long-term care. Still, we cannot be sure how the implementation of these tests in LTCFs would affect the accuracy of these tests. For example, while the selection of the residents suspected of UTI in our study was performed by the elderly care physicians, having an easy and better accessible test might change the selection process of residents suspected of UTI changing the a-prior chance, which influences the accuracy of a test[45].

It is difficult to distinguish asymptomatic bacteriuria from 'true' UTI in older adults. Residents may have symptoms mimicking UTI or may not be able to express complaints. Currently, elderly care physicians rely on the dipstick test, which is unreliable to diagnose UTIs. In our study, the bedside tests showed an increased rate of misclassifications which could potentially lead to either overtreatment or undertreatment of residents. Yet, we did not compare it with the dipstick, which is frequently used in LTCFs and is notoriously inaccurate in diagnosing UTI[7,46,47]. The addition of the bedside tests to daily practice, even with the low accuracy, might still reduce inappropriate antibiotic use due to the faster availability of results. Additionally, it would give LTCFs more independence to perform susceptibility testing at the weekends and holidays.

Implications for future research

While the error rates for diagnostic tests were above the acceptance rate used by the FDA, there is still potential for bedside tests[48]. They might not be accurate enough to be used instead of the urine culture, but perhaps they could be used instead of the dipstick test and in combination with the standard urine culture to optimize antibiotic treatment.

As discussed in an earlier paragraph, the NHS has started a project to remove the dipstick from current practice. Instead of removing diagnostic tests prior to starting empirical antibiotics, bedside tests might be used instead of a regular dipstick. A negative bedside test would result in the early termination or withholding of antibiotic treatment, or if the uropathogen

is considered resistant according to the bedside test, therapy could be switched to more effective antibiotics at an earlier stage. Additionally, only samples from patients with positive bedside tests would be submitted for lab-based culture, which would reduce the number of – in hindsight – unnecessary culture procedures.

Future research for novel diagnostic tests in the LFTC is still warranted to provide more certainty in the UTI diagnosis.

OVERALL CONCLUSIONS

In this thesis, I set out to improve antibiotic prescribing in two populations with an increased incidence of UTI. Using novel statistical analyses, we have tried to show that the optimal treatment duration for cystitis is still unknown, but might be shorter than widely assumed and used. Hopefully, future studies will provide more definitive evidence.

Despite that we have studied several strategies to improve the diagnosis and treatment of UTI in the older adults residing in LTCFs, we have not resolved the problem of inappropriate antibiotic use in this population. Yet, these studies provided new insights on what to improve in clinical practice and how to move forward in future studies. Studies on removing diagnostic uncertainty, either by improved guidance on signs and symptoms related to UTI or by a novel diagnostic test, are very much warranted.

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7

SUMMARY

SUMMARY

Urinary tract infections (UTI) are one of the most common bacterial infections in humans and are the main reason for prescribing antibiotics. Part of the antibiotic prescription for UTIs might be unnecessary as the diagnosis of UTIs in some populations is unreliable and antibiotics might not be necessary due to the self-limiting nature of UTIs in young healthy women. Optimising antibiotic use is important to reduce the spread of antibiotic resistance and prevent complications attributed to antibiotic use. This thesis has the purpose to study several strategies to optimise antibiotic use for UTIs in two specific risk groups, namely older adults and women with diabetes mellitus.

In this summary, we will discuss the background of UTIs and the complexity of diagnosing UTIs. Secondly, we will summarise the most important findings of this thesis. This has been divided into three parts: (1) antibiotic stewardship intervention in long-term care facilities, (2) treatment of cystitis in women with diabetes mellitus and (3) diagnosis of UTI in older adults in long-term care facilities. Finally, we will briefly summarize the most important implications of this thesis.

Urinary tract infections

A urinary tract infection is a bacterial infection of the lower urinary tract, for example, the bladder and the urethra, or the higher urinary tract, like the kidneys. A UTI can be diagnosed based on the combination of (1) symptoms related to UTI and (2) the presence of white blood cells and bacteria in the urine.

While previously urine was considered a sterile fluid, currently the presence of bacteria in urine, especially in older adults, does not have to indicate an active infection. The presence of bacteria in the urine without any clinical symptoms related to UTI is called asymptomatic bacteriuria. The treatment of asymptomatic bacteriuria does not have a significant health advantage and is only indicated in a few specific situations.

But when a patient's health deteriorates, often UTI is seen as a possible cause of the deterioration and especially when a patient has bacteriuria. Currently, there are no diagnostic tests to distinguish between patients with asymptomatic and symptomatic bacteriuria. And while guidelines try to provide recommendations for diagnosing symptomatic bacteriuria, non-specific complaints remain an important reason for starting antibiotics in patients with asymptomatic bacteriuria. One of the possible options to reduce antibiotic treatment and promote guideline-adherent prescribing is the introduction of antibiotic stewardship programmes.

Part 1: Antibiotic stewardship interventions in long-term care facilities

In 2019, there were over 115 000 older adults living in nursing homes in the Netherlands. As the Dutch population grows older on average, it is expected that this number will increase. The urinary tract infection is the most common bacterial infection in long-term care facilities and can lead to a serious decrease in the quality of life of older adults. This population has an increased risk of developing a UTI, but additional older adults have an increased risk of developing complications related to the infection or the treatment. Thus, every antibiotic prescription should be deliberately considered.

