URINARY TRACT INFECTIONS IN GENERAL PRACTICE

Diagnostic strategies, bacteriology, and treatment options for multi-resistant bacteria

Marianne Bollestad

The Antibiotic Centre of Primary Care,

Department of General Practice,

Institute of Health and Society,

University of Oslo, Oslo, Norway

2019

Contents

Scientific environment

The ideas for this thesis spur from the research environment at the Antibiotic Centre for Primary Care, Department of General Practice, Institute of Health and Society, Faculty of Medicine, University of Oslo.

The candidate and the main supervisor, Morten Lindbæk, have their workplaces at the Antibiotic Centre for Primary Care. Morten Lindbæk is a professor in general practice. The co-supervisor Nils Grude is a consultant in clinical microbiology employed at Vestfold Hospital Trust and a part time employee at the Antibiotic Centre for Primary Care. During the PhD period the candidate has worked part-time at the Division of Infectious Diseases, Department of Medicine, Stavanger University Hospital. The clinical and academic input from colleagues at the hospital has been of great value during the thesis period.

Hege Salvesen Blix, professor at the Pharmaceutical Institute, University of Oslo and Hanne Brekke, consultant in clinical microbiology, Department of Medical Microbiology, Oslo University Hospital, provided valuable contributions to Paper II. Ingvild Vik, PhD student at the Antibiotic Centre for Primary Care and general practitioner at the Oslo Accident and Emergency Outpatient Clinic (OAEOC) has been an important collaborator on Papers II and III.

Paper IV was performed collaboratively with several microbiology departments in Norway.

The candidate, supervisors and collaborators collectively represent a diverse academic and clinical foundation for research on urinary tract infections (UTIs).

Acknowledgements

Abbreviations

AIC: Aikaike information criterion

CA: community acquired

CFU: colony forming units

ESBL: extended spectrum β-lactamase

CI: confidence interval

ESCMID: European Society for Microbiology and Infectious Diseases

EUCAST: European Committee on Antimicrobial Susceptibility Testing

ECDC: European Centre for Disease Prevention and Control

GP: general practitioner

HA: hospital acquired

IDSA: Infectious Disease Society of America

IRR: incidence rate ratio

MALDI-TOF: matrix-assisted laser desorption ionization-time of flight

MIC: minimal inhibitory concentration

NB: negative binomial

NORM: The Norwegian Organisation for Surveillance of Antimicrobial Resistance

NorPD: The Norwegian Prescription Database

NSAID: non-steroidal anti-inflammatory drug

OAEOC: Oslo Accident and Emergency Outpatient Clinic

OOH: out of hours

PBP: penicillin binding proteins

PCR: polymerase chain reaction

POC: point of care

PPV: positive predictive value

STI: sexually transmitted infection

UTI: urinary tract infection

Summary

Background

UTIs are common infections handled in primary care. The thesis explores diagnostic strategies and bacteriology of uncomplicated, lower UTIs. The thesis also evaluates a possible narrow-spectrum antibiotic treatment for UTI caused by extended spectrum β-lactamase (ESBL) producing *E. coli*.

Methods

Paper I: A prospective, randomised, controlled trial to evaluate a standardised diagnostic algorithm for uncomplicated lower UTIs.

Paper II: A retrospective comparison of cohorts to evaluate the bacteriological findings and resistance patterns in urine samples from women with uncomplicated lower UTIs over a 15 year time period in Norway.

Paper III: A prospective, single-centre cohort study to evaluate factors which predict longer symptom duration following empiric antibiotic treatment for a UTI and significant bacteriuria.

Paper IV: Prospective, multi-centre observational cohort study to evaluate the clinical and bacteriological efficacy of pivmecillinam treatment on uncomplicated lower UTIs caused by ESBL *E. coli* versus non-ESBL *E. coli*.

Results

Paper I: A median of three days until symptom resolution was noticed in both the group treated according to the diagnostic algorithm and the control group (log rank test p=0.3). During the follow-up period, 12% of the patients treated according to the diagnostic algorithm contacted a doctor versus 18% in the control group (p = 0.08).

Paper II: The main bacteriological agent in all the three study populations was *E. coli,* ranging from 78% to 82%. For *E. coli*, resistance to pivmecillinam demonstrated some variation, but retained below 9%.

Paper III: Urine dipstick positivity for nitrite (OR 3.22, 95% confidence interval (CI) 1.58–7.01, p<0.01) was associated with an increased probability of significant bacteriuria. The findings with a leukocyte esterase value of 2 or 3 + were associated with significant bacteriuria, but did not reach significance. Severe symptoms or significant bacteriuria were not predictors of longer symptom duration after empirical treatment.

Paper IV: The median duration until symptom resolution after treatment initiation was five days for the ESBL cases and three days for the non-ESBL controls, p<0.01. Among the patients treated with pivmecillinam 400 mg thrice daily, there was no significant difference in the risk for treatment failure between the ESBL cases and the non-ESBL controls regardless of the treatment duration (≤ 5 days OR 2.17, 95% CI 0.31-14.64, p=0.43, >5 days OR 2.16, 95% CI 0.32-14.65, p=0.43).b The ESBL cases demonstrated significantly higher rates of in vitro resistance to many other commonly used oral treatment options for UTI, including trimethoprim, co-trimoxazole and ciprofloxacin.

Implications of findings

A validated and standardised clinical registration form is a safe method to identify women with uncomplicated lower UTI who are likely to respond to antibiotic treatment. Stronger symptoms do not correlate with significant bacteriuria at presentation or protracted duration of symptoms following empiric treatment. However, strong symptoms can still be an indication for immediate antibiotics due to discomfort. Nitrofurantoin and pivmecillinam are appropriate first choice agents for empiric treatment of uncomplicated lower UTIs, and increased consumption of pivmecillinam has not caused marked increase in resistance rates for *E. coli.*

ESBL producing isolates demonstrate marked *in vitro* co-resistance to several oral treatment options. However, pivmecillinam treatment in dosage of 400 mg x 3 is a viable treatment option for community acquired (CA) UTI caused by ESBL producing *E. coli.*

List of papers

- Bollestad M, Grude N, Lindbaek M. A randomised controlled trial of a diagnostic algorithm for symptoms of uncomplicated cystitis at an out-of-hours service. Scand J Prim Health Care 2015;33:57-64. Published.

- Bollestad M (co-first author), Vik I (co-first author), Grude N, Blix HS, Brekke H, Morten Lindbaek. Bacteriology in uncomplicated urinary tract infections in Norwegian general practice from 2001-2015. Brit J Gen Pract Open 2017 DOI: https://doi.org/10.3399/bjgpopen17X101145. Published.

- Bollestad M, Vik I, Grude N, Lindbaek M. Predictors of symptom duration and bacteriuria in uncomplicated urinary tract infection. Scand J Prim Health Care. 2018;3:1-9. Published.

- Bollestad M, Grude N, Solhaug S, Raffelsberger N, Handal N, Nilsen HJ, Romstad M, Emmer A, Tveten Y, Soeraas A, Jenum P, Jenum S, Moeller-Stray J, Weme E, Lindbaek M, Simonsen GS. Clinical and bacteriological efficacy of pivmecillinam treatment for uncomplicated urinary tract infections caused by ESBL-producing *Escherichia coli*: a prospective, multi-centre, observational cohort study. J Antimicrob Chemother. 2018;73:2503-2509. Published.

Aim and objectives of the thesis

The overall aim of this thesis was to improve the handling of UTIs diagnosed and treated in primary health care and highlight the current challenges, including increased resistance rates and the presence of multi-resistant microbes.

The objectives of the individual studies were:

Paper 1: To compare the clinical outcome of patients presenting with symptoms of acute uncomplicated UTI who were treated after a regular consultation by a doctor, with patients who received treatment following a diagnostic algorithm. The secondary objectives of the study were to compare the safety and rate of complications in the two groups.

Paper II: To evaluate the bacteriological findings and resistance patterns in the urine samples from women with uncomplicated lower UTI in three cohorts during the time period of 2001-2015 in Norway, and assess the relationship between the use of antimicrobial agents in the treatment of UTI and the resistance patterns in the country during 2000-2015.

Paper III: To identify the factors which predict a significantly longer duration of symptoms in patients with acute uncomplicated UTI after empirical antibiotic treatment and to identify the factors predicting significant bacteriuria in patients presenting with an acute uncomplicated UTI.

Paper IV: To examine the clinical and bacteriological efficacies of pivmecillinam treatment on CA-UTI caused by ESBL producing *E. coli* versus CA-UTI caused by non-ESBL producing *E. coli* in an out-patient setting.

1. Introduction

1.1   Preface

Whenever I am asked what the topic of my thesis is, the answer UTI very often seems to evoke interest, especially among non-healthcare personnel. This interest is possibly due to personal experiences with the condition. Uncomplicated lower UTIs are common. Although the condition is painful, the risk of progression to an upper UTI is low, even without antibiotic treatment. Antibiotic treatment is the current cornerstone of UTI treatment and accounts for a large proportion of total antibiotic prescriptions (1, 2). Symptom duration is longer for patients who do not receive antimicrobial therapy (3-7).

From a global perspective, the total antibiotic consumption, specifically the use of broad-spectrum antibiotics, is worrying (8). Alternative treatment strategies to known antibiotics are limited (9, 10).

The swift increase in the prevalence of ESBL producing Enterobacteriaceae causing infections including CA-lower UTIs poses therapeutic challenges. Even though the clinical condition is relatively mild, the microbe's resistance pattern may warrant broad spectrum antibiotics. Possible narrow spectrum alternatives are sought after.

My thesis explores the diagnostic methods and strategies for the treatment of UTIs in general practice. Furthermore, I have studied the resistance patterns, and specifically ESBL producing *E. coli* and the possibility of a narrow-spectrum treatment option (pivmecillinam).

1.2 Urinary tract infection

1.2.1 Definition

UTIs are categorised as lower/upper and uncomplicated/complicated.

A lower UTI (cystitis) is diagnosed when the presenting symptoms affect only the bladder. The cardinal symptoms include pollakisuria, dysuria and urgency. An upper UTI is suspected if the acute symptoms also include flank pain and/or fever (> 38°C) (11).

A UTI can be complicated or uncomplicated depending on the presence of comorbidity. An uncomplicated UTI is limited to otherwise healthy individuals who are diagnosed outside the hospital and possess no known abnormality of the urinary tract. For women, the definition applies if they also are pre-menopausal and non-pregnant (11-13).

UTIs are classified as complicated in persons with comorbidity that may affect the treatment outcome in a negative manner. Relevant conditions include: infections acquired while in hospital care, signs of sepsis, instrumentation of the urinary tract, anatomical abnormalities of the urinary tract, diabetes mellitus, immunosuppression, pregnancy, recent antibiotic use and kidney failure (11-13).

Complicated UTIs may be more difficult to diagnose due to subtle and/or atypical symptoms and might also be quite challenging to treat because of the increased risk of multi-resistant bacteria and inadequate treatment response, for example due to anatomical defects (11-13).

The most common presentation in general practice is an uncomplicated lower UTI.

1.2.2 Epidemiology

Urinary tract infection is common worldwide, and is the most common infection diagnosed in women in a primary health care setting (14).

Around 37% of adult women in England report having had at least one UTI in their lifetime, and 29% report more than one episode. Approximately half of women reported their last episode as fairly or very severe and the vast majority (95%) consulted a health professional for assessment and treatment (14-16). A world-wide prevalence of 0.7% is estimated for CA UTIs (17).

An annual incidence of 0.5% -0.7% is reported for uncomplicated lower UTIs in young women (18). However, a much larger percentage (around 20%) report dysuria (19). The rate of lower UTIs is much higher than that of upper UTIs. It is estimated that around 12-13 cases of the latter occur per 10 000 of the female outpatient population (20).

The human anatomy possesses the urethra as an opening for the excretion of urine. The structure, however, simultaneously allows the entry of microbes into the bladder and the urinary tract. Owing to this factor, UTIs occur commonly. For women, the proximity of the urethra to the vaginal and rectal openings and the short distance from the urethral opening to the bladder is associated with the increased frequency of UTIs (21). Bacterial influx to the bladder may result in colonisation or infection. Host and bacterial factors play a part in determining the risk of an infection.

A marked increase in antibiotic consumption is observed in late teenage women, which corresponds to, and is partially explained by the increased incidence in UTIs from this age onwards.

Figure 1. Proportion of the Norwegian population who dispensed at least one prescription of antibiotics in ambulatory care in 2017 (1).

The exact incidence is difficult to estimate as the disease is not reported (13). In addition, the diagnostic criteria of UTIs, uncomplicated lower UTIs especially, are a topic of debate. The main point of discussion is whether or not the diagnosis can and should be made based on the symptoms alone (22, 23).

CA-UTIs in men have traditionally been viewed as complicated infections and antimicrobials with relatively high tissue absorption are prescribed for longer duration. Nevertheless, in the last approximately five years publications have challenged this notion and have suggested that men with lower UTIs without other complicating factors should be treated with empiric first choice agents as recommended for women (24).

A study from Ireland compared the male and female treatment outcomes with the first-line treatment choice of nitrofurantoin. The re-consultation rates were similar for both the genders treated with the drug. In accordance with the guidelines for treatment of UTI in Ireland the men included in the study were treated for seven days versus three

days for women. The authors recommend that men and women should receive empiric first-line treatment according to the guidelines (25).

1.2.3 Diagnosis

For uncomplicated lower UTIs, clinical symptoms (dysuria, urinary frequency and urgency) are the mainstay of diagnostics. A presentation with typical clinical symptoms and the absence of vaginal symptoms (vaginal discharge or irritation) yielded a sensitivity of about 90% based on the findings of a meta-analysis (26). A review article uncovered that a combination of symptoms and signs (nitrite positive, leukocyte esterase positive, hematuria, moderately severe dysuria and moderately severe nocturia) provided a sensitivity of 76% and a relatively acceptable specificity of 74% (27). The correlation between patient-initiated treatment and confirmed UTI diagnosis varies: studies with poorer correlation have indicated a relatively high percentage of vaginal symptoms and chlamydia infections (28-30).

Women with a history of cystitis, frequent somatic symptoms, presence of bacteria resistant to the chosen antibiotic regime and severe symptoms at baseline are more likely to have symptoms of acute cystitis lasting longer than three days after the initiation of treatment (31).

A urine dipstick analysis may be recommended as a part of the diagnostic procedure (14, 26, 32, 33). Detection of nitrites, leukocyte esterase and nitrites, or erythrocytes and nitrites on the urine dipstick is considered to be moderately sensitive and specific for detecting UTI when using a positive culture as the gold standard (33-36).

Noticeably, when a positive urine culture is used as the gold standard, a negative urinary dipstick test cannot rule out the diagnosis in women with high pretest probability (31). Antibiotic treatment administered to women with clinically suspected UTI but negative urine dipstick test significantly reduces their symptoms (37).

Clinical examination has not been proven to improve the diagnostic accuracy of UTIs (38). A urine culture is not routinely recommended for CA, uncomplicated lower UTIs (23, 39).

Relying on clinical practice guidelines is an established tool for the management of uncomplicated lower UTIs. Evaluation following the implementation of clinical guidelines has revealed that its use has decreased the laboratory utilisation and overall costs while improving the adherence to antibiotic guidelines (40-42).

A validated, self-reporting questionnaire as a diagnostic aid is of great value for identifying women with uncomplicated lower UTIs who qualify for standard treatment regimens. The presence of symptoms suggestive of uncomplicated lower UTI (dysuria, urgency and frequency) and the absence of symptoms and signs suggestive of other conditions (vaginal irritation/discharge and fever) determine inclusion. Relevant complicating factors (diabetes mellitus, pregnancy) exclude screened women from further treatment according to the algorithm (43).

Acute pyelonephritis is diagnosed by the presence of clinical symptoms (fever, rigors or costovertebral angle tenderness) and relevant bacteriuria (44,45). A urine culture is recommended for all patients with suspected pyelonephritis (uncomplicated or complicated) (23).