Besides the risk for the individual patient, increased use of antibiotics in long-term care facilities can result in increased antibiotic resistance locally. While the guideline advises starting antibiotics in older adults with specific symptoms of UTI, antibiotic treatment is often started in older adults with non-specific complaints, like delirium, general feeling of being unwell or decreased appetite. These non-specific symptoms can result from different etiologies including non-infectious diseases. Several factors contribute to a low threshold for starting antibiotics for suspected UTI. For example, the high perceived risk of developing complications due to missed infections and the difficulty of recognising specific signs, especially as a significant part of older adults living in long-term care facilities have problems communicating their symptoms, because of dementia or hearing loss. Secondly, the efficacy of diagnostic tests is limited in older adults due to high levels of asymptomatic bacteriuria. Thirdly, a limited knowledge about how to manage residents with non-specific complaints could play an additional role.

To stimulate guideline-compliant antibiotic treatment, antibiotic stewardship programs have been developed. These programs try to actively measure and improve antibiotic use, especially by educating the prescribers. These programs are mandatory in Dutch hospitals since 2015 but are being used in several other healthcare organisations, like long-term care facilities. The *Antibiotic Stewardship Targetting Urinary Tract Infections in Dutch Long-term care facilities (ASUTID)* trial is an antibiotic stewardship program developed for local long-term care facilities based on the Dutch Guideline for UTI in frail older adults which was developed by the Dutch Association of Elderly Care Physicians (Verenso). The program consisted of education about UTIs and audit and feedback on the treatment choices of the attending physicians.

In **Chapter two**, it was shown that the introduction of an antibiotic stewardship intervention did not result in a decrease in antibiotic treatment days, either in total or specified for UTI use. Contrary to that initial finding, there was a significant decrease in the number of prescriptions for UTI-related antibiotics. A possible reason for these conflicting results is

that while fewer people were treated for a UTI, those who did receive a prescription were treated longer in the intervention period.

As most antibiotic stewardship programs rely strongly on education to change behaviour in prescribers, the data of the ASUTID trial was used to compare prescribing behaviours of attending physicians before and during the intervention. In **Chapter three,** it is shown that physicians did start fewer antibiotic prescriptions in older adults with non-specific complaints, like delirium or general malaise, but the proportion of people either overtreated or undertreated with antibiotics did not change. This shows that even though antibiotic treatment days did not decrease significantly, there was a change in the behaviour of prescribing physicians.

Concluding, while the trial showed a few positive results, it was too modest to significantly decrease antibiotic use in long-term care facilities. The developed antibiotic stewardship program used several methods to improve prescribing, but it is yet unknown which stewardship methods are most effective to change prescribing behaviour in elderly care physicians. Additional studies to measure the effect of these different bundles of methods can be useful to develop a successful antibiotic stewardship program.

Part 2: Treatment of cystitis in diabetes mellitus

Besides older adults, people with diabetes mellitus are also at risk of developing UTIs as well as complications of the infection. Therefore, the Dutch College of General Practitioners advises treating cystitis in women with diabetes mellitus as complicated UTI i.e. seven days nitrofurantoin, instead of five days. In **Chapter four** retrospective and observational data from the Julius General Practitioner Network (JHN) was used to study the risk of UTI in women with diabetes mellitus. By using the JHN the risk of selection bias and information bias was diminished as data from almost 75 GP offices are included in the network and GPs participating in the network have mandatory coding training. To reduce confounding, inversed propensity weighting and an instrumental variable analysis were used. Both methods rearrange the data to form comparable groups, though both use a different way.

The study showed that a large proportion of women with diabetes were treated for five instead of seven days. Shorter treatment duration did not result in a clinically significant increase in new infections. This was also true for older women, women using insulin or women with an increased HbA1c. We concluded that the treatment of cystitis in women with diabetes can be reduced to five days of nitrofurantoin without discerning concerns for safety.

Part 3: Diagnosis of UTI in older adults

Due to the difficulty to recognize UTIs in long-term care residents due to communication problems, healthcare personnel rely heavily on diagnostic tests. One of the most used tests to detect bacteriuria is the dipstick for nitrite and leukocytes. A few advantages of the test are that it is easy and quick to perform. But due to the high prevalence of asymptomatic bacteriuria in older adults, its usefulness in diagnosing UTIs is relatively low in this population. Another commonly used test is the urine culture. A few advantages of this test are the determination and quantification of the causative bacteria and their susceptibility pattern. To perform this test, urine must be collected, sent to the microbiology laboratory, processed, grown for 24 hours and tested for causative pathogen and its susceptibility, which all can be delayed for a myriad of reasons. A negative culture, a culture without growth of bacteria, is often known within 24 hours, but the turnaround time, the time between collecting the sample and receiving the result, can take up to three days. When a culture is positive, it can even take five to seven days. Especially in shorter antibiotic courses, the culture might be of limited value for elderly care physicians.

A specific test that can be performed in the proximity of the resident could assist physicians in their decisions making. In **Chapter five**, we studied two bed-side tests that might provide quick and reliable information on the susceptibility of a possible causative pathogen. The study showed that while both tests can reduce the turnaround time to 24 hours, the reliability of the two tests was substantially lower than the currently used urine culture. Both tests had difficulty differentiating between a causative pathogen and contamination or skin bacteria. Since long-term care residents are often frail and have an increased risk of complications of an infection, we advise to not use these tests as a replacement of regular urine culture. Additional research is needed to determine if combined use of a bedside test in combination with current diagnostic tests is beneficial to guide empirical antibiotic use using the bed-side test, while streamlining antibiotic stewardship with the regular urine culture.

Finally, in **Chapter six**, we interpret the most important results of the thesis. We also make suggestions for future research, which includes studies of the effectiveness of antibiotic stewardship methods and the incorporation of bed-side tests next to current diagnostic tests. While we continue our search for reliable diagnostic tests for UTI in older adults, we advise to currently to focus on the guidance of health care personnel, both physicians and nurses, on recognizing UTIs and how to cope with residents with non-specific complaints.