1.2.4 Treatment options

Antimicrobial agents are the mainstay for treating UTIs. Refraining from antibiotic therapy has been shown to increase the duration of symptoms and decrease the rate of clinical and bacteriological cure (4, 31, 46, 47).

Current Norwegian guidelines recommend pivmecillinam 200 mg x 3 for three days, nitrofurantoin 50 mg x 3 for three days and trimethoprim 160 mg x 2 or 300 mg x 1 for 1-3 days as equal empirical treatment options for uncomplicated lower UTI. For complicated lower UTI the same agents are recommended, however the length of the treatment should be extended to 5-7 days (48).

A three-day treatment regimen for uncomplicated lower UTIs is shown to be equally effective in providing symptomatic relief when compared with longer treatment regimens (5 days or longer). Nevertheless, the rate of bacteriological cure is higher in the groups who received treatment for a prolonged duration (49, 50).

For upper UTIs, that following clinical consideration can be treated out of the hospital, co-trimoxazole 160 mg + 800 mg (2 tablets) x 2 is recommended. Pivmecillinam 400 mg x 3 and ciprofloxacin 500 mg x 2 can also be used. The recommended treatment duration is 7-10 days (48).

Guidelines for the other Scandinavian countries (Sweden and Denmark) are generally in line with the Norwegian recommendations, but the Swedish guidelines for uncomplicated lower UTIs endorse only pivmecillinam and nitrofurantoin as first choice agents for empiric treatment. Trimethoprim and cefadroxil (a cephalosporin) are recommended as second choice treatment options (51).

Swedish guidelines include two of the third generation cephalosporins (cefixim and ceftubutin) as the second choice oral treatment options for acute pyelonephritis (febrile UTI) (51).

Noticeably, trimethoprim is not considered as a first line agent in Denmark for uncomplicated lower UTIs and co-trimoxazole is not included as an empiric oral treatment option for acute pyelonephritis (52).

Guidelines for other European countries differ somewhat from those existing in Norway and Scandinavia. Specifically pivmecillinam is not considered a first choice agent for antimicrobial treatment of lower UTIs, but as a secondary choice. Several nations including France recommend fosfomycin as a first choice empiric agent (53-56).

The Infectious Disease Society of America (IDSA) recommends nitrofurantoin, co-trimoxazole, fosfomycin or pivmecillinam as first choice empiric agents for lower uncomplicated UTIs (39, 57). The most commonly used Australian guidelines recommend trimethoprim, cephalexin, amoxicillin clavulanic acid and nitrofurantoin as equal first choice agents. Fosfomycin and pivmecillinam are not registered antimicrobial agents, but are available via a special access scheme (58).

Internationally recommended oral treatment options for acute pyelonephritis include ciprofloxacin, amoxicillin clavulanic acid and cephalexin. Australian guidelines also advise trimethoprim as an oral treatment option for mild pyelonephritis (55, 58).

Fosfomycin and nitrofurantoin have gained international focus as oral empiric treatment options owing to the increased rates of multi-drug resistant microbes (including ESBL producing Enterobacteriaceae) (59). A recent study has identified nitrofurantoin to be superior to fosfomycin for the clinical and bacteriological cure of uncomplicated lower UTIs (60).

International treatment guidelines with relevant adjustments to local resistance data, clinical aspects, safety data and pharmacokinetics are enticing possibilities and would possibly pave the way to an enhanced focus on the correct use of antimicrobial agents.

1.2.5 Management strategies for uncomplicated lower UTIs

Uncomplicated lower UTIs account for the vast majority of UTIs diagnosed in primary health care setting and emphasis has been placed on identifying alternative, antibiotic sparing treatment strategies.

The use of delayed prescription in which empiric antibiotic therapy is started only after 48 hours following diagnosis if the symptoms persist has been shown to decrease the use of antimicrobial treatment for uncomplicated lower UTIs by about 20%. However, the duration of symptoms increased (61).

Non-steroidal anti-inflammatory drugs (NSAIDs) have been studied in several randomised controlled trials published in the last few years. These drugs are inferior to antibiotics in obtaining symptomatic relief, but can constitute an appropriate treatment strategy for a selected group of women (62). The difference between the two groups varies in the published studies, perhaps due to different choices of empiric antimicrobial therapy and NSAID, including their dosage. Existing data cannot adequately address whether or not the use of NSAIDs during an infection increases the risk of progression to pyelonephritis (3, 6, 7, 63). A meta-analysis is planned to address this issue (Ingvild Vik, personal communication).

Ibuprofen given along with a delayed prescription for uncomplicated lower UTI has been established to reduce the number of patients resorting to antibiotics by one per seven women (64).

It is noteworthy that adequate hydration reduces the episodes of recurrent uncomplicated UTIs and should be ensured for all women at risk (65).

1.2.6 Bacteriology and bacteriological resistance

Escherichia coli (E. coli) is the most common pathogen isolated in CA-UTI (66, 67). Other pathogens commonly identified are *Staphylococcus saprophyticus (S. saprophyticus)*, *Klebsiella pneumoniae (K. pneumoniae), Enterococcus species (spp.), Enterobacter spp.* and *Proteus mirabilis (P. mirabilis)* (68, 69).

In uncomplicated UTIs, *E. coli's* dominance as the causative agent is more prominent (75%) than in complicated UTIs (65%). *S. saprophyticus* and *K. pneumoniae* are the second most common agents (both 6%). In complicated UTIs, *Enterococcus spp.* (11%), *K. pneumoniae* (8%) and *Candida albicans (C. albicans)* (7%) are the second most common agents (70).

In men too, *E. coli* is the dominant bacterial agent responsible for 51% of UTIs in all age groups. The other half consists of various organisms including *Klebsiella spp., P. mirabilis* and *Enterococcus spp.* (71).

It has been shown that a rather large percentage of women with typical symptoms of UTI have a negative urine culture (approximately 20-30 %). The use of polymerase chain reaction (PCR) to enhance the bacteriological diagnostic methods has shown that in nearly all urine samples of women with typical symptoms, a uropathogen is found. As with conventional uropathogen culturing, *E. coli* is by far the most dominant microbial agent when this technique is used (72).

Data on uropathogen distribution in uncomplicated CA-UTI from Belgium spanning a 20-year period (1995-2005-2015) have reported the species distribution to be relatively stable, with an insignificant increase in the rate of *E. coli* isolation (78.4%-80.3%-81.6%). *S. saprophyticus* was the second most commonly isolated agent in all three

cohorts studied, and there was no significant change in how frequently the microbe was isolated (73).

E. coli has displayed low resistance to fosfomycin and nitrofurantoin in the past two decades and the sensitivity remains at nearly 100% (73-76).

European data depict a significant increase in the resistance of *E. coli* to commonly used oral treatment options for UTI, namely fluoroquinolones, co-trimoxazole and trimethoprim. Increased *E. coli* resistance towards nitrofurantoin is also reported in some studies (76-78).

Canadian data on uncomplicated UTIs from 2015 showed comparable sensitivity rates for co-trimoxazole and nitrofurantoin, but the research reported higher rates of ciprofloxacin sensitivity than the European data (90.3%) (79). The Australian data are in line with Canadian findings on reporting lower levels of ciprofloxacin resistance for *E. coli* causing UTI (7.3% resistance). Trimethoprim and co-trimoxazole resistance rates exceed 20% (80).

Data from Poland contradict these observations and claim high overall resistance rates for the common uropathogens to first-line treatment regimens, including fosfomycin and nitrofurantoin (81).

Multi-drug resistant bacteria causing UTIs are increasing, with ESBL producing Enterobacteriaceae being the most prevalent and clinically important group. Data from the European Centre for Disease Prevention and Control (ECDC) in 2017 found that all European countries report ESBL producing *E. coli* at 5% and above for the invasive isolates. The vast majority of European countries report percentages between 10 and 25, whereas Italy, Slovakia, Bulgaria and Cyprus stand out with percentages between 25 and 50 (82).

UTIs caused by ESBL producing microbes are not negligible with rates nearing 10% even in countries with low resistance (83).

Updated knowledge on local microbial findings and resistance rates is important as UTIs are common and tend to be treated empirically. As the ESBL producing

Enterobacteriaceae are relatively common, empiric treatment should account for this subgroup in many of countries. Sentinel surveillance is suggested as a method of keeping this knowledge up to date as national and international guidelines do not suggest routine culturing of urine samples from uncomplicated UTIs (84-86).

Justly, emphasis is placed on the resistance rates at the group level: however, the effect on the individual following antibiotic treatment is not negligible. A meta-analysis also uncovered that persons receiving antibiotics for a respiratory tract infection or a UTI develop bacterial resistance to the given drug. This effect was most prominent in the first month succeeding treatment but could last up to 12 months (87).

1.3 ESBL producing microbes

1.3.1 Background

Knowledge of transferable resistance to cephalosporins by the use of plasmids was gained in the 1980s (88, 89). There has been a steady rise in infections caused by multi-resistant bacteria in general. The rise in ESBL producing Enterobacteriaceae is an especially worrying situation (1, 83, 90-93). The role of such organisms in CA-UTIs has been a clinically relevant issue since the late 1990s (94).
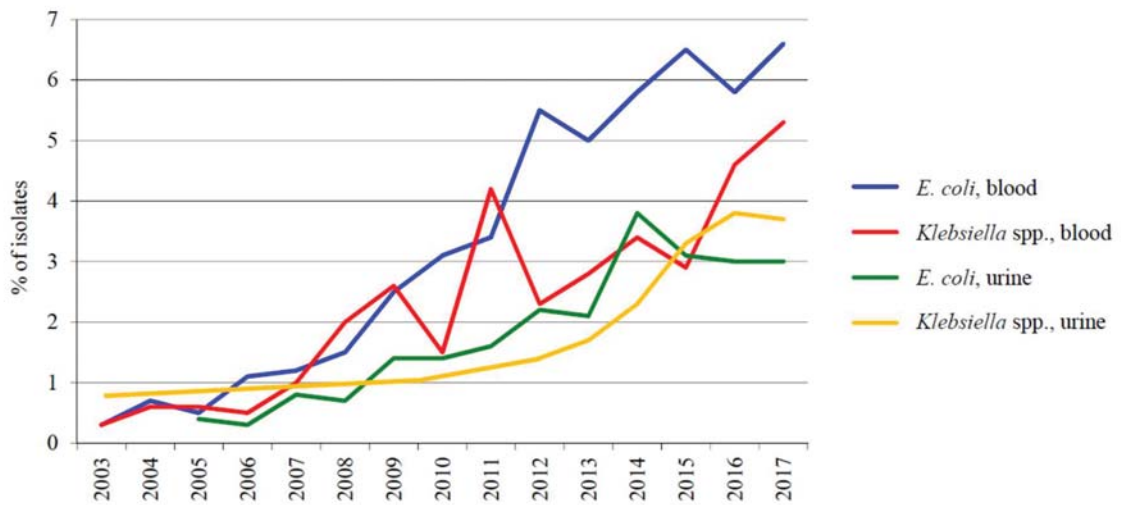
Figure 2. ESBL producing E. coli and K. pneumoniae isolated from blood and urine samples in 2017 in Norway.

The term ESBL was originally coined to elucidate the difference from broad spectrum β-lactamases, and to signify the fact that ESBLs also mediate resistance to extended spectrum cephalosporins.

ESBL are enzymes that offer resistance to most β-lactam antibiotics, including penicillin, cephalosporin and the monobactam aztreonam, by hydrolysing the β-lactam ring. Current classification methods divide ESBLs into classic ESBLs ($ESBL_A$), mixed ESBLs ($ESBL_M$) and carbapenemases ($ESBL_{CARBA}$). Examples of $ESBL_A$ β-lactamases include CTX-M, TEM-ESBLs and SHV ESBLs. Class $ESBL_M$ β-lactamases are divided into two subgroups which include plasmid mediated Amp C ($ESBL_{M-C}$) and OXA ESBLs ($ESBL_{M-D}$). For $ESBL_{CARBA}$, a subdivision into $ESBL_{CARBA-A}$ (fex KPC), $ESBL_{CARBA-B}$ (MBL) and $ESBL_{CARBA-D}$ (OXA-carbapenemase) is suggested (94,95).

$ESBL_A$ producers are non-susceptible to extended-spectrum cephalosporins and exhibit clavulanic acid synergy. $ESBL_M$ producers are non-susceptible to extended-spectrum cephalosporins and possess the phenotype $ESBL_{M-C}$ or the genotype $ESBL_{M-D}$. $ESBL_{CARBA}$ are non-susceptible to extended spectrum-cephalosporins and at least one carbapenem and $ESBL_{CARBA}$ are detected with phenotypic and/or genotypic methods (95).

Known risk factors for CA bacteriuria caused by ESBL-producing Enterobacteriaceae include clinical and lifestyle factors. Travel to North-America, Africa and Asia and recreational fresh water swimming are associated with increased risk of ESBL carriage (83, 96). Clinical factors comprise old age, use of proton pump inhibitors or H2 blockers, recurrent UTIs, prostatic disease, prior hospitalisation, and recent use of antibiotics (fluoroquinolones and penicillins, except pivmecillinam) (83, 91, 92, 96-99).

Following colonisation by ESBL producing Enterobacteriaceae, the duration of faecal carriage and the risk factors for prolonged carriage are not completely known. A Norwegian study of individuals with CA-UTIs caused by ESBL producing *E. coli* or *K. pneumoniae* estimated the ESBL point prevalence at follow-up. The authors discerned a prevalence of 61% after four months, 39% after 13 months and 15% after three years or more of follow-up. It is noteworthy that the known risk factors of infections caused by ESBL producing microbes, including recent antibiotic use and travel to high-prevalence countries, were not associated with prolonged ESBL carriage. However, certain phylogroups of *E. coli* were linked with prolonged faecal carriage (100). This finding is supported by Swedish research which found that 43% of the included patients were still carriers 12 months following their initial infection (101).

Nonetheless, studies concerning travel to high-endemic areas reported shorter duration of faecal carriage (< 3 months) (102).

1.3.2 Treatment options

For hospitalised patients infected with ESBL producing Enterobacteriaceae, antibiotics are usually administered intravenously and the drugs of choice are the carbapenem. Aminoglycosides are viable alternatives (103-105). Broad-spectrum β-lactams may be plausible alternatives based on the resistance data (fex ceftazidim-avibactam and piperacillin-tazobactam), however clinical data are limited (106-108).

A cephalosporin (cefotaxime) with the addition of amoxicillin clavulanic acid has demonstrated *in vitro* synergy in the treatment of ESBL producing *E. coli*. *In vivo* studies in a murine model noted the combination to be as effective as imipenem (109).

These drugs are broad-spectrum agents and oral formulations are not available, hence they are not plausible options for the treatment of mild to moderate CA infections.

Oral treatment options are limited for patients infected with ESBL-producing Enterobacteriaceae. Fosfomycin, pivmecillinam, oral β-lactam antibiotic and clavulanic acid combination, and nitrofurantoin have been identified as potential alternatives based on antimicrobial susceptibility testing.

A pharmacodynamic study has suggested that nitrofurantoin is effective against ESBL producing *E. coli*, and *in vitro* studies indicate a relatively low resistance rate (9%) for ESBL producing *E. coli* (110-112). However, the drug should be considered as an alternative only in cases of lower UTIs.

ESBL producing Enterobacteriaceae show low levels of resistance to fosfomycin (113-115). Data on clinical cure are sparse: nevertheless in a study from India 93% of patients with UTI caused by ESBL producing Enterobacteriaceae were reported to be cured following fosfomycin treatment (n=28) (116). The drug has also been suggested as an appropriate outpatient or step-down therapy for patients with UTI caused by ESBL producing Enterobacteriaceae (104).

Clinical studies on the efficacy of pivmecillinam treatment for CA-UTI caused by ESBL-producing Enterobacteriaceae are limited and involve a small sample size (117-121).