8

APPENDICES

Dutch Summary

List of publications

Acknowledgements

About the author

NEDERLANDSE SAMENVATTING

Urineweginfecties (UWI) zijn één van de meest voorkomende bacteriële infecties in mensen en zijn de meest voorkomende regels voor het voorschrijven van antibiotica. Een deel van deze behandelingen is mogelijk niet noodzakelijk omdat UWI in sommige populaties moeilijk te diagnosticeren is en bij jonge gezonde vrouwen is het geven van antibiotica mogelijk niet nodig doordat UWI self-limiting kan zijn. Het optimaliseren van antibiotica gebruik voor UWI is noodzakelijk om de ontwikkeling van antibiotica resistentie te beperken en complicaties van antibiotische behandeling te voorkomen. Dit proefschrift heeft als doel antibiotica gebruik voor UWI in twee specifieke groepen NL ouderen die wonen in langdurige zorginstellingen en vrouwen met diabetes mellitus, effectiever toe te passen.

Deze samenvatting zal eerst de achtergrond van de urineweginfectie en de complexiteit van het diagnosticeren van UWI beschrijven. Daarna zullen de meest belangrijke bevindingen van dit proefschrift worden besproken. Deze worden verdeeld in drie delen: (1) de toepassing van antibiotic stewardship interventies in langdurige zorginstellingen, (2) de behandelduur van cystitis in vrouwen met diabetes mellitus en als laatste (3) nieuwe diagnostiek naar UWI in ouderen in langdurige zorginstellingen. Als laatste zullen de implicaties van het proefschrift worden besproken.

Urineweginfecties

Een UWI kan zowel een bacteriële infectie van de lagere urinewegen, zoals de blaas en plasbuis maar ook de hogere urinewegen zoals de nieren en het weefsel rondom de urinewegen, betreffen. Dit zorgt ervoor dat de ernst van een UWI kan verschillen van een fysiek ongemak tot een levensbedreigende infectie. Naast dat de locatie van de UWI een rol speelt in de ernst van de infectie, spelen ook patiënt-gerelateerde factoren een grote rol in de ernst van de infectie. Oudere patiënten of patiënten met een verlaagde weerstand zoals bij diabetes mellitus het geval is, hebben een hoger risico op een gecompliceerd beloop.

Cystitis, ook wel blaasontsteking, wordt verdeeld in ongecompliceerde en gecompliceerde cystitis. Dit hangt af van het risico dat patiënten lopen op complicaties, zoals koorts, abcessen en sepsis. Van een ongecompliceerde cystitis is enkel sprake wanneer het een blaasontsteking in niet-zwangere vrouw zonder afwijkingen aan de urinewegen betreft. De gecompliceerde cystitis wordt gezien in een gemêleerde groep van mannen en vrouwen met een hoger risico op complicaties, door een verlaagde weerstand en/of afwijkingen van de urinewegen.

De diagnose wordt gesteld op basis van een combinatie van (1) de symptomen passende bij een urineweginfectie en (2) de aanwezigheid van bacteriën in de urine. Deze klinische symptomen betreffen klachten zoals pijn bij het plassen, vaak plassen van kleine hoeveelhe-

den urine of de aandrang om te plassen. Ook weinig specifieke klachten zoals verwardheid, algehele malaise en koorts kunnen optreden.

Bacteriën in de urine kunnen worden aangetoond via een aantal methodes, zowel direct als indirect. Met een kweek van de urine of een dipslide is het mogelijk om de bacteriën direct op een kweekmedium te groeien. Met een urine dipstick is het mogelijk om indirect bacteriën aan te tonen door het aantonen van nitriet, een afbraakproduct van een aantal bacteriën of door de aanwezigheid van leukocyten, die verhoogd zijn door een reactie van het lichaam op de infectie.

Hoewel eerder werd gedacht dat urine altijd steriel moet zijn, lijkt de aanwezigheid van bacteriën in de urine, met name bij ouderen, niet per se te berusten op een actieve infectie. Indien er bacteriën in de urine zonder symptomen passende bij een UWI wordt gesproken van asymptomatische bacteriurie. Onderzoek heeft eerder al laten zien dat het behandelen van asymptomatische bacteriurie in principe geen meerwaarde heeft voor de gezondheid en alleen in uitzonderlijke situaties noodzakelijk is.

Wanneer de gezondheid van een patiënt achteruitgaat, wordt vaak gedacht aan een UWI met name wanneer er sprake is van bacteriurie onafhankelijk van de aanwezige symptomen. Er zijn op het moment geen onderzoeken die kunnen differentiëren tussen asymptomatisch bacteriurie en een UWI. Richtlijnen geven advies voor het diagnosticeren van een UWI, maar aspecifieke klachten blijven een belangrijke reden voor het starten van antibiotica in patiënten met asymptomatische bacteriurie. Een optie om antibiotica gebruik te verminderen, is door de introductie van antibiotic stewardship programma's.

Antibiotic stewardship interventies in langdurige zorginstellingen

In 2019 woonden er ruim 115 000 mensen in een verzorgings- of verpleeghuis. Dit getal zal enkel groter worden, naarmate vergrijzing toeneemt. In dit soort zorginstellingen is UWI de meest voorkomende infectie en kan leiden tot een forse verslechtering van de kwaliteit van leven van ouderen. Naast dat ouderen een hoger risico hebben voor het ontwikkeling van infecties, hebben zij ook een groter risico op het ontwikkelen van complicaties van de infectie of de behandeling. Elke antibiotische behandeling moet dus bewust worden overwogen.