Preliminary results are inconsistent and vary from favourable bacteriological and clinical cure rates to instances of failure.

The largest clinical study consisting of 41 patients with CA-UTI caused by ESBL producing *E. coli* identified that 44% demonstrated clinical treatment failure with the use pivmecillinam during the follow-up period. High minimal inhibitory concentration (MIC) values have been suggested as a predictor of treatment failure (118).

One study has indicated increased rates of pivmecillinam resistance with the use of a high inoculum (10^6 colony forming units (cfu)/spot versus 10^4 cfu/spot): the addition of clavulanic acid reversed the resistance and increased the sensitivity from 40% to 98% (122).

1.4 Pivmecillinam

Pivmecillinam is widely used in the Scandinavian countries, and the drug is included in internationally recommended empirical treatment guidelines for uncomplicated lower UTIs (39, 48). The worldwide increase in the incidence of resistant Gram negative microbes causing hospital acquired (HA) and CA-UTIs has led to increased interest in older antimicrobial agents, including pivmecillinam.

The use of pivmecillinam was first reported in 1972 (123). Clinical cure rates for uncomplicated lower UTIs with pivmecillinam treatment are high (124). The compound is a 6-amidinopenicillanic acid derivative with selective activity against Gram-negative bacteria. Pivmecillinam, the pivaloyloxymethyl ester of mecillinam, is absorbed from the gastrointestinal tract and hydrolysed to its active form of mecillinam (125).
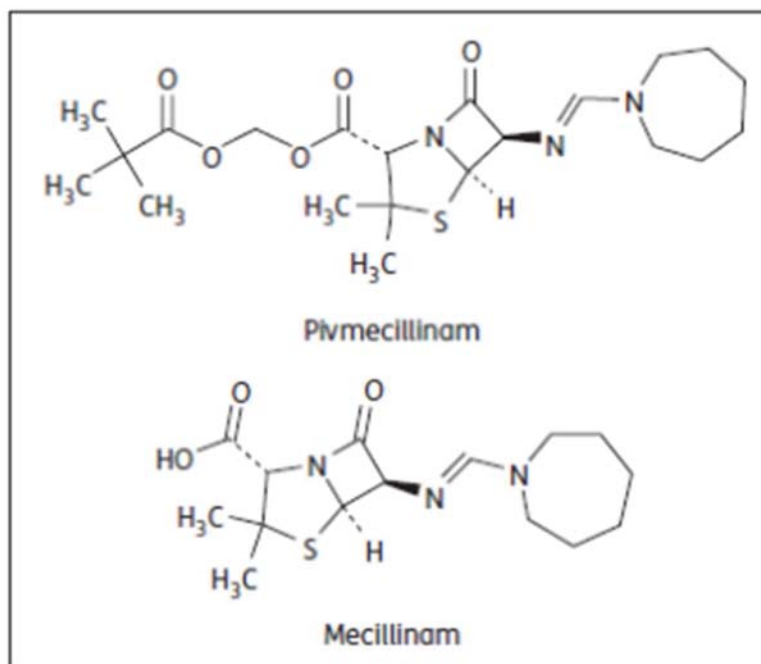
Figure 3. Chemical structure of pivmecillinam and the active form mecillinam (126).

The antimicrobial agent displays the beneficial characteristics of being highly concentrated in urine, possesses the ability to be administered in the case of impaired renal function, and exerts minimal impact on the gut and vaginal flora (126-129).

Peak plasma concentrations are reached within one hour (5mg/kg) for a dose of 400 mg pivmecillinam given to an adult. Mecillinam is well distributed in the body fluids, but only lower concentrations are detected in the foetus and breast milk. Over 40% of the ingested dose is excreted in the urine within the first 12 hours (130).

Pivmecillinam has potent antimicrobial activity against Enterobacteriaceae which include the most common uropathogen *E. coli*, *K. pneumoniae* and *P. mirabilis*. Treatment effect has also been demonstrated against the Gram positive microbe *S. saprophyticus*, owing to the high concentration of the drug in the urine (67).

β-lactams are a large group of commonly used antibiotics which have been known for a long time, and their capacity to interfere with bacterial cell wall assembly has been recognized since the 1950s (131). The specific pharmacokinetic and pharmacodynamic

properties of mecillinam have been researched and established to be related to the MIC of the drug. The drug exerts bactericidal effects (132).

The β-lactam drug class is known to target specific enzymes named penicillin binding proteins (PBPs), which are important components of the bacterial cell wall. Bacterial cells are surrounded by a cell wall, which protects the cytoplasmic membrane from rupturing due to osmotic forces. Bacteria are dependent on the cell wall for growth, cell division and maintenance of their cellular structure. The bacterial cell wall is composed of glycan chains with attached peptides that are cross-linked to adjacent glycans to form a mesh structure (133). The synthesis of the peptidoglycan polymer is disrupted by the β-lactam antibiotics owing to inactivation of the enzyme PBP (134).

Bacteria possess several PBPs which build peptidoglycans (135). Most β-lactam drugs inhibit several PBPs, thereby making the exact process difficult to interpret. However, mecillinam inhibits only PBP 2 in *E. coli.* Hence, the drug's effect on *E. coli* has been studied in detail to identify the exact mechanism by which the β-lactam antibiotics induce cell death. It has been asserted that mecillinam interferes with the peptidoglycan synthesis and induces a cycle of the compound's synthesis and degradation, which consumes the cellular resources. Inhibition of PBPs leads to several changes in the bacterial structure, including irregularities in the cell wall elongation and predefined permeability. These changes may lead to cell death and lysis (133).

Mecillinam's specific and high affinity for PBP-2 is a possible explanation for several observed synergistic effects. *In vitro* synergistic effects has been observed with the combination of mecillinam and other β-lactams for the treatment of infections by Enterobacteriaceae (136). For β-lactamase producing Enterobacteriaceae isolates with mecillinam resistance, effect has been noted upon the addition of clavulanic acid or sulfbactam (a β-lactamase inhibitor) (137-138).

Widespread use of pivmecillinam over many years has not caused any significant increase in resistance rates among uropathogenic *E. coli,* and the practice has exerted only limited effects on the normal microflora (128, 129). In a study comparing the

antimicrobial activity of mecillinam with other β-lactam antibiotics, the drug displayed significantly greater antibacterial potency and stability to β-lactamase hydrolysis in the TEM-, IRT- and AmpC-producing isolates (139). Owing to its's limited resistance driving effect and evidence of significantly higher antibacterial potency and *in vitro* stability to β-lactamase hydrolysis than other penicillins, pivmecillinam has recently been suggested as an oral treatment option for CA-UTI caused by ESBL-producing Enterobacteriaceae (1, 121, 126, 139-141).

A study of pivmecillinam versus placebo in bacteria resistant to mecillinam treatment (80% *E. coli,* but the study included other uropathogens as well) demonstrated higher cure rates and lower mean symptom scores at follow-up for the cohort treated with pivmecillinam (67). At the time of publication, the authors speculated as to whether the treatment response for *in vitro* resistant microbes was related to comparatively higher concentration of mecillinam in urine and the relatively low MIC for the uropathogens.

Reversion of a specific type of mecillinam resistance (cysB gene mutation) by *E. coli* has been demonstrated. The authors found that the isolates were more susceptible to mecillinam when grown in urine, and some of the strains demonstrated complete reversion of resistance. In addition, a correlation was observed between low osmolality and increased antibiotic susceptibility (142).

Therefore, several factors support the use of pivmecillinam as an empiric treatment choice for CA-UTI.

According to the Norwegian national guidelines, pivmecillinam is recommended at a dosage of 200 mg administered thrice daily for three days to treat uncomplicated lower UTIs. Furthermore, the drug can be considered as an oral treatment option for acute pyelonephritis at a dosage of 400 mg given thrice daily for 7-10 days (48).

The antibiotic is commonly used in the Nordic countries for acute uncomplicated UTIs, and is among the four recommended agents for the first-line therapy of acute uncomplicated UTIs. However, the drug has limited availability internationally. In the International Clinical Practice Guidelines from 2011 endorsed by Infectious Disease

Society of American (IDSA) and European Society of Microbiology and Infectious Diseases (ESCMID) a dose of 400 mg for 3-7 days is recommended (39).

2. Material and Methods

2.1 Table 1 - Overview of the studies

Paper	I-The diagnostic algorithm study	II-The bacteriology study	III- The predictor study	IV-The ESBL UTI study
Design	Prospective, randomised, controlled trial.	Retrospective, comparison of cohorts.	Prospective, single-centre cohort study.	Prospective, multi-centre, observational cohort study.
Study population	Women aged 16-55 years (n 441).	Women aged 16-55 years (n 186, 406, 259).	Women aged 16-55 years (n 441).	Women aged ≥16 years with pivmecillinam-treated UTIs caused by *E. coli* with or without ESBL production (n 88, 74).
Data collection period	2010-2011	2001, 2010-2011, 2013-2015	2010-2011	2013-2016
Data collection method	Registration of data pertaining to women with symptoms of uncomplicated cystitis presenting at a primary care out-of-hours service.	Recruitment of patients from general practice at three different time periods.	Registration of data pertaining to women with symptoms of uncomplicated cystitis presenting at a primary care out-of-hours service.	Recruitment of data from general practice.
Data analysis	Descriptive analyses. Kaplan-Meier plot to evaluate the primary outcome measure.	Descriptive analyses. Chi square calculator to compare the aggregated data.	Descriptive analyses. Logistic regression analyses to identify the predictors of bacteriuria, and negative binomial model to identify the predictors of longer symptom duration.	Descriptive analyses. Kaplan Meier and log rank tests to evaluate the time until symptom resolution. Logistic regression models.

2.2 The study settings

Patient recruitment for the data presented in the studies was performed in the general practice setting.

In Norway, universal health care is provided for all the inhabitants. From 2001, all the residents are assigned to a general practitioner (GP) of their choice. These professionals play a central role in the health care system, and are responsible for the assessment, treatment and follow-up of their patients. Referral to hospital care is made by the GP. As of 31.12.2017, 99.3% of the nation's population was registered with a GP receiving reimbursement from the government. The number of practicing GPs is increasing, and as of 31.12.2017, 4759 practitioners with government reimbursement were registered. The average number of persons registered per GP was 1106 at the same point of time (143).

The first cohort (2010-2011) of papers II and IV were recruited in the general practice setting.

GP run out-of-hours (OOH) services exist in all municipalities (143). Admissions to secondary care after the regular office hours is largely done through OOH services, in Norwegian: Legevakt. In circumstances of acute emergencies, patients are driven directly to the emergency departments by ambulance personnel.

Data collection for paper I, III and the latter two cohorts of papers II were performed at the Oslo OOH service, OAEOC.

2.3 The diagnostic algorithm study

Data collection

Since 2007, OAEOC has utilised a diagnostic algorithm to identify women with suspected uncomplicated lower UTI (figure 4).

Diagnostic algorithm: uncomplicated UTI

	Yes	No
Are you a woman aged 16-55 years?	☐	☐
Do you have –painful urination? *mild* ☐ *moderate* ☐ *strong* ☐	☐	☐
-increased frequency of urination? *mild* ☐ *moderate* ☐ *strong* ☐	☐	☐
-increased need to urinate?	☐	☐
-visible hematuria?	☐	☐
Are you pregnant or breastfeeding (infant under 1 month of age)? ☐		☐
Do you have diabetes or kidney disease?	☐	☐
Do you have -fever?	☐	☐
-reduced general condition?	☐	☐
-back/flank/stomach pain?	☐	☐
Do you have -increased vaginal secretion?	☐	☐
-itching/irritation?	☐	☐
-STRONG lower abdominal pain?	☐	☐
Have you had pain for more than 7 days?	☐	☐
Have you in the past 4 weeks had a urinary tract infection or used a urinary tract catheter?	☐	☐
Are you using antibiotics now?	☐	☐
Have you previously had an allergic reaction to penicillin?	☐	☐
Do you have esophageal passage problems?	☐	☐
Do you use the medication Probecid?	☐	☐
Temperature (<38° C)	☐	☐

	Delegated treatment	Doctor's consultation
Treatment chosen by support staff:	☐	☐

Figure 4. Diagnostic algorithm.

The algorithm was developed by Endre Sandvik, the head of OAEOC at that time, on the basis of known UTI symptoms. Relevant exclusion criteria included symptoms and comorbidities suggesting a complicated UTI or other diagnoses. The diagnostic algorithm had not been validated before the present study.

In the course of 14 months from September 2010 to November 2011, 441 women in the age group of 16-55 years were included in the study. The criteria for inclusion were dysuria and increased frequency of urination. Visible hematuria and enhanced urinary urge were also registered, but such factors did not determine inclusion. The criteria for exclusion were relevant co-morbidities (diabetes, kidney disease, or

esophageal passage problems), symptoms indicative of pyelonephritis, complicated UTI or sexually transmitted infection (STI), ongoing antibiotic/probenecid treatment, fever, and previous allergic reaction to penicillin.

All patients included in the study fulfilled the criteria for treatment according to the diagnostic algorithm; however, the individuals were randomised to therapy according to the diagnostic algorithm or a regular doctor's consultation after the screening.

Randomisation was performed by the registering nurse by drawing the number '1' or '2' from an envelope, which was generated by the study coordinator in equal amounts. We did not use block randomisation. At the end of the inclusion period, a higher number was included in the group treated as per the diagnostic algorithm (242) versus the control group (191).
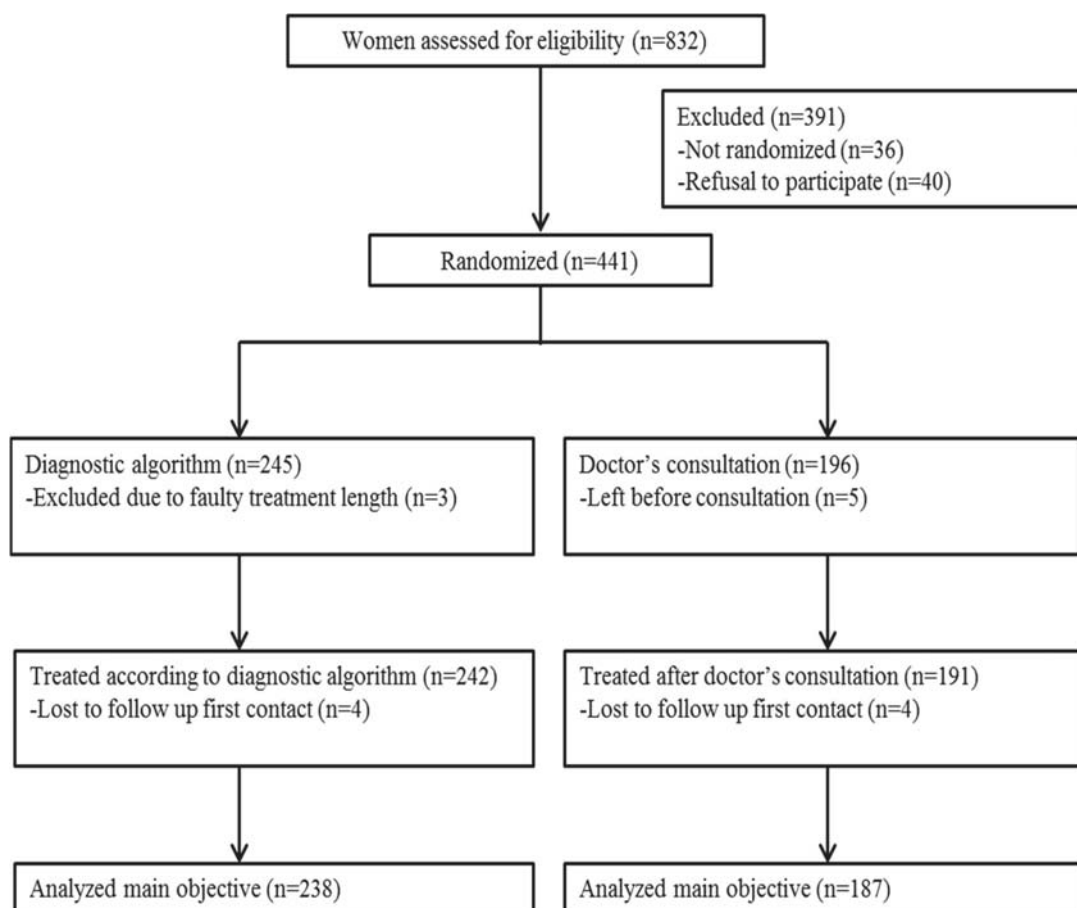
Figure 5. Trial flow chart: randomised controlled trial of a diagnostic algorithm for uncomplicated cystitis at an OOH service in Oslo, Norway.