Naast het risico voor de individuele patiënt, kan het hoge gebruik van antibiotica voor o.a. UWI resulteren tot toename van lokale antibiotica resistentie. Hoewel het geldend advies is om alleen antibiotica te starten bij patiënten met specifieke klachten van een UWI wordt er toch regelmatig antibiotica gestart bij ouderen met aspecifieke klachten zoals verwardheid, algehele malaise of verminderde intake. Deze aspecifieke klachten kunnen ontstaan door een veelheid van verschillende problemen. De lage drempel om antibiotica te starten bij een

verdenking op een UWI is ontstaan door een aantal redenen. Zo ervaren artsen het risico op het missen van een infectie en daardoor ontstaan van complicaties als hoog. Daarnaast is het uitvragen van specifieke klachten in deze populatie lastig door het frequent voorkomen van communicatie problemen door o.a. dementie en hardhorendheid. Ook is de specificiteit van diagnostische onderzoeken laag door het veelvuldig voorkomen van asymptomatische bacteriurie.

Om correct antibiotica gebruik te stimuleren, zijn er antibiotic stewardship programma's ontwikkeld. Deze programma's proberen antibiotica gebruik systemisch te meten en verbeteren door middel van educatie van de voorschrijvers. Sinds 2015 zijn deze programma's verplicht in Nederlandse ziekenhuizen, maar worden ook steeds meer in andere zorg zoals langdurige zorginstellingen toegepast. In de *Antibiotic stewardship Targetting Urinary Tract Infections in Dutch long-term care facilities* (ASUTID) trial is een antibiotic stewardship programma ontwikkeld specifiek voor urineweginfecties in langdurige zorginstellingen gebaseerd op de richtlijn voor behandeling van urineweginfecties in fragiele ouderen van de Nederlandse Vereniging van specialisten ouderengeneeskunde (Verenso). Het programma bestond uit onderwijs over UWI en audit en feedback op de persoonlijk behandelkeuzes van de behandelend artsen in de zorginstelling.

In **hoofdstuk twee** werd beschreven dat de introductie van een antibiotic stewardship programma niet resulteerde in een afname van het antibiotica gebruik, zowel in totaal als antibiotica specifiek voor antibiotica gebruik. In tegenstelling tot deze bevinding werd er wel een afname van het aantal antibiotica recepten die vaak voor UWI worden voorgeschreven. Een mogelijke reden voor deze conflicterende resultaten is dat minder mensen worden behandeld voor een UWI, maar dat de gemiddelde behandeling langer is geworden. behandeld met antibiotica.

Het effect van de meeste antibiotic stewardship programma's zijn afhankelijk van een gedragsverandering in de voorschrijvers. De data van de ASUTID is gebruik om te kijken of voorschrijfgedrag van de voorschrijvers verschilde tussen de controle en interventie periode.

In **hoofdstuk drie** wordt aangetoond dat artsen minder vaak antibiotica voorschreven voor ouderen met aspecifieke klachten zoals verwardheid of algehele malaise, maar het percentage ouderen die overbehandeld of onderbehandeld veranderde niet. Dit laat zien dat hoewel er geen significante afname was van het antibiotica gebruik, het gedrag van de voorschrijvers wel veranderde.

Concluderend, ondanks dat het onderzoek een aantal positieve resultaten liet zien, was het te weinig om een significante daling in het gebruik van antibiotica te bewerkstelligen. Het

ontwikkelde antibiotic stewardship programma bestond uit verschillende methodes om het voorschrijfgedrag te verbeteren, maar het is onbekend welke methodes het effectiefst zijn. Onze aanbeveling is daarom dat in toekomstig onderzoek wordt gekeken naar welke methodes het meest effectief zijn. Deze informatie kan dan gebruikt worden om een antibiotic stewardship programma op te stellen dat wel effectief antibiotica gebruik kan verlagen.

De behandelduur van cystitis in diabetes mellitus

Bij het uitvoeren van onderzoek moet er rekening gehouden worden met het ontstaan van verstoringen in de data, ook wel bias genoemd. Er zijn drie vormen van bias, namelijk selectie bias, informatie bias en confounding. Hoewel er bij alle onderzoeksmethodes rekening gehouden moet worden met bias, is observationele onderzoek met name gevoelig voor bias.

Selectie bias ontstaat als je een niet representatieve selectie van de onderzoekspopulatie neemt, bijvoorbeeld door het selecteren van patiënten die goed reageren op een behandeling, waardoor het effect wordt overschat.

Informatie bias is wanneer gegevens verkeerd worden gemeten of niet worden geregistreerd, bijvoorbeeld door typfouten (willekeurig) of een foutieve meetmethode (niet willekeurig). De kans hierop is groter bij retrospectief onderzoek omdat data vaak eerder zijn verzameld en missende data niet teruggevonden kunnen worden.

De laatste vorm is confounding. Hierbij is er sprake van verstorende factoren in de data die effect hebben op de uitkomst van het onderzoek maar ook op de afhankelijke factoren. Een voorbeeld hiervan is dat als je het effect van alcohol op het risico op een hartaanval onderzoekt, beide beïnvloed kunnen worden door roken. Rokers drinken mogelijk meer alcohol en hebben ook meer kans op een hartaanval. Je moet dan rekening houden met roken in je studie. In randomized controlled trials wordt door middel van loten patiënten lukraak verdeeld over de onderzoeksgroepen waardoor twee vergelijkbare groepen ontstaan. Dit is niet mogelijk bij observationeel onderzoek. Achteraf kan er gebruik gemaakt worden van epidemiologische methodes om eventuele verschillen in de patiëntgroepen te corrigeren, maar dit is minder effectief. Dit is de reden waarom randomized controlled trials de voorkeur hebben boven observationeel onderzoek. Maar de nadelen van randomized controlled trials zijn dat ze duur zijn en lang kunnen duren. In gevallen waarbij randomized controlled trials niet mogelijk of beschikbaar zijn, kunnen observationele onderzoeken toch zinvolle informatie leveren zolang er rekening wordt gehouden met de nadelen zoals bias.