The group treated according to the diagnostic algorithm received pivmecillinam 200 mg x 3 for three days. The treatment of patients in the control group was left to the doctor's discretion. The attending physician was unaware that the patient was included in the study and fulfilled the criteria of the diagnostic algorithm.

Urine dipstick findings were evaluated in both groups along with urine samples collected for culturing on the day of presentation at the OOH service. Furthermore, the samples were also sent to the laboratory one week after the completion of treatment. All urine samples were cultured at the Department of Medical Microbiology, Oslo University Hospital, Ullevål according to established procedures for identification of the causative agents and resistance patterns. The uropathogens were quantified in cfu/mL. Significant bacteriuria was defined based on the current European guidelines (45).

The follow-up included a telephone call from the study coordinator one week after the contact and two weeks after the treatment was completed. During the first follow-up telephone call, the following data were registered: country of birth; first language; municipality of residence; type of antibiotic and number of days taken (to register potential deviations from the treatment given); number of days until symptom-free; contact with the health care system during the follow-up period, cause of the contact and/or new antibiotic prescribed. Two-weeks after the treatment, the following data were registered: symptoms of a UTI during the two-week follow-up; contact with the health care system during the follow-up period, cause of contact and/or new antibiotic treatment prescribed.

Data analyses

To identify the potential differences between the two groups, the demographic and clinical data at presentation were examined. The bacteriological parameters were evaluated at presentation and in the follow-up urine culture to identify the differences in the rate of single culture isolates at presentation and the proportion of persisting bacteriuria in the follow-up sample.

41

The main clinical outcome was the number of days until resolution of the symptoms. The proportion of patients who contacted a doctor in the follow-up period and the proportion who received a second antibiotic prescription were analysed in the study cohorts.

Statistical methods

All analyses were performed using SPSS (Released 2009, PASW Statistics for Windows, version 18.0. Chicago: SPSS Inc.).

Statistical power of the data was based on symptom relief in 85% of the control group versus 75% in the group treated according to the diagnostic algorithm by day four and a given power of 80% and a p-value of <5% (two-sided test). Sample size calculation indicated that 250 patients were needed in each group.

Descriptive analysis of data was done. For comparison of the proportions, p-value was calculated using Pearson Chi-Square test.

For evaluating the primary outcome measurement, a Kaplan Meier plot was utilised.

2.4 The bacteriology study

Data collection and analyses

We compared the bacteriology and resistance patterns in the urine cultures of women with uncomplicated UTIs presenting in a general practice setting during three different time-periods in Norway. The material consisted of 184 urine cultures from 2001, 406 from 2010-2011 and 259 from 2013-2015.

The first study was performed in the county of Telemark in 2001. This investigation enrolled arbitrarily selected women presenting to the GP practitioner with symptoms of an uncomplicated UTI for which they received antibiotics. Fresh midstream urine samples were sent to the local microbiology department in sterile containers with 1.6% boric acid. Significant bacteriuria was defined as pure or dominant growth of $\geq 10^4$ cfu/mL for all the pathogens. Antimicrobial susceptibility breakpoints were set according to the Norwegian Working Group on Antibiotics (146, 147).

The next two studies were performed at OAEOC, Department of Emergency General Practice. Sequential consulting women were enrolled in the time periods of September 2010-November 2011 and April 2013-December 2015.

In the 2010-2011 study inclusion criteria were determined by a diagnostic algorithm based on established symptoms and risk factors for complicated UTI. This research was conducted to validate a specific diagnostic algorithm, and the results have been published as paper I in this thesis.

In the 2013-2015 study the same inclusion criteria were applied to identify women with uncomplicated UTI (3).

For the two latter studies a fresh midstream urine sample was sent to the Department of Microbiology, Oslo University Hospital, Ullevål, in sterile containers with 1.6% boric acid. The uropathogens were quantified in cfu/mL. Significant bacteriuria was defined according to current European guidelines as $\geq 10^3$ /mL for primary pathogens, $\geq 10^4$/mL for secondary pathogens and $\geq 10^5$/mL for doubtful pathogens (44). Clinical breakpoints were acquired from the European Committee on Antimicrobial Susceptibility Testing (EUCAST), which have remained unchanged since 2010 (147).

Data on antibiotic use were collected from two nation-wide databases; the Norwegian Drug Wholesale Statistics Database and the Norwegian Prescription Database (NorPD) (148). The former database logs the sales of all medicines in Norway, while the latter contains a complete list of all prescription drugs dispensed by pharmacies in the country since 2004.

National resistance patterns were collected from the Norwegian Organisation for Surveillance of Antimicrobial Resistance (NORM). From 2000 onwards, NORM has provided annual reports on the national usage of antimicrobial agents and the occurrence of resistance (1). Data on resistance were compared with the total use (wholesale statistics) of the selected antibiotics.

Statistical methods

The results of this study represent a retrospective comparison and a power calculation was not performed. IBM SPSS statistics 23.0 was used for descriptive analyses of the data. The aggregated data were compared using a chi square calculator with a significance level of 0.05 (149).

2.5 The predictor study

Data collection

The analyses were based on the study described in paper I.

Data analyses and statistical methods

For analytical purposes, the cohort was divided into three age groups: 16–22, 23–28 and ≥29 years.

The traditional negative binomial (NB2) model was fitted to the count data for identifying the factors that predict longer symptom duration. The NB2 was chosen to account for over-dispersion of the data, which was confirmed with the Pearson dispersion statistics (4.31).

Selection of factors into the final model proceeded with the elimination of the predictor with the largest P-value at each stage before the model was refitted. The Aikaike Information Criterion (AIC) was also estimated, which was employed to compare all the subsequent models; the smaller the AIC, the better the model. Therefore, each subsequent step eliminated the least significant variable in the model until the AIC estimate was higher than in the previous step. However, in each stage, the variable age was retained regardless of its predictive power.

To identify factors predicting significant bacteriuria sensitivity, specificity and positive predictive values (PPV) were first calculated.

Binary logistic regression models were applied to ascertain the predictors of significant bacteriuria. Firstly, univariate logistic regression models were fitted to the

data for discerning the significant predictors. Secondly, those predictors, together with the clinically relevant ones, were used to fit a multivariate logistic regression model. To assess the accuracy and discriminative value of the final prediction model, the area under the receiver operating characteristic curve was calculated.

All statistical analyses were performed using SPSS 22, and significance was set at $p<0.05$.

2.6 The ESBL UTI study

Study design and data collection

This work is a prospective, observational, multi-centre study of women with CA-UTI caused by ESBL-producing *E. coli* and a control group of non-ESBL-producing *E. coli*.

In collaboration with the primary care physician, study coordinators at eight different microbiological laboratories conducted preliminary screening according to the following inclusion criteria: women aged ≥16 with symptoms of UTI, significant monoculture growth of ESBL-producing *E. coli* in urine sample (≥10^3 cfu/mL) and treated with pivmecillinam (dose and treatment length determined by the treating physician). Patients were excluded if, prior to inclusion, they had been hospitalised >48 hours during the past 90 days, had received haemodialysis or intravenous chemotherapy within the last 30 days, had received specialised medical treatment at home, including change of permanent urinary catheter in the last 30 days, were unable to provide informed consent or had a urine culture containing ESBL-producing bacteria identified within the last six months. No patients with indwelling urinary catheters were included.

Candidate cases were invited by their primary care physician to a consultation two weeks after the end of the treatment, which represents the follow-up period. Treatment failure was defined as persistent symptoms leading to a second antibiotic prescription during the follow-up.

For all patients, a clean-catch morning urine control sample was analysed no later than two weeks after the end of the treatment. Nonetheless, in case of clinical treatment failure, the urine sample taken at the time of initiating the alternative treatment was included for analysis.

The control patients adhered to the same protocol as the ESBL cases. Inclusion criteria were identical for both the groups with respect to antibiotic treatment, geographical origin and time period of inclusion. Initially, both ESBL cases and the non-ESBL controls were matched 1:1 for age (+/- 5 years), but the inclusion of non-ESBL controls proved to be challenging. Therefore, after approval by the regional ethics committee, matching by age was abandoned; however, the other inclusion criteria remained unchanged. Twenty-seven matched cases and controls were included according to the initial protocol.

Data analyses

Urine sample culturing, species identification and antibiotic susceptibility testing were performed according to the laboratory's standard procedures. *E. coli* resistant to third generation cephalosporins were examined for ESBL-production. Nordic clinical breakpoints were in line with EUCAST. (148)

Species identification was verified by the use of matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) (Bruker Daltonics, Germany) according to the manufacturer's instruction. MIC of pivmecillinam was determined using the MIC gradient test (Liofilchem®, Italy) as per the EUCAST methodology and clinical breakpoints.

ESBL production was confirmed by the double disk synergy test using cefotaxime and ceftazidime with and without clavulanic acid (Becton Dickinson, USA), in keeping with the manufacturer's procedure.

Statistical methods

Statistical power was calculated based on 60% efficacy among the ESBL cases versus 80% efficacy among the non-ESBL controls for complete symptom resolution by day

three. This measure provided a relative difference of 25% with β 80% and α 5%. Sample size calculation indicated that 82 patients were needed in each group, which was increased to 100 to compensate for possible drop-outs.

Kaplan-Meier and log-rank tests were utilised to estimate the time until symptom resolution. Treatment failure was analysed using a binary logistic regression model. A two-way interaction term for treatment length and group (treatment) was employed to understand the effect of treatment over time. The modelling process proceeded in two steps: firstly, crude estimates of odds ratio (OR) were obtained from logistic models adjusted for the interaction of treatment length and group only. Secondly, the models fitted in step 1 were further adjusted for clinical factors. All the models were fitted using StataSE 14, and the significance level was set at $p=0.05$. The collected data were analysed by the use of SPSS version 24.

2.7 Ethics

All persons included in the prospective trials were included only after obtaining informed consent. The participation was voluntary, and the members received written information about their right to withdraw from the study at any time. All data were anonymised so that they could not be traced back to any participant without the anonymisation key which was kept in a separate, locked location. The data were securely maintained in locked devices as per the regulations. The studies were performed in accordance with the principles outlined in the Declaration of Helsinki.

Paper I

Participation was voluntary. Written informed consent was obtained. Confidentiality for patients was kept by a one-way encrypted ID-number.

Approval was obtained from the Regional Committees for Medical and Health Research Ethics in Norway (reference number: 2010/486).

Paper II

All three studies were conducted in accordance with the Declaration of Helsinki and current national and institutional standards. The last two studies were both approved by the Regional Committees for Medical and Health Research Ethics in Norway (reference numbers 2010/486 and 2012/1569). The first study was an observational study and did not require a specific approval from the ethical committee at that time.

Paper III

The participation was voluntary, and written informed consent was obtained. Confidentiality of the patients was maintained by a one-way encrypted ID-number.

Approval was obtained from the Regional Committees for Medical and Health Research Ethics in Norway (reference number: 2010/486).

Paper IV

The participation was voluntary and written informed consent was obtained. Confidentiality of the patients was maintained by a one-way encrypted ID-number. The study was registered with the Regional Committees for Medical and Health Research Ethics in Norway, (reference number: 2011/2214) and Clinical Trials (ID: NCT01531023).

3. RESULTS

3.1 The diagnostic algorithm study

By day four, 188 out of 238 (79%) in the group treated on the basis of the diagnostic algorithm and 134 out of 187 (72%) in the control group were symptom free (p=0.09). A median of three days until symptom resolution was noticed in both the groups, with log rank test p=0.3.

No significant differences existed between the diagnostic algorithm group and the control group either in the growth rate of single culture bacteria or in the clinical and demographic findings at presentation.

In the control group, the vast majority were diagnosed with cystitis, and the other diagnoses were pyelonephritis (2), bacterial vaginosis (1), cystitis and other illness (bacterial vaginosis and muscular pain) (2) and lack of illness (2).

In the group examined by a doctor, 80% were treated with pivmecillinam. The other prescribed antibiotics were trimethoprim (13%) and nitrofurantoin (6%). Two patients (1%) were not given any antibiotic treatment.

During the follow-up period, 12% of the patients treated according to the diagnostic algorithm contacted a doctor versus 18% in the control group (p = 0.08).

Among those patients who made a follow-up contact, significant bacteriuria was noted in 19% of the urine specimens in the diagnostic algorithm group and 26% in the control group. For those who did not contact a doctor again, 10% significant bacteriuria was observed in both the groups

The follow-up period was devoid of severe pyelonephritis cases or hospital admissions.

3.2 The bacteriology study

All the three study populations represented adult women aged 15-65 years and experiencing uncomplicated UTIs. The first group represented an older cohort (mean age 38.3 years), whereas the mean age of the two groups from the OAEOC was 27.1 years.

Significant bacterial growth was found in 57%-74% of all urine samples cultured. The main bacteriological agent in all the three study populations was *E. coli*, ranging from 78% to 82%. The second most common isolate was *S. saprophyticus*, ranging from 6% to 17% (table 2).

Microbe	2001 n (%)	2010-2011 n (%)	2013-15 n (%)
E. coli	112 (82.4)*	180 (78.3)*	129 (81.6)*
S. saprophyticus	8 (5.9)*	38 (16.5)*	22 (13.9)*
Enterobacter spp.	0*	1 (0.4)*	4 (2.5)*
Enterococcus faecalis	3 (2.2)*	2 (0.9)*	1 (0.6)*
Klebsiella spp.	6 (4.4)*	5 (2.2)*	2 (1.3)*
Proteus spp.	5 (3.7)*	4 (1.7)*	0*
S. aureus	2 (1.5)*	0*	0*
No significant growth	48 (26.1)°	176 (43.3)°	101 (39.0)°
Total number of cultures with significant bacteriuria	136 (73.9)°	230 (56.7)°	158 (61.0)°
Total number of cultures	184	406	259

* % of total number of cultures with significant bacteriuria

° % of total number of cultures

Table 2. Bacteriological findings in the study cohorts.

For *E. coli,* resistance to pivmecillinam demonstrated some variation, but retained below 9%. The resistance to nitrofurantoin was negligible. In case of trimethoprim, the resistance substantially increased from 2001 to 2010/2011 and then stabilised at around 20%. Amoxicillin resistance exhibited some variations, but remained stable at around 30%. *S. saprophyticus* isolates depicted an increase in resistance to amoxicillin from 2010-2011 to 2013-2015. However, the organism did not show an increase in resistance to nitrofurantoin, co-trimoxazole or trimethoprim.

None of the changes in the resistance rates were statistically significant.

There was a steady rise in the total consumption of selected antibiotics commonly used to treat urinary tract infections during the period 2000-2015; however, from 2012 onwards, there has been an overall reduction in antibiotic usage (figure 6).
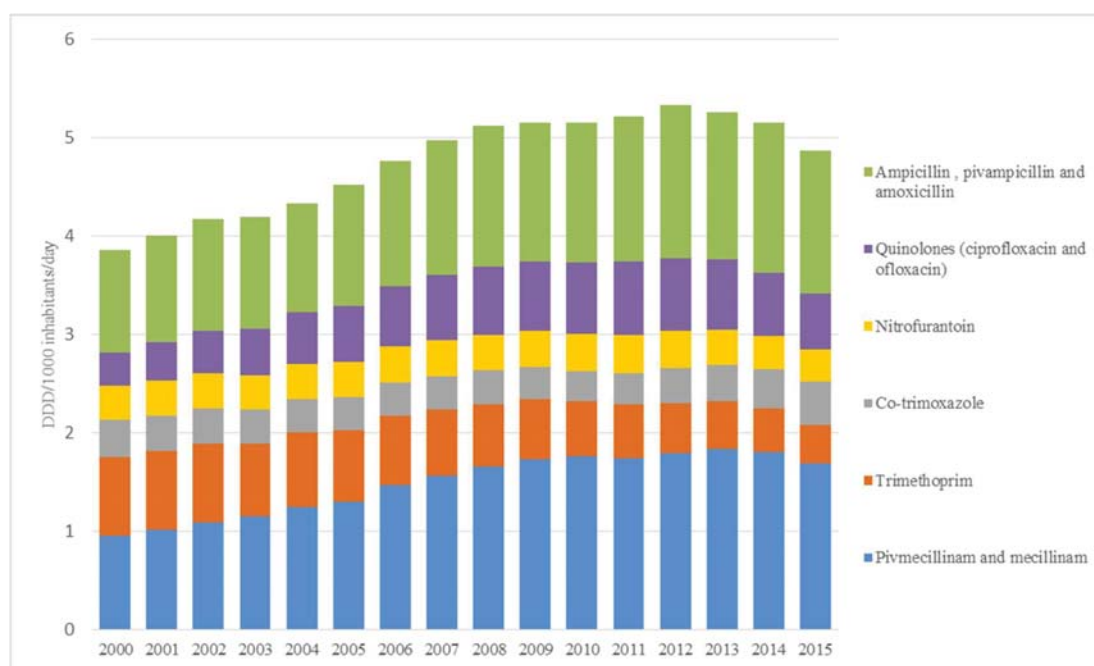
Figure 6. Total use of selected antibiotics commonly used to treat urinary tract infections in Norway (wholesale statistics).

Data on the preferred antibiotics for treating uncomplicated UTIs revealed an increase in pivmecillinam and fall in trimethoprim consumption, while the use of nitrofurantoin and co-trimoxazole remained stable.

Women used more antibiotics than men and were more frequently prescribed pivmecillinam, while quinolones were more often prescribed for men.

The relationship between the consumption of the two most commonly used antibiotics, trimethoprim and pivmecillinam, and *E. coli* resistance rates was analysed for our study cohorts and national data. For trimethoprim, there was a reduction in usage over the last 15 years, but the resistance of *E. coli* to the drug slightly increased. For pivmecillinam, there was a clear rise in consumption occurring during the study period, with a minimal decrease over the last two years. The resistance rates of *E. coli* to the antibiotic depicted some variation, but the overall trend was a slight increase.

3.3 The predictor paper

Urine dipstick positivity for nitrite (OR 3.22, 95% CI 1.58–7.01, $p<0.01$) was associated with an increased probability of significant bacteriuria. The findings with a leukocyte esterase value of 3+ (OR 2.40, 95% CI 0.88–6.05, $p=0.09$) or a leukocyte esterase value of 2+ (OR 2.51, 95% CI 0.92–6.83, $p=0.07$) were associated with significant bacteriuria, but did not reach significance.

Logistic regression analysis indicated that neither age nor pronounced clinical symptoms upon presentation correlated with the presence of significant bacteriuria.

Severe symptoms or substantial bacteriuria were not significant predictors of longer symptom duration after empirical treatment. The presence of leukocyte esterase 1+ on the urine test strip (incidence rate ratio (IRR) 1.93, 95% CI 1.23-3.01 $p<0.01$) and the significant growth of a microbe resistant to the given antibiotic (IRR 1.41, 95% CI 1.07-1.89, $p=0.02$) predicted significantly longer symptom duration in the multivariate analyses.

3.4 The ESBL UTI study

Eighty-eight ESBL cases and 74 non-ESBL controls treated with oral pivmecillinam were included in the study. Cases and controls were similar in age (the mean age of the ESBL cases was 49.4 and that of the non-ESBL controls was 50.1, p=0.82) and clinical presentation; however, reduced general condition was noted in a significantly greater proportion of ESBL cases than the non-ESBL controls (33.9% versus 22.9%, p=0.04). Reduced general condition was associated with increased risk of treatment failure both in univariate (OR 3.19, 95% CI 1.50-6.80, p <0.01) and multivariate analyses (OR 2.84, 95% CI 1.18-6.84, p=0.02).

No differences in the relevant comorbidities were found.

Thirty-seven of the 87 ESBL cases (42.5%) were treated with pivmecillinam 200 mg administered thrice daily versus 48/73 (65.8%) of the non-ESBL controls. The remaining patients were treated with 400 mg of the drug given thrice daily.

The median duration until symptom resolution after treatment initiation was five days for the ESBL cases and three days for the non-ESBL controls, p<0.01.

Among the patients treated with pivmecillinam 400 mg thrice daily, there was no significant difference in the risk for treatment failure between the ESBL cases and the non-ESBL controls regardless of the treatment duration ($\leq$ 5 days OR 2.17, 95% CI 0.31-14.64, p=0.43, >5 days OR 2.16, 95% CI 0.32-14.65, p=0.43).

A pivmecillinam dosage of 200 mg given three times daily for $\leq$ 5 days was associated with treatment failure (OR 4.77, 95% CI 1.40-19.44, p=0.03) in the ESBL *E. coli* group.

The proportion of women warranting a second antibiotic prescription during the follow-up period was higher for the ESBL cases (30/88 (34.1%) than the controls 10/72 (13.9%), p= 0.003). One patient in the ESBL group was admitted during the follow-up period and treated with ampicillin and gentamicin for pyelonephritis.

Persistent bacteriuria was non-significantly more common among the ESBL cases than in the control group (15/81 (18.5%) versus 6/67 (9.0%), p= 0.10).

The *E. coli* isolates from the ESBL cases and those from the non-ESBL controls possessed similar levels of *in vitro* resistance to pivmecillinam and nitrofurantoin. The ESBL cases, however, demonstrated significantly higher rates of *in vitro* resistance to many other commonly used oral treatment options for UTI, including trimethoprim, co-trimoxazole and ciprofloxacin.

The vast majority of ESBL *E. coli* isolates had pivmecillinam MIC values ≤ 2 mg/L (84/86, 97.7 %).

4. Discussion

4.1 Main findings

- There was no significant difference in the time to symptom resolution or the rate of reconsultation with a doctor during the follow-up period between the diagnostic algorithm and control groups. No cases of severe pyelonephritis or hospital admission were encountered during the follow-up period **(Paper I)**.

- During 2001-2015, a stable and high susceptibility to pivmecillinam and nitrofurantoin was found for the *E. coli* isolates causing uncomplicated UTIs in the country. For trimethoprim, there was a reduction in usage over the last 15 years. For mecillinam, there was a clear rise in consumption during the study period. The resistance rates of *E. coli* exhibited some variations, but the overall trend was a slight increase in mecillinam resistance **(Paper II)**.

- Positive urine dipstick results for nitrite and leukocytes (3+, 2+) were associated with an increased probability of significant bacteriuria. More pronounced symptoms did not correlate with the presence of significant bacteriuria or longer symptom duration following empiric treatment. The presence of leukocyte esterase 1+ on the urine dipstick and the presence of a microbe resistant to the given antibiotic predicted longer symptom duration **(Paper III)**.

- The administration of pivmecillinam 400 mg thrice daily yielded comparable clinical and bacteriological cure rates in women with *E. coli* CA-UTI irrespective of ESBL production. Persistent bacteriuria was non-significantly more common in the ESBL cohort than in the non-ESBL controls **(Paper IV)**.

4.2 Methodological considerations

The majority of clinical contacts take place in the primary care setting, but research projects are more commonly performed in secondary care. Nonetheless, primary care research is a necessary prerequisite for treatment advances in the domain. Several factors are responsible for this uneven distribution. The patients typically spend only a short time in the healthcare institution, and the prescribed treatment is typically initiated and completed at home. For many of the conditions, a follow-up consultation is not warranted. Besides, physicians work in smaller offices, thereby leading to logistic challenges.

The following sections describe the methodological considerations in the research projects that are a part of this thesis. As data inclusion has taken place in the primary care setting, the process has given valuable insights into the relevant challenges and possibilities.

4.2.1 The diagnostic algorithm study

A randomised controlled trial

At the time of implementing the diagnostic algorithm (2007), the method was not validated. A prospective study was needed to evaluate the usage and a randomised controlled trial is considered the best method to compare two different practices.

The diagnostic algorithm is a standardised method for identifying patients with suspected uncomplicated lower UTI. To evaluate whether or not the algorithm coincided with clinical practice, the diagnostic findings from a regular doctor's consultation were used for comparison. As the algorithm had not been previously validated, this study was conducted as a superiority trial with symptomatic resolution as the main outcome variable. Although we initially hypothesised that the doctors' consultation would be more effective (superior) compared to the questionnaire, our findings suggest that perhaps a non-inferiority design would have been adequate to address the research question.

Sample size calculation

The sample size calculation is described in the methods section (section 2.3). Resolution of symptoms was defined as the primary outcome as it is the clinical measure of cure. Bacteriological culture follow-up is not routinely recommended for uncomplicated lower UTIs (23).

According to studies on antibiotic treatment for uncomplicated lower UTIs, the sample size calculation was based on an expectation of symptomatic relief for 85% of patients in the control group by day four (46). For the calculation, a difference of 10% was chosen as a clinically significant decrease in the number of women with complete symptom resolution by day four. This choice was based on discussions with colleagues and PhD supervisors. It was reasoned that the treatment outcome of the two study cohorts would not differ.

Inclusion and exclusion criteria

The basis for inclusion was the presence of cardinal UTI symptoms without factors associated with complicated infections, upper UTIs or other causes of similar symptoms. This symptom-based strategy was recommended by the Norwegian national guidelines, and served as the basis of the diagnostic algorithm employed at the OAEOC (23). The study sought to validate the algorithm's clinical use. Adjustments were considered prior to initiating the study but later abandoned as the clinical experience was good and the practice was supported by a previously published larger meta-analysis (26).

Randomisation

The process of inclusion and randomisation proved to be challenging. Randomisation was conducted by the registering nurse at the OAEOC who drew a number (1 or 2) from an envelope. Block randomisation was not considered initially as the procedure was meant to take place at one centre with a defined number of ones and twos in the envelope. As the inclusion proceeded, it was noted that a larger number of patients were present in the diagnostic algorithm group. Each completed registration form was signed by the respective nurse, and it was noted that a few of them had only included patients in the diagnostic algorithm group. This issue was discussed with the persons

involved, and it was observed that the procedure had not been followed as described in the methods section. For this reason, all the patients included by this method were omitted (n=36, see figure 5). Diversion from the protocol was confirmed at an advanced stage of the inclusion process, and the trial was ended when the time frame agreed upon with the OAEOC was reached. The study was time consuming for a department with a large turnover of patients, and a prolonged inclusion period was decided against. The demographic and clinical characteristics of the two groups did not reveal significant differences at presentation, and they were hence considered to represent comparable cohorts.

The control group

The women in the control group were identified as eligible for inclusion in the study by the registration nurse; however they were seen by a doctor who was not aware that the screening process had been done. Before the commencement of the study as well as during it, identification of women who fulfilled the criteria of the diagnostic algorithm in the electronic medical records used by doctors was not practiced. Hence, the treating doctors were not aware that the screened women were eligible for treatment following the diagnostic algorithm. The study did not comprise change in practice or involvement from the doctors; therefore, the individual consultations are not likely to be biased by the ongoing research.

4.2.2 The bacteriology study

Recruitment of the patients

For comparison, the data from three study cohorts were used. The inclusion process and setting for the latter two study cohorts were identical. For the first study cohort, the inclusion took place in general practice with recruitment from several separate practices in the county of Telemark (one of the 19 counties in Norway). The cohorts recruited at the OAEOC represented a younger age group than the one from general practice. The latter two cohorts were recruited from the county of Oslo, which comprises the city and the surrounding suburbs, and represents mostly urban population.

The geographical variation between the first and the latter two cohorts could possibly have impacted the bacteriological findings; however, Telemark county also consists of several urban areas and is located in the South-Eastern part of Norway, just like Oslo.

The mean age of the eldest cohort was 38 years and represented women of child-bearing age. The cohorts were considered comparable with regards to age. Elderly women experience an increased incidence of UTIs (66).

For the latter two studies, the identification of eligible women was made by the diagnostic algorithm described under paper I. For the first study, the recognition of an uncomplicated lower UTI was left to the GP's discretion. The current guidelines for diagnosis of UTI in general practice were established before the study periods (23). The guidelines recommend that the diagnosis of uncomplicated lower UTI should be based on cardinal symptoms, and they do not advise further diagnostic steps unless complicating factors exist. As the identification of eligible women for all the three studies was based on cardinal symptoms of uncomplicated lower UTI, we deemed the cohorts to be comparable. In support of this view, the results of paper I were available at the time of analysis, which validated the correlation between the diagnostic algorithm and the conclusion following a regular doctor's consultation.

Bacteriological findings

The microbiological evaluation of the urine culture obtained at presentation was performed according to the national and international guidelines which prevailed at the time of the respective studies. In 2001 (between the first and the second inclusion periods), a guideline for urine analysis was published by ESCMID. In this document, uropathogens were defined as primary, secondary and doubtful. Significant bacteriuria was defined in line with the current European guidelines as $\geq 10^3$/mL for primary pathogens, $\geq 10^4$/mL for secondary pathogens and $\geq 10^5$/mL for doubtful pathogens (45). In comparison, for the first cohort, significant bacteriuria was defined as pure or dominant growth of $\geq 10^4$ cfu/mL for all the pathogens. *E. coli* and *S. saprophyticus* make up the common and fairly common primary pathogens as per the ESCMID document. As the definition of significant bacteriuria was changed between the first

and the latter study periods, bias resulting from a higher proportion of the pathogens being defined as primary could be expected in the latter two cohorts. Studies have proven that lower counts of *E. coli* ($\geq 10^2$/mL) are relevant in the case of typical UTI symptoms (150, 151). However, the latter two studies did not reveal a higher proportion of *E. coli* even though they did show elevated counts of *S. saprophyticus*. Another plausible partial explanation is that the latter two cohorts consisted of younger populations, and *S. saprophyticus* is more commonly a causative uropathogen in such women.

Resistance

The susceptibility breakpoints for the isolated microbes were evaluated according to values furnished by the Norwegian Working Group on Antibiotics for the first study and EUCAST for the latter two. The EUCAST values have remained unchanged since 2010 (146, 147). No differences were discerned between the mecillinam MIC values for *E. coli* during the three time periods.

To evaluate the association between antibiotic consumption and microbial resistance, data on antibiotic use were collected from two nationwide databases: the Norwegian Drug Wholesale Statistics Database and the NorPD (148). The former captures the sales of all medicines in the country, while the latter includes information on all prescriptions dispensed at Norwegian pharmacies to individual outpatients since 2004. Both databases merely provide estimates of the antibiotic load to which the population is exposed. As the analysis was conducted retrospectively, a history of antibiotic consumption for each included individual was not available. The findings were considered relevant as the effect of antibiotic use on the resistance rates is of interest on several levels (individual, groups of persons, national and international). Our findings are relevant for the Norwegian national data.

Sample size calculation/power analysis

This study was a retrospective analysis and the sample size calculations for the relevant data were not performed with respect to this research. A retrospective power analysis was discussed but eventually ruled out as such calculations are done to

understand how one might characterize the findings in the future for a particular study design and specifications. The data are presented with CI wherever available, and retrospective power analysis would not yield additional information (152).