Naast de ouderen, zijn mensen met diabetes mellitus (DM) een risico groep voor het ontwikkelen van een UWI, maar ook voor een gecompliceerd beloop. In de richtlijn van het Nederlands Genootschap van Huisartsen (NHG) is daarom het advies om cystitis in

vrouwen met DM met zeven dagen nitrofurantoïne in plaats van de gebruikelijke vijf dagen bij gezonde, niet-zwangere vrouwen. In **hoofdstuk vier** is gebruik gemaakt van retrospectieve en observationele data verzameld door huisartsen participerend in het Julius Huisartsen Netwerk (JHN) om het risico op het ontwikkelen van UWI in vrouwen met diabetes mellitus te onderzoeken. Door het gebruik van de JHN database is het risico op selectie bias en informatie bias geminimaliseerd doordat de database gebruik maakt van data van bijna 75 huisartsenpraktijken, die allemaal getraind zijn in het correct invullen van de database. Daarnaast is gebruik gemaakt van epidemiologische methodes genaamd *inversed propensity weighting* en *instrumental variable analysis* om het risico op confounding te verlagen. Beide methodes hergroeperen op twee verschillende manieren de data om vergelijkbare groepen te vormen.

Uit de data van het JHN bleek dat veel huisartsen een cystitis in vrouwen met DM met vijf dagen nitrofurantoïne worden behandeld in plaats van de geadviseerde zeven dagen. De kortere behandelduur leidde niet tot klinisch significant meer infecties. Dit gold ook voor vrouwen die ouder waren, insuline gebruikten en/of slecht waren ingesteld op de antidiabetica op basis van een hoog HbA1c. Hieruit blijkt dat mogelijk de antibiotica duur van nitrofurantoïne voor cystitis in vrouwen met diabetes mellitus verkort kan worden naar vijf dagen zonder opvallende veiligheidsrisico voor de patiënten. De aanbeveling uit dit onderzoek is dan ook om cystitis in vrouwen met DM te behandelen met vijf dagen nitrofurantoïne.

Diagnostiek naar UWI in ouderen

Door de moeizame herkenning van UWI in langdurige zorginstellingen door communicatie problematiek in ouderen woonden in zorginstellingen, vertrouwt zorgpersoneel op de uitslagen van diagnostische onderzoeken voor de diagnose van UWI. Het meest gebruikte onderzoek om bacteriën in de urine vast te stellen is de dipstick test voor nitriet en leukocyten. Voordelen van deze test zijn dat het makkelijk en ook snel uit te voeren is. Maar door de hoge incidentie van asymptomatische bacteriurie in ouderen is de toevoegende waarde aan de diagnose UWI laag.

Een ander veel gebruikt onderzoek is de urine kweek. Het grote voordeel van deze test is dat het informatie geeft over de verwekker van de infectie en het resistentiepatroon. Voor dit onderzoek moet urine worden afgenomen en verstuurd worden naar een microbiologisch lab. Aldaar wordt de urine verwerkt en aangebracht op een kweek medium waarop bacteriën groeien. De groeiende bacteriën kunnen geïdentificeerd worden en resistentiepatronen getest worden. Bij al deze stappen kan vertraging oplopen. Een negatieve kweek, een kweek zonder groei, is meestal na 24 uur bekend, maar de *turnaround time,* de tijd tussen afname van de urine en het ontvangen van de uitslag door de arts, kan oplopen tot drie dagen. Bij een positieve kweek kan het zelfs vijf tot zeven dagen duren. Met name bij kortere antibiotica

kuren kan de waarde van de urinekweek voor specialist ouderengeneeskundigen daarom beperkt zijn.

Een betrouwbare test die in de buurt van de patiënt, zogenaamd bed-side test, kan uitgevoerd worden, zou artsen kunnen assisteren in het nemen van de juiste beslissing voor het starten van antibiotica. In **hoofdstuk 5** is daarom gekeken naar twee bed-side testen die mogelijk snelle informatie over de gevoeligheid van de mogelijk verwekker van de UWI kunnen leveren. Beide tests waren relatief eenvoudig in te zetten op locatie waardoor de *turnaround time* verkort zou worden naar 24 uur. Echter de betrouwbaarheid van de testen was lager dan de huidig gebruikte urinekweek. Dit komt ten dele omdat de tests niet goed konden differentiëren tussen een mogelijke verwekker van urineweginfectie en gewone huidflora en/of contaminatie van de urine. Gezien dat de bewoners van langdurige zorginstellingen vaak fragiele ouderen zijn, waarbij het risico op complicaties verhoogd is, is het ons advies om deze tests niet te gebruiken in plaats van huidige diagnostiek zoals de urinekweek. Verdere onderzoek naar gecombineerd gebruik van deze tests in combinatie met de urinekweek lijkt zinvol.