4.2.3 The predictor study

The questionnaire

Data analysis was based on women included in the study, as described in paper I. The questionnaire comprised clinical presentations, including the intensity of the cardinal UTI symptoms, age, dipstick and bacteriological findings with resistance patterns. All women presenting with factors that increase the risk of an upper UTI or common alternative diagnoses (STI) and relevant comorbidity with regard to the risk of complicated and serious infections were excluded.

The questionnaire did not probe the complete medical, social and psychological history. Hence, those factors which could influence the duration of reported symptoms or significant bacteriuria were possibly not identified. As the study was primarily designed to validate the diagnostic algorithm for women with uncomplicated lower UTIs and ensure the feasibility of the study with regard to the time needed to enroll patients, it was decided against including additional questions. In light of the discussions on the strategies to decrease antibiotic consumption for mild and common bacterial infections, we attempted to evaluate which factors were possibly associated with a suboptimal response to antibiotic treatment (longer duration of symptoms following empiric treatment) and significant bacteriuria. The available data, along with the relevant clinical and bacteriological findings, were considered relevant to evaluate this association.

The questionnaire excluded postmenopausal women and those presenting with symptoms associated with upper UTIs. Hence, some of the excluded women could possibly have an uncomplicated lower UTI, but were removed from the analyses owing to the exclusion criteria. However, the study represents a relatively large proportion of patients who receive treatment for UTI in general practice.

At the time of designing the protocol, the Norwegian national guidelines indicated that women in the age group of 16-55 years were more likely to have an uncomplicated UTI when presenting to the GP with symptoms of the infection and could hence be prescribed treatment without being seen by a doctor (23). This guideline was the rationale for our choice of the age group.

Current data on the consumption of antibiotics commonly used to treat UTIs assert that there is a peak in the usage for women aged 16-28, followed by a gradual increase from age 55 (1). The relatively low mean age in the study (27 years) is in line with this finding. Uncomplicated UTIs are common and hence potential sources of antibiotic overprescribing. We believe that the potential to reduce the unnecessary use of antibiotics is greater in this group, and an analysis of factors predicting inadequate response to empiric antibiotic treatment and significant bacteriuria are relevant for it.

Confounding factors

The women included in the diagnostic algorithm and control groups were pooled into one dataset for this study. With regard to the duration of symptoms following the commencement of treatment, the univariate analysis was adjusted for this variable but did not show significance.

4.2.4 The ESBL-UTI study

Geographical considerations

The design of a study which accounts for a representative proportion of patients treated in primary care entails several challenges. First, as Norway is a relatively sparsely populated country with rural and urban areas, it was pertinent to ensure that patients from all these groups were recruited. The Norwegian health service is divided into four regional health authorities (Northern/nord, Central/midt-Norge, Western/vest and South-Eastern/sør-øst) (figure 7) (153).

Figure 7. Overview of the regional health authorities in Norway (Northern/nord, Central/midt-Norge, Western/vest and South-Eastern/sør-øst).

Recruitment proceeded from the microbiological laboratories in all the four regions. Each laboratory received samples from a large number of GPs and 76 different municipalities in the country. Norway consisted of 426 municipalities in 2017. Hence, patients were included from a relatively large percentage of municipalities, but by far from all.

Recruitment of patients from the primary care setting

To successfully include patients in the study, cooperation with the individual GPs was essential. As the percentage of ESBL-producing Enterobacteriaceae has escalated even in primary care, many GPs have personal experience with the difficulties in finding adequate oral treatment options. This focus could spur some physicians to exhibit increased interest in partaking in the study. The same rationale also applies to patients with UTI caused by ESBL-producing *E. coli*. This fact was reflected in the difficulties

faced while including control patients; the drop-out rates were higher in this category, which resulted in a lower number of control patients than ESBL cases.

The difficulties encountered in recruiting controls were more profound than expected. To account for the increased number of drop-outs in the control group, the criterion of matching the participants according to the age was omitted during the inclusion period. This change of protocol was approved by the ethics committee.

Owing to the challenges in the recruitment of controls, the study was terminated just short of the planned number of included candidates (74/82). The reason for termination was that the required number of ESBL cases was reached and the planned time of inclusion was over. A prolonged inclusion period for the controls was considered but not implemented as the inclusion of both ESBL cases and controls should be done within the same time frame.

The potential cohort for controls was large. As there was no significant difference in the clinical and demographic data between the two cohorts, we concluded that the difficulties faced and the adjustments made in inclusion most probably did not lead to a bias capable of compromising the finding and that the control cohort was representative.

Identification of study candidates in the microbiological laboratories

For the eight participating laboratories, study coordinators were appointed for planning and data collection. These individuals were co-authors of the main publication and were dedicated to the task of identifying possible patients for inclusion based on the urine culture findings. Each GP included a few patients and was in many instances introduced to the study for the first time with a written information leaflet and a proposal to inform, screen and include the patients. Written information was prior to the study start sent to all the GPs through a newsletter which was meant to convey practice-related news. What percentage of the physicians actually read this information and developed an acquaintance with the process before receiving an invitation to recruit a patient remains unknown.

Inclusion and exclusion criteria

The study population was chosen to represent CA infections and was limited to women. Hence, the data are not representative of the entire population. Patients with suspected HA infections due to hospitalisation or undergoing specialised medical treatment were excluded.

The rationale behind the exclusion of men at the time of planning the study was that UTIs in men were always complicated and the administered antibiotic had to demonstrate a high level of penetration into the prostatic tissue. Following administration of the drug, prostate concentration of mecillinam is about one half of the serum concentration (156). However, current research challenges this notion. It is suggested that for UTI without other complicating factors except the gender, empiric treatment options for men should be equivalent to those for women but for a longer duration. In a similar future study, male patients should be included.

Consent for participation

The included patients provided consent to participate in the study during the follow-up consultation with the GP. In the planning stages, a study with prospective inclusion of all women with UTI treated in primary care was discussed, but disregarded as the total number of included patients would have to be a very large number to obtain the planned number of ESBL cases. The inclusion of such a large number of patients who were not the primary targets of the study was considered unethical.

Sample size calculation

The sample size calculation is described in the methods section (section 2.6). The primary outcome and basis for the sample size calculation was complete symptom resolution by day three. Symptom resolution was chosen over bacteriological cure as symptomatic treatment outcome is used to define clinical cure for the UTIs treated in primary care. Symptomatic cure following empiric antibiotic treatment was expected to be around 80% versus 60% for patients with ESBL-producing *E. coli*. The expected values were based on antibiotic versus placebo studies in which the placebo illustrated

the expected effect of pivmecillinam on ESBL-producing *E. coli* (46). Comparable studies were not available at the time of planning (118).

4.3 Discussion of results

4.3.1 The feasibility of a symptom-based diagnostic algorithm

Our findings showed that the algorithm identified women with an uncomplicated lower UTI when the diagnostic decision following a regular doctor's consultation was employed as the gold standard. The two cohorts also had comparable clinical courses.

The established symptom-based diagnostic strategy has been debated recently as the focus on ways to decrease antibiotic consumption and the associated drug resistance has increased.

It has been suggested that cases of STI are overlooked in case of young women presenting with dysuria to the emergency departments (29). No cases of *Chlamydia trachomatis* infection were identified in the control group (paper I), but two patients were diagnosed with bacterial vaginosis. Our study cohort was also young with a mean age of 27 years. A possible interpretation is that the questionnaire identifies women with symptoms suggestive of an STI by the use of relevant exclusion criteria. A written and standardised set of exclusion criteria ensures that all the relevant ones are considered for each patient.

The need for standardised inclusion and exclusion criteria is also highlighted as the diagnosis of uncomplicated lower UTI based on symptoms alone has been shown to not correlate adequately with the conclusion following a doctor's consultation (30).

Positive urine dipstick results for nitrite and leukocyte esterase (2+, 3+) were associated with significant bacteriuria; however, strong symptoms were not linked to significant bacteriuria or longer duration of symptoms following empiric treatment (paper III).

The use of patient near bacteriological diagnostics (Flexicult^{TM}) tests have been advocated as a method of ensuring that antibiotic treatment is given only to women

with an identified uropathogen and symptoms of a UTI (155). The use of the Flexicult™ test and hence accepting that the presence of an identified uropathogen is the gold standard for diagnosis could potentially lead to reduced antibiotic prescription. However, it has been seen that Flexicult™ tests have a high sensitivity and low specificity when compared with the standard urine culture which could lead to overtreatment (22).

In paper I we found that 12.9% of patients with a negative primary urine culture and 16.1% of those with significant growth of a uropathogen did not recover during the follow-up period, which implies that women with a negative urine sample but typical symptoms respond to empiric antibiotic treatment.

Our findings suggest that a combination of cardinal symptoms (independent of severity) and the exclusion of symptoms and findings suggestive of a complicated UTI or an alternative diagnosis is a feasible method for identifying women with acute, uncomplicated UTI in a general practice setting.

Symptomatic resolution is widely accepted as the main treatment outcome for uncomplicated lower UTIs. Delayed prescription and the use of analgesics (possibly not anti-inflammatory agents) should be recommended to women with a low probability of longer symptom duration following empiric treatment (31).

4.3.2 Trends in the bacteriology and resistance patterns of common uropathogens

E. coli dominated as the most common cause of UTI throughout the study period, and this finding is in line with international data (66, 67, 70). Empiric treatment choices for uncomplicated lower UTIs must be adequate considering the regional *E. coli* resistance rates (68). Other commonly identified pathogens from CA-UTIs comprise *S. saprophyticus*, *K. pneumoniae, Enterococcus spp., Enterobacter spp.* and *P. mirabilis* (68, 69).

As routine culturing of urine samples from patients who present with symptoms of uncomplicated lower UTI is not recommended the need for sentinel surveillance has

been advocated. Our comparison of the national surveillance data from Norway (NORM data) which include both HA and CA-UTIs, and uncomplicated lower UTIs did not reveal significant differences in the resistance rates for the most common uropathogens. Other studies have found increased rates of resistance for samples acquired from hospitalised patients. The use of hospital-based data for recommending empiric treatment of CA-UTIs may lead to unnecessary use of broad spectrum antimicrobial agents (78, 156). Systematic surveillance of unselected samples from patients with uncomplicated lower UTIs should be universally performed to provide a basis for international guidelines with local adjustments.

Response to antibiotic treatment did not correlate with the presence or absence of significant bacteriuria in our study (paper III). In addition, a negative urine dipstick cannot rule out antibiotic response (37). A possible explanation for this finding is that current standards for urine culture do not identify all the relevant infections. Quantitative PCR technology has demonstrated that for culture-negative patients with symptomatic UTI *E. coli* can be isolated in approximately 95% of the samples (72).

Other possible technological options for point of care (POC) testing include MALDI-TOF, flow cytometry and fluorescent in situ hybridization (FISH) which could facilitate concomitant antimicrobial susceptibility testing in the future. Even though these techniques are fast and highly sensitive, the utilisation is expensive and hence are not sustainable in the primary care setting as of now (157).

4.3.3 Empiric treatment guidelines based on the bacteriological findings

Paper I validates the use of a diagnostic algorithm to identify women with uncomplicated lower UTIs. A standardised diagnostic procedure to identify women who can be treated based on the guidelines may enhance adherence to first choice antibiotic treatment. Studies have demonstrated that adherence to the guidelines is often suboptimal, thereby leading to increased antibiotic consumption (158). Feedback on prescription has documented the effect of adherence to guidelines (159). An intervention which focused on increased use of the recommended first-choice agent for

uncomplicated lower UTI demonstrated not only a heightened use of nitrofurantoin as desired, but also an increase in total antibiotic prescriptions (160).

Introducing international guidelines for empiric antimicrobial treatment is an enticing prospect. The possibility of setting a global standard to streamline when antibiotics should be prescribed for treating common infections and what treatments should be considered as the first-line options could be of immense value in the fight against resistance. Adjustments to local resistance data, clinical aspects, safety-related statistics and pharmacokinetics would be needed; nonetheless, common guidelines that serve as a "backbone" to make informed decisions could help improve antibiotic stewardship. Importantly, the guidelines should not promote the use of broad-spectrum agents in countries where the resistance rates do not warrant their application. Empiric first-choice agents could be listed, preferably accompanied by valid reasons. This practice could form a basis for national guidelines that take the aforementioned relevant factors into consideration.

The applicability of the guidelines would depend on continuous updates to ensure that the recommendations are in line with current knowledge. To ensure that relevant narrow-spectrum agents are available, antibiotic use should be regulated by an international non-profit organisation to minimise political influence. The World Health Organisation could possibly be an appropriate administrator.

4.3.4 Is pivmecillinam a feasible treatment option for CA-UTI caused by ESBL producing E. coli?

From the 1990s until today increased resistance in Gram-negative bacteria have come to dominate over resistant Gram-positive pathogens (including methicillin resistant Staphylococcus aureus (MRSA)). ESBL producing Enterobacteriaceae are a particular therapeutic challenge (90).

Oral treatment options are needed to avoid hospitalisation of persons with mild infections caused by ESBL producing microbes. The first reports on pivmecillinam treatment for ESBL producing Enterobacteriaceae suggested a possible effect.

However, as only few patients were involved in the studies and/or substantial variations prevailed in the clinical presentation, no conclusions could be drawn (117-120, 161).

The isolates from our study displayed marked co-resistance to other non β-lactam oral treatment options for CA- UTIs, including trimethoprim, co-trimoxazole and ciprofloxacin, based on *in vitro* susceptibility testing. This data supports previously published findings (118). Susceptibility to nitrofurantoin and pivmecillinam was high. This finding emphasizes the challenges in identifying possible oral treatment options for CA uncomplicated lower UTIs.

In 2014 a study which included 41 patients receiving pivmecillinam for the treatment of CA-UTI caused by ESBL producing *E. coli* demonstrated a significantly higher rate of treatment failure in the cohort with UTI caused by ESBL producing *E. coli* (44%) than in the control group (14%). Multivariate analyses asserted that each doubling of MIC was associated with more pronounced treatment failure (OR 2.0, CI 1.4-3.0, p< 0.001). Our results also established the presence of significantly higher rates of treatment failure (and need for a second antibiotic prescription) in the ESBL producing cohort, 34%, versus 14% in the control group. Subgroup stratification was performed which revealed interesting data regarding the cohort treated with 400 mg pivmecillinam thrice daily. Regardless of the treatment duration no significant difference in the risk of treatment failure was observed between the ESBL cases and the non-ESBL controls.

As the vast majority of ESBL isolates exhibited MIC values ≤ 2 mg/L (84/86, 97.7%) an evaluation of treatment/response failure according to MIC values was not performed.

Our findings suggest that a higher treatment dosage correlates with improved clinical treatment response. Bactericidal activity of β-lactam antibiotics is dependent on the duration for which the drug concentration exceeds MIC at the site of infection. The efficacy of these drugs is challenged when the concentrations do not exceed MIC for 40%-50% of the dosing interval. The duration can be enhanced with higher dosages

for oral treatment options (162). A study has proven that with a dosage of 400 mg given thrice a day, the urine concentrations of pivmecillinam exceeded MIC in 50% of the strains for 24 hours and in 90% of the strains for approximately 21 hours (163).

A study on serum drug concentrations following ingestion of pivmecillinam was conducted to evaluate the necessary dosage for exceeding MIC values. Susceptible ESBL-producing *E. coli* was used for this *in vitro* study that involved Monte Carlo pharmacokinetic and pharmacodynamics methods. Based on these findings, the authors suggested a raised dosage of 800 mg administered four times daily for UTIs caused by ESBL-producing *E. coli.* A total dose of pivmecillinam 60 mg/kg is tolerated by adults (164). For non-ESBL uncomplicated lower UTIs, there is no strong evidence to suggest that a higher dosage could improve the clinical outcome (165).

Pivmecillinam is concentrated in urine, which helps ensure adequate exposure to the drug (125). Organ-specific breakpoints would perhaps provide a more accurate presentation of the expected treatment results for UTIs.