Als laatst wordt er in **hoofdstuk 6** een interpretatie van de belangrijkste resultaten gegeven met aanbevelingen voor toekomstig onderzoek. Hierbij worden er aanbeveling gedaan voor vervolgstudies naar de effectiviteit van verschillende methodes voor antibiotic stewardship programma's en het introduceren van bed side tests naast de gebruikelijke zorg. Aanbeveling voor de praktijk zijn onder meer de verbetering begeleiding van artsen in langdurige zorginstellingen hoe om te gaan met klachten die verdacht zijn voor urineweginfectie, enerzijds door praktische aanbevelingen voor het herkennen van klachten passend bij urineweginfecties of door inzet van nieuwe diagnostische onderzoeken.

LIST OF PUBLICATIONS

Publications related to this thesis

Hendriks-Spoor KD, Wille FL, Doesschate TT, Dorigo-Zetsma JW, Verheij TJM, van Werkhoven CH. Five versus seven days of nitrofurantoin for urinary tract infections in women with diabetes: a retrospective cohort study. Clin Microbiol Infect. 2021 Jul 7:S1198-743X(21)00365-7. doi: 10.1016/j.cmi.2021.06.034. Epub ahead of print. PMID: 34245906.

Publications not related to this thesis

Ten Doesschate T, **Hendriks K**, van Werkhoven CH, van der Hout EC, Platteel TN, Groenewegen IAM, Muller AE, Hoepelman AIM, Bonten MJM, Geerlings SE. Nitrofurantoin 100 mg versus 50 mg prophylaxis for urinary tract infections, a cohort study. Clin Microbiol Infect. 2021 Jun 7:S1198-743X(21)00299-8. doi: 10.1016/j.cmi.2021.05.048. Epub ahead of print. PMID: 34111584.

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ACKNOWLEDGEMENTS

In de laatste 5 jaar heb ik met veel verschillende en inspirerende mensen mogen samenwerken en ik ben vele dank verschuldigd. Veel mensen weten dat mijn promotie tijd een zware periode is geweest; niet alleen het promotie traject op zich, maar vooral ook buiten het promoveren om. Ik wil iedereen die direct of indirect mij heeft geholpen om op dit punt te komen bedanken. Ik besef mij dat het niet mogelijk is om iedereen te benoemen in dit dankwoord, maar ik ga een poging wagen.

Graag wil ik mijn promotors **prof. dr. M.J.M. Bonten en prof. dr. T.J.M. Verheij en copromotoren dr. J.W. Zetsma** en **dr. C.H. van Werkhoven** bedanken voor hun inbreng en begeleiding bij het volbrengen van mijn promotietraject.

Beste **Marc**, ik wil u ontzettend bedanken voor het vertrouwen dat je mij hebt gegeven toen je mij in 2017 de kans gaf om onderzoek te doen binnen een inspirerende onderzoeksgroep. Ik heb zoveel geleerd van deze gevarieerde groep waar epidemiologen, microbiologen, internisten, huisartsen, apothekers, longartsen en kinderartsen samenwerkten voor één passie namelijk infectieziekten. Daarnaast kreeg ik de kans om de opleiding epidemiologie te volgen die hele nieuwe werelden voor mij heeft geopend. Marc, bedankt voor uw kritische en scherpzinnig blik deze jaren.

Beste **Theo**, ik ben nog steeds ontzettend dankbaar dat je deze promotie kandidaat aannam die ondanks al bijna halverwege haar promotie vooral nog ideeën had over wat ze wilde doen, maar nog weinig op papier had staan. Uw jarenlange ervaring en kennis hielpen mij mijn ideeën helder op papier zetten en u stond altijd klaar om even te overleggen. Uw onvermoeide begeleiding heeft zeker gezorgd dat dit proefschrift tot een goed einde is gekomen.

Beste **Wendelien**, bedankt voor de begeleiding van mijn eerste stapjes binnen de microbiologie, die wonderlijke wereld onder de microscoop, terwijl ik daarvoor zolang met de macroscopie, genaamd de patiënt, had gewerkt. Uw ervaring in de kliniek heeft mij zeer geholpen met dit proefschrift. Bedankt voor de vrijheid die u mij gegund heeft om mijn eigen pad te vinden, ook al is deze niet binnen de microbiologie.

Beste **Henri**, ik denk niet dat ik je genoeg kan bedanken. Toen ik het promoveren door een myriade van redenen niet meer zag zitten, ben ik naar je toegestapt. Jouw hulp bij het heropstarten van mijn werkzaamheden in combinatie met jouw uitgebreide epidemiologische kennis beviel zo goed at ik je vroeg om mijn copromotor te worden. Het is niet zonder reden dat je in 2019 ‘Supervisor van het jaar’ bent geworden. Samen met een andere promovendi

bedacht ik de 'WWHD'; de 'What would Henri do'. Ik zal ieder geval nog regelmatig terugdenken aan je tips. Bedankt voor alles.

En mijn derde copromotor: **Dr. P.D. van der Linden**. Beste Paul, bedankt voor je tijd terwijl je het altijd zo druk had. Hoewel wij op papier officieel afscheid van elkaar als copromotor en promotie-kandidaat hadden genomen, ben je officieus altijd mijn derde copromotor gebleven. Ik ben je nog steeds ontzettend dankbaar voor het geven van die ruimte zodat Henri jouw stokje (ten dele) kon overnemen toen ik aanvullende epidemiologische hulp nodig had om mijn proefschrift tot een goede einde te brengen. Maar ook buiten het onderzoek doen, heb ik veel van je mogen leren. Als arts-assistent Interne Geneeskunde had ik eerder alleen contact wanneer ik de dalteparine weer eens onder gedoseerd had bij een hoger BMI. In het A-team in Tergooi werd mij pas echt duidelijk hoe belangrijk jullie zijn binnen gezondheidszorg. Voor mij nu aan elke A-team tafel een apotheker.

Beste artsen van Amaris, Hilverzorg, Inovum en Vivium, sommige van jullie heb ik lang mogen meemaken, sommige wat korter. Wat een onderschat vak voeren jullie toch uit. Ik wil jullie allemaal ontzettend bedanken voor de energie die jullie in de ASUTID-studie en COMPARE-studie hebben gestoken. Gewoon omdat wij samen het idee hadden dat er verbetering mogelijk was, want budget was er eigenlijk niet. Dit proefschrift is vooral ontstaan dankzij jullie.

De leden van mijn promotiecommissie: **prof. dr. N.J. de Wit, prof. dr. J.A.J.W. Kluijtmans, prof. dr. L.M.O. de Kort, prof. dr. C.M.P.M. Hertogh, prof. dr. J. Gussekloo** en **Dr. T. Platteel**, bedankt voor het beoordelen van mijn proefschrift en jullie bereidheid zitting te nemen in de oppositie.

Ik wil alle medewerkers van de microbiologie in het Tergooi bedanken. **Anneke, Bas, David, Jolanda, Linda, Karin, Shira, Renee, Roland, Rino, Zena**, en zo veel anderen, met jullie heb ik ontzettend fijn mogen samenwerken, zowel op het lab als daarbuiten. Bedankt voor alle koffiemomenten, lunchmomenten en jullie inzichten in de microbiologie met iemand die nog nooit een kweek had verricht voordat ze bij jullie kwam.

Beste **Cornelis Timmerman, Leendert Bakker**, dank voor jullie inzicht binnen de microbiologie en het werk eromheen. Dank voor jullie kritische nood tijdens het updaten van het antibiotica boekje. Ik neem nooit meer blind een richtlijn aan omdat het een richtlijn is. Misschien komen we elkaar nog een keer tegen, eventueel op Bonaire?

Beste kamergenootjes in het Tergooi, **Suzanne, Jarne** en **Alette**, dank voor de gezelligheid op het kamertje. Ik heb veel van jullie mogen leren. Dank voor de kennis en het fungeren als klankbord zo nu en dan. Ook dank voor de hulp met de ASUTID-studie. Elk van jullie had

ik graag langer als kamergenootje willen hebben, maar ik hoop dat jullie allemaal jullie eigen plek hebben gevonden.

Beste **Paul de Vries, Matthijs Silvermann**, bedankt voor jullie bijdrages aan het A-team van het Tergooi. Als iemand die jaren bij de interne had gezeten en nu tussen de microbiologen zat, was er altijd weer een momentje van herkenning in jullie verhalen van de afdeling. Ik hoop jullie ooit terug te zien op de internistendagen.

Beste (XE)WMM groep, **Annabel, Claudia, Darren, Diana, Denise, Emma, Fien, Fleur, Gerrita, Henri, Jan, Janneke, Inger, Kirsten, Lufang, Maaike, Marc, Marjolein, Martin, Meri, Mirjam, Mui Nienke Paternotte, Nienke Plantinga, Tess, Tessa, Thijs, Thomas, Tim, Sharon, Valentijn,** dank voor jullie kritische noot en het delen van jullie eigen kennis. Jullie hebben mij allemaal ontzettend geïnspireerd door jullie eigen verhalen en dromen, van postdoc worden, consultant buiten de gezondheidzorg worden en verhuizen naar het buitenland. Jullie hebben mij laten beseffen dat er een hele wereld buiten de interne geneeskunde is. Dank dat jullie mijn hoogte- en dieptepunten aan hoorden en mij steunden in deze tijden. Dank dat jullie de ECCMID's tot een succes maakten. (Eervolle vermelding voor Thomas voor de officiële ECCMID bingo kaart). Ik wou dat we meer congressen hadden kunnen meemaken, maar helaas gooide corona roet in het eten. Ik hoop jullie allemaal weer eens tegen te komen. Ik trakteer!

Beste collega's uit het Ikazia, lieve **Kaziaantjes**, ik was ontzettend blij dat ik weer de kliniek in mocht, maar ik heb het jullie het eerste jaar niet makkelijk gemaakt met regelmatige afwezigheid. Maar dat mocht de pret niet drukken. Het Ikazia is gezegend met zulke zo'n leuke groep assistenten, die ook nog eens keihard kan werken. Ik heb het geluk dat ik nog een aantal jaar bij jullie mag blijven, dus laten we er een feestje van maken.

Beste **drs. Wabbijn**, lieve Marike, bedankt dat je mij hebt aangenomen in het Ikazia. Ik had nog flink wat werk te doen aan mijn promotie maar desondanks heb jij mij aangenomen. Je hebt mij de ruimte gegeven om dit proefschrift af te maken én mij te ondersteunen toen ik solliciteerde naar de opleiding Interne Geneeskunde. Het Ikazia is een ontzettend gezellig groep en ik als Brabantse voel mij er helemaal thuis. Ik ben ontzettend blij dat ik de komende jaren bij jullie mag blijven.

Beste **drs. Thijs-Visser**, lieve Martine, als mijn mentor in het Ikazia, heb ik het je niet makkelijk gemaakt. Er leek altijd wel iets te zijn! Maar als ik je nodig had, is daar altijd je luisterend oor. Jij durfde de besluiten te nemen, die ik niet durfde. Ik hoop dat we de komende 3 jaar nog veel gezellige koffiemomentjes hebben.