A clinical study on the effect of higher dosages for CA-UTIs caused by ESBL-producing *E. coli* is warranted. The recurrence rates of UTIs caused by cephalosporin resistant Enterobacteriaceae have been shown to be higher if the empiric treatment is inadequate (166). Hence, a long-term follow-up study is also required to identify the rate of recurrence following pivmecillinam treatment of ESBL-producing *E. coli*.

5. Clinical implications of the findings

- A validated and standardised clinical registration form is a safe method to identify women with uncomplicated lower UTI who are likely to respond to antibiotic treatment. This simplification of the treatment strategy can lead to shorter waiting time for the patient, better adherence to the antibiotic guidelines and a more rational use of consultation time in the outpatient clinics.

- Stronger symptoms do not correlate with significant bacteriuria at presentation or protracted duration of symptoms following empiric treatment. However, strong symptoms can still be an indication for immediate antibiotic therapy owing to discomfort for the patient.

- Urine dipstick positivity for nitrite and leukocyte esterase (2+ and 3+) is associated with significant bacteriuria.

- Nitrofurantoin and pivmecillinam are appropriate first-choice agents for empiric treatment of uncomplicated lower UTIs. The use of trimethoprim as an empiric first-choice agent is compromised by increased resistance rates.

- Higher consumption of pivmecillinam has not augmented the resistance rates in *E. coli.*

- Pivmecillinam treatment at a dosage of 400 mg thrice daily is a viable treatment option for CA-UTI caused by ESBL producing *E. coli*.

- Duration of symptoms is longer for UTIs caused by ESBL producing *E. coli* when compared with non-ESBL controls (5 vs 3 days).

- Reduced general condition is associated with treatment failure in patients with ESBL producing *E. coli* infections as well as in non-ESBL controls, thereby suggesting the need for increased follow-up.

- ESBL isolates demonstrate marked *in vitro* co-resistance to other oral treatment options including trimethoprim, co-trimoxazole and ciprofloxacin. This finding highlights the need for alternative oral treatment options and the potential for pivmecillinam use.

6. Future research

Methods to improve the diagnosis and handling of women with suspected UTI

Precise diagnostic methods of UTIs are called for in the form of POC tests which could identify the causative microbe with adequate sensitivity and specificity (including ESBL production) and provide the resistance pattern (157, 167, 168). Advances in these aspects could ensure that appropriate narrow-spectrum antibiotic treatment is given. The current practice of culture-based diagnostics is flawed owing to the low sensitivity rates and the time lapse until obtaining the results. With medical advances, an improved microbiological gold standard for the diagnosis of UTI will hopefully be established.

Treatment options

The possibility of using established narrow-spectrum antibiotics should be thoroughly explored. Collateral sensitivity is an interesting mechanism which could possibly be employed to utilise antimicrobial agents against which certain microbes have developed resistance (169).

Antibiotic treatment does not distinguish between pathogenic and non-pathogenic beneficial microbes. The removal of beneficial microbes is potentially harmful (170, 171). Bacteriophage therapies and monoclonal antibodies are potential future treatment options, but they are merely in the early stages of development (172, 173). Therapeutic modalities which are not affected by the current bacterial resistance mechanisms is an interesting future prospect for dealing with multi-resistant bacteria.

Current research should focus on developing sustainable treatment options for a longer time period. Effective prophylactic strategies to reduce the need for antibiotic treatment could prove useful in the future. Many variables need to be considered for reducing the infection rate and severity. Host susceptibility and virulence potential (virulence factor genes and phylogenetic groups) of the bacterial strain probably play a part in determining the UTI risk and outcome (174, 175).

Bacterial lysates or microbe-specific vaccines are enticing possibilities (176, 177).

Even though efforts to develop an effective vaccine are promising, challenges are posed by the wide variations in genes associated with uropathogenic *E. coli* strains. Vaccines targeting extra-intestinal pathogenic *E. coli* strains demonstrated favorable safety results, but the clinical trial was underpowered to detect a significant reduction in vaccine-specific response (176).

7. References:

1.   NORM/NORM-VET 2017. Usage of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Norway. Tromsø / Oslo 2018. ISSN:1502-2307 (print) / 1890-9965 (electronic).

2.   Baerheim A. Empirical treatment of uncomplicated cystitis. Scand J Prim Health Care. 2012;30:1-2.

3.   Vik I, Bollestad M, Grude N, Baerheim A, Damsgaard E, Neumark T, et al. Ibuprofen versus pivmecillinam for uncomplicated urinary tract infection in women-A double-blind, randomised non-inferiority trial. PLoS Med. 2018;15:e1002569.

4.   Falagas ME, Kotsantis IK, Vouloumanou EK, Rafailidis PI. Antibiotics versus placebo in the treatment of women with uncomplicated cystitis: a meta-analysis of randomised controlled trials. J Infect. 2009;58:91-102.

5.   Ferry SA, Holm SE, Stenlund H, Lundholm R, Monsen TJ. The natural course of uncomplicated lower urinary tract infection in women illustrated by a randomised placebo controlled study. Scand J Infect Dis. 2004;36:296-301.

6.   Kronenberg A, Butikofer L, Odutayo A, Muhlemann K, da Costa BR, Battaglia M, et al. Symptomatic treatment of uncomplicated lower urinary tract infections in the ambulatory setting: randomised, double blind trial. BMJ. 2017;359:j4784.

7.   Gagyor I, Bleidorn J, Kochen MM, Schmiemann G, Wegscheider K, Hummers-Pradier E. Ibuprofen versus fosfomycin for uncomplicated urinary tract infection in women: randomised controlled trial. BMJ. 2015;351:h6544.

8.   Van Boeckel TP, Gandra S, Ashok A, Caudron Q, Grenfell BT, Levin SA, et al. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. Lancet Infect Dis. 2014;14:742-50.

9.   Czaplewski L, Bax R, Clokie M, Dawson M, Fairhead H, Fischetti VA, et al. Alternatives to antibiotics-a pipeline portfolio review. Lancet Infect Dis. 2016;16:239-51.

10.   Foxman B, Buxton M. Alternative approaches to conventional treatment of acute uncomplicated urinary tract infection in women. Curr Infect Dis Rep. 2013;15:124-9.

11.   Kranz J, Schmidt S, Lebert C, Schneidewind L, Mandraka F, Kunze M, et al. The 2017 Update of the German Clinical Guideline on Epidemiology, Diagnostics, Therapy, Prevention, and Management of Uncomplicated Urinary Tract Infections in Adult Patients: Part 1. Urol Int. 2018;100:263-70.

12.   Hooton TM. Clinical practice. Uncomplicated urinary tract infection. N Engl J Med. 2012;366:1028-37.

13.   Foxman B. The epidemiology of urinary tract infection. Nat Rev Urol. 2010;7:653-60.

14.   Colgan R, Williams M. Diagnosis and treatment of acute uncomplicated cystitis. Am Fam Physician. 2011;84:771-6.

15.   Butler CC, Hawking MK, Quigley A, McNulty CA. Incidence, severity, help seeking, and management of uncomplicated urinary tract infection: a population-based survey. Brit J Gen Pract. 2015;65:e702-7.

16.   Foxman B, Barlow R, D'Arcy H, Gillespie B, Sobel JD. Urinary tract infection: self-reported incidence and associated costs. Ann Epidemiol. 2000;10:509-15.

17.   Tandogdu Z, Wagenlehner FM. Global epidemiology of urinary tract infections. Curr Opin Infect Dis. 2016;29:73-9.

18.   Hooton TM, Scholes D, Stapleton AE, Roberts PL, Winter C, Gupta K, et al. A prospective study of asymptomatic bacteriuria in sexually active young women. N Engl J Med. 2000;343:992-7.

19. Hunskaar S. Nyrer og urinveier. [Kidneys and the urinary tract]. Allmennmedisin. 3rd edition. Oslo: Gyldendal;2013. p. 644.

20.   Czaja CA, Scholes D, Hooton TM, Stamm WE. Population-based epidemiologic analysis of acute pyelonephritis. Clin Infect Dis. 2007;45:273-80.

21.   Hooton TM, Scholes D, Hughes JP, Winter C, Roberts PL, Stapleton AE, et al. A prospective study of risk factors for symptomatic urinary tract infection in young women. N Engl J Med. 1996;335:468-74.

22.   Holm A, Cordoba G, Sorensen TM, Jessen LR, Frimodt-Moller N, Siersma V, et al. Clinical accuracy of point-of-care urine culture in general practice. Scand J Prim Health Care. 2017;35:170-7.

23.   Flottorp S, Oxman AD, Cooper JG, Hjortdahl P, Sandberg S, Vorland LH. Retningslinjer for diagnostikk og behandling av akutte vannlatingsplager hos kvinner [Guidelines for diagnosis and treatment of acute urinary tract problems in women]. Tidsskr Nor Laegeforen. 2000;120:1748-53.

24.   Drekonja DM, Rector TS, Cutting A, Johnson JR. Urinary tract infection in male veterans: treatment patterns and outcomes. JAMA Intern Med. 2013;173:62-8.

25.   Tandan M, Duane S, Cormican M, Murphy AW, Vellinga A. Reconsultation and Antimicrobial Treatment of Urinary Tract Infection in Male and Female Patients in General Practice. Antibiotics. 2016;5:31.

26.   Bent S, Nallamothu BK, Simel DL, Fihn SD, Saint S. Does this woman have an acute uncomplicated urinary tract infection? JAMA. 2002;287:2701-10.

27.   Schmiemann G, Kniehl E, Gebhardt K, Matejczyk MM, Hummers-Pradier E. The diagnosis of urinary tract infection: a systematic review. Dtsch Arztebl Int. 2010;107:361-7.

28.   Gupta K, Hooton TM, Roberts PL, Stamm WE. Patient-initiated treatment of uncomplicated recurrent urinary tract infections in young women. Ann Intern Med. 2001;135:9-16.

29.   Wilbanks MD, Galbraith JW, Geisler WM. Dysuria in the emergency department: missed diagnosis of Chlamydia trachomatis. West J Emerg Med. 2014;15:227-30.

30.   Donofrio JC, Weiner SG. Female patient self-diagnosis compared with emergency physician diagnosis of urinary tract infection. J Emerg Med.2013;45:969-73.

31.   Little P, Merriman R, Turner S, Rumsby K, Warner G, Lowes JA, et al. Presentation, pattern, and natural course of severe symptoms, and role of antibiotics and antibiotic resistance among patients presenting with suspected uncomplicated urinary tract infection in primary care: observational study. BMJ. 2010;340:b5633.

32.   Bent S, Saint S. The optimal use of diagnostic testing in women with acute uncomplicated cystitis. Am J Med. 2002;113:20s-8s.

33.   Giesen LG, Cousins G, Dimitrov BD, van de Laar FA, Fahey T. Predicting acute uncomplicated urinary tract infection in women: a systematic review of the diagnostic accuracy of symptoms and signs. BMC Fam Pract. 2010;11:78.

34.   Little P, Turner S, Rumsby K, Jones R, Warner G, Moore M, et al. Validating the prediction of lower urinary tract infection in primary care: sensitivity and specificity of urinary dipsticks and clinical scores in women. Br J Gen Pract. 2010;60:495-500.

35.   Hurlbut TA, 3rd, Littenberg B. The diagnostic accuracy of rapid dipstick tests to predict urinary tract infection. Am J Clin Patol. 1991;96:582-8.

36.   Meister L, Morley EJ, Scheer D, Sinert R. History and physical examination plus laboratory testing for the diagnosis of adult female urinary tract infection. Acad Emerg Med. 2013;20:631-45.

37.   Richards D, Toop L, Chambers S, Fletcher L. Response to antibiotics of women with symptoms of urinary tract infection but negative dipstick urine test results: double blind randomised controlled trial. BMJ. 2005;331:143.

38.   Medina-Bombardo D, Jover-Palmer A. Does clinical examination aid in the diagnosis of urinary tract infections in women? A systematic review and meta-analysis. BMC Fam Pract. 2011;12:111.

39.   Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis. 2011;52:e103-20.

40.   Saint S, Scholes D, Fihn SD, Farrell RG, Stamm WE. The effectiveness of a clinical practice guideline for the management of presumed uncomplicated urinary tract infection in women. The Am J Med. 1999;106:636-41.

41.   Komaroff AL, Sawayer K, Flatley M, Browne C. Nurse practitioner management of common respiratory and genitourinary infections, using protocols. Nurs rES. 1976;25:84-9.

42. O'Connor PJ, Solberg LI, Christianson J, Amundson G, Mosser G. Mechanism of action and impact of a cystitis clinical practice guideline on outcomes and costs of care in an HMO. Jt Comm J Qual Improv. 1996;22:673-82.

43. Alidjanov JF, Abdufattaev UA, Makhsudov SA, Pilatz A, Akilov FA, Naber KG, et al. New self-reporting questionnaire to assess urinary tract infections and differential diagnosis: acute cystitis symptom score. Urol Int. 2014;92:230-6.

44. Fox MT, Melia MT, Same RG, Conley AT, Tamma PD. A Seven-Day Course of TMP-SMX May Be as Effective as a Seven-Day Course of Ciprofloxacin for the Treatment of Pyelonephritis. Am J Med. 2017;130:842-5.

45. Aspevall O, Hallander H, Gant V, Kouri T. European guidelines for urinalysis: a collaborative document produced by European clinical microbiologists and clinical chemists under ECLM in collaboration with ESCMID. Clin Microbiol Infect. 2001;7:173-8.

46. Christiaens TC, De Meyere M, Verschraegen G, Peersman W, Heytens S, De Maeseneer JM. Randomised controlled trial of nitrofurantoin versus placebo in the treatment of uncomplicated urinary tract infection in adult women. Br J Gen Pract. 2002;52:729-34.

47. Ferry SA, Holm SE, Stenlund H, Lundholm R, Monsen TJ. Clinical and bacteriological outcome of different doses and duration of pivmecillinam compared with placebo therapy of uncomplicated lower urinary tract infection in women: the LUTIW project. Scand J Prim Health Care. 2007;25:49-57.

48. Norwegian Directorate of Health. Antibiotikabruk i primærhelsetjenesten. [National guidelines for antibiotic use in primary care 2016]. [cited 04.03.19]. Available from: http://www.antibiotikaiallmennpraksis.no

49. Katchman EA, Milo G, Paul M, Christiaens T, Baerheim A, Leibovici L. Three-day vs longer duration of antibiotic treatment for cystitis in women: systematic review and meta-analysis. Am J Med. 2005;118:1196-207.

50. Milo G, Katchman EA, Paul M, Christiaens T, Baerheim A, Leibovici L. Duration of antibacterial treatment for uncomplicated urinary tract infection in women. Cochrane Database Syst Rev. 2005:Cd004682.

51. Swedish Medical Products Agency. Läkemedelsbehandling av urinvägsinfektioner i öppenvård – behandlingsrekommendation. [Treatment recommendations for urinary tract infections in general practice 2017]. [cited 04.03.19] Available from: https://lakemedelsverket.se/upload/halso-och-sjukvard/behandlingsrekommendationer/Information-fran-lakemedelsverket-nr-5-2017-behandlingsrekommendation.pdf

52.   Johansen IS, Gerstoft J, Helweg-Larsen J, Engberg J, Frimodt-Møller N, Böcher S et al. Vejledning i brug af antibiotika. [Recommendations for antibiotic use]. 2018 [cited 04.03.19] Available from: http://pro.medicin.dk/Specielleemner/Emner/318019#a000.

53.   The National Institute for Health and Care Excellence. Urinary tract infection (lower):antimicrobial prescribing. 2018 [cited 04.03.19] Available from: https://www.nice.org.uk/guidance/ng109/resources/urinary-tract-infection-lower-antimicrobial-prescribing-pdf-66141546350533.

54.   Caron F, Galperine T, Flateau C, Azria R, Bonacorsi S, Bruyere F, et al. Practice guidelines for the management of adult community-acquired urinary tract infections. Med Mal Infect. 2018;48:327-58.