Beste paranimf, lieve **Inger**, bedankt dat jij er voor mij was. Jij was ongeveer 2 jaar eerder dan mij begonnen en het reilen en zeilen van promotie doen was voor jou al een bekende weg. Gelukkig wilde je graag al je tips en tricks met mij delen. Als ik vastzat in een probleem, kon ik je altijd bellen. Ik denk niet dat ik de eindstreep had gehaald zonder jouw luisterend oor. Met jouw humor kon ik mijn frustratie omzetten in energie om toch door te zetten. Ik ben daarom ook blij dat jij naast mij wilt staan als paranimf terwijl ik de laatste loodjes doorloop.

Beste paranimf, lieve **Inge** (niet te warren met Inger!), ik weet dat wij als zusjes altijd een haat-liefde verhouding hebben gehad. Maar ik denk dat je niet weet hoe trots ik op je ben. Ik heb altijd een beetje meer op jou willen lijken. Je bent een ontzettende vastbijter en laat niets zomaar over je heen gaan. Ik vind dat met het afronden van mijn promotie ik een beetje meer op je ben gaan lijken. Nu zijn we samen enorme doorzetters. Bedankt dat jij naast mij wilt staan als paranimf, ook al zei je ja terwijl je geen idee had wat het in hield.

Lieve **Kai**, onze liefde voor infectieziekten heeft ons al sinds de opleiding met elkaar verbonden. Naast onze flauw humor natuurlijk. Al vanaf het moment dat we samen op hetzelfde oudste coschap solliciteerde en gelukkig allebei werden aangenomen. En later samen in het Sint Elisabeth tot laat in de avond brieven schreven voor die talloze patiënten die we overdag hadden gezien. Ik heb al eerder gezegd, ik mis die avonden echt. Maar jij ging naar Groningen en ik naar Breda. Ik hoop toch ooit nog samen met je te werken en samen naar congressen te gaan. Je bent een fijne vriend en een goede arts.

Lieve **Frijke, Daan** en **Hilde**, bedankt dat jullie er waren voor de ontnuchterende momenten buiten het ziekenhuis. Jullie helpen mij herinneren dat er meer kanten aan het leven zitten dan het arts zijn. Gewoon naar een concert en gewoon kletsen, een keer niet over die ene patiënt; dit helpt mij ontzettend herinneren dat er nog een andere Kelly is. Help mij herinneren als ik weer een keer te veel aan het werk ben. @Daan: soms is het moedigste wat je kan doen, is gewoon jezelf zijn. Jij hebt mij dat laten zien en ik zal proberen om wat meer mijzelf te zijn, al is het onder een witte jas.

Lieve **papa**, ik wou dat je hier was. Dat ik een harde werker en doorzetter ben, heb ik niet van een vreemde. Ook je gulheid met je tijd, zal ik altijd herinneren en proberen uit te dragen. Dank je voor de tijd die ons hebt gegeven. Lieve **mama**, het waren tropenjaren hé? Niet zoals de fijne jaren op Curaçao waar we lekker op het strand zaten, maar van die jaren met maanden waar je opeens 10 jaar ouder wordt. Jij snapte het toen ik overspannen raakte, ook al vonden sommige het moeilijk te accepteren. Dank je wel voor je begrip en luisterend oor.

Lieve **Dion**, zoals jij zelf al vaker aangaf, heb jij misschien wel het ergste geleden van ons tweeën. Toen je mij leerde kennen in mijn tweede jaar geneeskunde, had je niet verwacht

dat je bijna 15 jaar later nog met een student zou samenwonen. Ook al was het nu een PhD-student. Toen het echt niet meer ging, was jij was de enige waar ik naar wilde luisteren. Want als een harde werker zoals jij zegt 'Stop' dan zal het wel waar zijn. Dank voor je geduld als ik weer 's avonds achter de computer zat. Ik hoop nog vele landen met je te bezoeken en misschien ooit in een tropisch land te settelen als je met pensioen kan (over 6 jaar toch?).

Kelly Hendriks, juli 2022

ABOUT THE AUTHOR

Kelly Dalva Hendriks-Spoor was born on September 25th 1987 in Oosterhout. She started secondary school at Mgr. Frencken college in Oosterhout but moved in her second year to Curaçao, where she finished secondary school at the Vespucci College in Willemstad. She moved back to the Netherlands to study Medicine at Maastricht University. During her electives, she focused on infectious diseases, which included an internship at the Steve Biko hospital in Pretoria South Africa and the Institute of Tropical Medicine in Antwerp, Belgium. In 2012, she obtained her degree in Medicine.

After obtaining her degree, she started working as a resident internal medicine not in training at The Sint Elisabeth Hospital in Tilburg and the Amphia in Breda from 2013 to 2016. In 2016, she started working as a physician-researcher in the department of Microbiology in the Tergooi MC hospitals taking on several antibiotic stewardship tasks. She continued her work as she started a PhD trajectory in the field of Infectious Diseases at The Julius Center for Health Science and Primary care under the supervision of Prof. Dr. M.J.M. Bonten (UMC, Julius Center), prof. Dr. T.J.M. Verheij (Julius Center), dr. P.D. van der Linden (Tergooi MC), dr. J.W. Dorigo-Zetsma (Tergooi MC) and dr. C.H.M. van Werkhoven (Julius center). During her PhD-trajectory she completed a postgraduate Epidemiology master with a specialization in Infectious Diseases.

During the completion of her thesis, she started working as a resident internal medicine not in training at Ikazia hospital in Rotterdam. In May of 2022, she started her residency in Internal medicine at the Ikazia hospital in Rotterdam, under the supervision of Drs. Marike Wabbijn and Dr. Adrienne Zandbergen (EMC). After her PhD defence, she would like to continue to be involved in the research of infectious diseases. Currently, she lives in Oosterhout, with her husband Dion and her dog, Lisha and two cats, Newt and Mary.