55.   Health Services I. Antimicrobial prescribing guidelines for primary care in Ireland. 2018 [cited 04.03.19] Available from: https://www.hse.ie/eng/services/list/2/gp/antibiotic-prescribing/conditions-and-treatments/urinary/.

56.   Kranz J, Schmidt S, Lebert C, Schneidewind L, Mandraka F, Kunze M, et al. The 2017 Update of the German Clinical Guideline on Epidemiology, Diagnostics, Therapy, Prevention, and Management of Uncomplicated Urinary Tract Infections in Adult Patients. Part II: Therapy and Prevention. Urol Int. 2018;100:271-8.

57.   Gupta K, Grigoryan L, Trautner B. Urinary Tract Infection. Ann Intern Med. 2017;167:Itc49-itc64.

58.   Therapeutic Guidelines Limited. Antibiotics. 2017. [cited 25.11.17] Available from: https://tgldcdp.tg.org.au/guideLine?guidelinePage=Antibiotic&frompage=etgcomplete.

59.   Walker E, Lyman A, Gupta K, Mahoney MV, Snyder GM, Hirsch EB. Clinical Management of an Increasing Threat: Outpatient Urinary Tract Infections Due to Multidrug-Resistant Uropathogens. Clin Infect DIs. 2016;63:960-5.

60.   Huttner A, Kowalczyk A, Turjeman A, Babich T, Brossier C, Eliakim-Raz N, et al. Effect of 5-Day Nitrofurantoin vs Single-Dose Fosfomycin on Clinical Resolution of Uncomplicated Lower Urinary Tract Infection in Women: A Randomised Clinical Trial. JAMA. 2018;319:1781-9.

61.   Little P, Moore MV, Turner S, Rumsby K, Warner G, Lowes JA, et al. Effectiveness of five different approaches in management of urinary tract infection: randomised controlled trial. BMJ. 2010;340:c199.

62.   Gagyor I, Haasenritter J, Bleidorn J, McIsaac W, Schmiemann G, Hummers-Pradier E, et al. Predicting antibiotic prescription after symptomatic treatment for urinary tract infection: development of a model using data from an RCT in general practice. Br J Gen Pract. 2016;66:e234-40.

63.   Bleidorn J, Gagyor I, Kochen MM, Wegscheider K, Hummers-Pradier E. Symptomatic treatment (ibuprofen) or antibiotics (ciprofloxacin) for uncomplicated urinary tract infection?--results of a randomised controlled pilot trial. BMC Med. 2010;8:30.

64.   Moore M, Trill J, Simpson C, Webley F, Radford M, Stanton L, et al. Uva-ursi extract and ibuprofen as alternative treatments for uncomplicated urinary tract infection in women (ATAFUTI): a factorial randomised trial. Clin Microbiol Infect. 2019. doi: 10.1016/j.cmi.2019.01.011. [Epub ahead of print]

65.   Hooton TM, Vecchio M, Iroz A, Tack I, Dornic Q, Seksek I, et al. Effect of Increased Daily Water Intake in Premenopausal Women With Recurrent Urinary Tract Infections: A Randomised Clinical Trial. JAMA Intern Med. 2018;178:1509-15.

66.   Foxman B. Urinary tract infection syndromes: occurrence, recurrence, bacteriology, risk factors, and disease burden. Infect Dis Clin North Am. 2014;28:1-13.

67.   Monsen TJ, Holm SE, Ferry BM, Ferry SA. Mecillinam resistance and outcome of pivmecillinam treatment in uncomplicated lower urinary tract infection in women. APMIS. 2014;122:317-23.

68.   Amna MA, Chazan B, Raz R, Edelstein H, Colodner R. Risk factors for non-Escherichia coli community-acquired bacteriuria. Infection. 2013;41:473-7.

69.   Adeghate J, Juhasz E, Pongracz J, Rimanoczy E, Kristof K. Does Staphylococcus Saprophyticus Cause Acute Cystitis only in Young Females, or is there more to the Story? A One-Year Comprehensive Study Done in Budapest, Hungary. Acta Microbiol Immunol Hung. 2016;63:57-67.

70.   Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nat Rev Microbiol. 2015;13:269-84.

71.   den Heijer CD, Penders J, Donker GA, Bruggeman CA, Stobberingh EE. The importance of gender-stratified antibiotic resistance surveillance of unselected uropathogens: a Dutch Nationwide Extramural Surveillance study. PLoS One. 2013;8:e60497.

72.   Heytens S, De Sutter A, Coorevits L, Cools P, Boelens J, Van Simaey L, et al. Women with symptoms of a urinary tract infection but a negative urine culture: PCR-based quantification of Escherichia coli suggests infection in most cases. Clinical Microbiol Infect. 2017;23:647-652.

73.   Heytens S, Boelens J, Claeys G, DeSutter A, Christiaens T. Uropathogen distribution and antimicrobial susceptibility in uncomplicated cystitis in Belgium, a high antibiotics prescribing country: 20-year surveillance. Eur J Clin Microbiol Infect Dis. 2016;36:105-113.

74.   De Backer D, Christiaens T, Heytens S, De Sutter A, Stobberingh EE, Verschraegen G. Evolution of bacterial susceptibility pattern of Escherichia coli in uncomplicated urinary tract infections in a country with high antibiotic consumption: a comparison of two surveys with a 10 year interval. J Antimicrob Chemother. 2008;62:364-8.

75.   Neuzillet Y, Naber KG, Schito G, Gualco L, Botto H. French results of the ARESC study: clinical aspects and epidemiology of antimicrobial resistance in female patients with cystitis. Implications for empiric therapy. Med Mal Infect. 2012;42:66-75.

76.   Malmartel A, Ghasarossian C. Epidemiology of urinary tract infections, bacterial species and resistances in primary care in France. Eur J Clin Microbiol Infect Dis. 2016;35:447-51.

77.   Kahlmeter G, Ahman J, Matuschek E. Antimicrobial Resistance of Escherichia coli Causing Uncomplicated Urinary Tract Infections: A European Update for 2014 and Comparison with 2000 and 2008. Infect Dis Ther. 2015;4:417-23.

78.   Chin TL, MacGowan AP, Bowker KE, Elder F, Beck CR, McNulty C. Prevalence of antibiotic resistance in Escherichia coli isolated from urine samples routinely referred by GPs in a large urban centre in south-west England. J Antimicrob Chemother. 2015;70:2167-9.

79.   Delisle G, Quach C, Domingo MC, Boudreault AA, Gourdeau M, Bernatchez H, et al. Escherichia coli antimicrobial susceptibility profile and cumulative antibiogram to guide empirical treatment of uncomplicated urinary tract infections in women in the province of Quebec, 2010-15. J Antimicrob Chemother. 2016;71:3562-7.

80.   Australian Commission on Safety and Quality in Health Care. AURA 2017: second Australian report on antimicrobial use and reistance in human health Sydnes. 2017 [Cited 04.03.19] Available from: https://www.safetyandquality.gov.au/antimicrobial-use-and-resistance-in-australia/resources-page/.

81.   Stefaniuk E, Suchocka U, Bosacka K, Hryniewicz W. Etiology and antibiotic susceptibility of bacterial pathogens responsible for community-acquired urinary tract infections in Poland. Eur J Clin Microbiol Infect Dis. 2016;35:1363-9.

82.   European Centre for Disease Prevention and Control. Surveillance of antimicrobial resistance in Europe- Annual report of the European Antimicrobial Resistance Surveillance Netweork (EARS-Net) 2017. 2018 [cited 25.01.19] Available from: https://ecdc.europa.eu/en/publications-data/surveillance-antimicrobial-resistance-europe-2017

83.   Reuland EA, Al Naiemi N, Kaiser AM, Heck M, Kluytmans JA, Savelkoul PH, et al. Prevalence and risk factors for carriage of ESBL-producing Enterobacteriaceae in Amsterdam. J Antimicrob Chemother. 2016;71:1076-82.

84.   Hillier S, Bell J, Heginbothom M, Roberts Z, Dunstan F, Howard A, et al. When do general practitioners request urine specimens for microbiology analysis? The applicability of antibiotic resistance surveillance based on routinely collected data. J Antimicrob Chemother. 2006;58:1303-6.

85.   Chin TL, McNulty C, Beck C, MacGowan A. Antimicrobial resistance surveillance in urinary tract infections in primary care. J Antimicrob Chemother. 2016;71:2723-8.

86.   Baerheim A, Digranes A, Hunskaar S. Are resistance patterns in uropathogens published by microbiological laboratories valid for general practice? APMIS. 1999;107:676-80.

87.   Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. BMJ. 2010;340:c2096.

88.   Knothe H, Shah P, Krcmery V, Antal M, Mitsuhashi S. Transferable resistance to cefotaxime, cefoxitin, cefamandole and cefuroxime in clinical isolates of Klebsiella pneumoniae and Serratia marcescens. Infection. 1983;11:315-7.

89.   Kliebe C, Nies BA, Meyer JF, Tolxdorff-Neutzling RM, Wiedemann B. Evolution of plasmid-coded resistance to broad-spectrum cephalosporins. Antimicrob Agents Chemother. 1985;28:302-7.

90.   Livermore DM. Fourteen years in resistance. Int J Antimicrob Agents. 2012;39:283-94.

91.   Oteo J, Perez-Vazquez M, Campos J. Extended-spectrum [β]-lactamase producing Escherichia coli: changing epidemiology and clinical impact. Curr Opin Infect Dis. 2010;23:320-6.

92.   Ben-Ami R, Rodriguez-Bano J, Arslan H, Pitout JD, Quentin C, Calbo ES, et al. A multinational survey of risk factors for infection with extended-spectrum β -lactamase-producing enterobacteriaceae in nonhospitalized patients. Clin Infect Dis. 2009;49:682-90.

93.   Zowawi HM, Harris PN, Roberts MJ, Tambyah PA, Schembri MA, Pezzani MD, et al. The emerging threat of multidrug-resistant Gram-negative bacteria in urology. Nat Rev Urol. 2015;12:570-84.

94.   Pitout JD, Laupland KB. Extended-spectrum β -lactamase-producing Enterobacteriaceae: an emerging public-health concern. Lancet Inf Dis. 2008;8:159-66.

95.   Giske CG, Sundsfjord AS, Kahlmeter G, Woodford N, Nordmann P, Paterson DL, et al. Redefining extended-spectrum β -lactamases: balancing science and clinical need. J Antimicrob Chemother. 2009;63:1-4.

96.   Soraas A, Sundsfjord A, Sandven I, Brunborg C, Jenum PA. Risk factors for community-acquired urinary tract infections caused by ESBL-producing enterobacteriaceae--a case-control study in a low prevalence country. PLoS One. 2013;8:e69581.

97.   Hertz FB, Schonning K, Rasmussen SC, Littauer P, Knudsen JD, Lobner-Olesen A, et al. Epidemiological factors associated with ESBL- and non ESBL-producing E. coli causing urinary tract infection in general practice. Infect Dis. 2016;48:241-5.

98.   Azap OK, Arslan H, Serefhanoglu K, Colakoglu S, Erdogan H, Timurkaynak F, et al. Risk factors for extended-spectrum β -lactamase positivity in uropathogenic Escherichia coli isolated from community-acquired urinary tract infections. Clin Microbiol Infect. 2010;16:147-51.

99.   Gopal Rao G, Batura D, Batura N, Nielsen PB. Key demographic characteristics of patients with bacteriuria due to extended spectrum β -lactamase (ESBL)-producing Enterobacteriaceae in a multiethnic community, in North West London. Infect Dis. 2015;47:719-24.

100.   Jorgensen SB, Soraas A, Sundsfjord A, Liestol K, Leegaard TM, Jenum PA. Fecal carriage of extended spectrum β -lactamase producing Escherichia coli and Klebsiella pneumoniae after urinary tract infection - A three year prospective cohort study. PLoS One. 2017;12:e0173510.

101.   Titelman E, Hasan CM, Iversen A, Naucler P, Kais M, Kalin M, et al. Faecal carriage of extended-spectrum β -lactamase-producing Enterobacteriaceae is common 12 months after infection and is related to strain factors. Clin Microbiol Infect. 2014;20:O508-15.

102.   Ruppe E, Armand-Lefevre L, Estellat C, Consigny PH, El Mniai A, Boussadia Y, et al. High Rate of Acquisition but Short Duration of Carriage of Multidrug-Resistant Enterobacteriaceae After Travel to the Tropics. Clin Infect Dis. 2015;61:593-600.

103.   Cho SY, Choi SM, Park SH, Lee DG, Choi JH, Yoo JH. Amikacin therapy for urinary tract infections caused by extended-spectrum β -lactamase-producing Escherichia coli. Korean J Intern Med. 2016;31:156-61.

104.   Veve MP, Wagner JL, Kenney RM, Grunwald JL, Davis SL. Comparison of fosfomycin to ertapenem for outpatient or step-down therapy of extended-spectrum β -lactamase urinary tract infections. Int J Antimcrob Agents. 2016;48:56-60.

105.   Trad MA, Zhong LH, Llorin RM, Tan SY, Chan M, Archuleta S, et al. Ertapenem in outpatient parenteral antimicrobial therapy for complicated urinary tract infections. J Chemother. 2017;29:25-9.

106.   Bouxom H, Fournier D, Bouiller K, Hocquet D, Bertrand X. What non-carbapenem antibiotics are active against ESBL-producing enterobacteriaceae? Int J Antimicrob Agents. 2018;52:100-103.

107.   Titelman E, Iversen A, Kahlmeter G, Giske CG. Antimicrobial susceptibility to parenteral and oral agents in a largely polyclonal collection of CTX-M-14 and CTX-M-15-producing Escherichia coli and Klebsiella pneumoniae. APMIS. 2011;119:853-63.

108.   Seo YB, Lee J, Kim YK, Lee SS, Lee JA, Kim HY, et al. Randomised controlled trial of piperacillin-tazobactam, cefepime and ertapenem for the treatment of urinary tract infection caused by extended-spectrum β -lactamase-producing Escherichia coli. BMC Infect Dis. 2017;17:404.

109.   Rossi B, Soubirou JF, Chau F, Massias L, Dion S, Lepeule R, et al. Cefotaxime and Amoxicillin-Clavulanate Synergism against Extended-Spectrum-β -Lactamase-Producing Escherichia coli in a Murine Model of Urinary Tract Infection. Antimicrob Agents Chemother. 2015;60:424-30.

110.   Meier S, Weber R, Zbinden R, Ruef C, Hasse B. Extended-spectrum β -lactamase-producing Gram-negative pathogens in community-acquired urinary tract infections: an increasing challenge for antimicrobial therapy. Infection. 2011;39:333-40.

111.	Zykov IN, Sundsfjord A, Smabrekke L, Samuelsen O. The antimicrobial activity of mecillinam, nitrofurantoin, temocillin and fosfomycin and comparative analysis of resistance patterns in a nationwide collection of ESBL-producing Escherichia coli in Norway 2010-2011. Infect Dis. 2016;48:99-107.

112.	Komp Lindgren P, Klockars O, Malmberg C, Cars O. Pharmacodynamic studies of nitrofurantoin against common uropathogens. J Antimicrob Chemother. 2015;70:1076-82.

113.	Auer S, Wojna A, Hell M. Oral treatment options for ambulatory patients with urinary tract infections caused by extended-spectrum-β -lactamase-producing Escherichia coli. Antimicrob Agents Chemother. 2010;54:4006-8.

114.	Sabharwal ER, Sharma R. Fosfomycin: An Alternative Therapy for the Treatment of UTI Amidst Escalating Antimicrobial Resistance. J Clin Diagn Res. 2015;9:Dc06-dc9.

115.	Linsenmeyer K, Strymish J, Weir S, Berg G, Brecher S, Gupta K. Activity of fosfomycin for ESBL uropathogens in community and hospitalized patients. Antimicrob Agents Chemother. 2015;60:1134-6.

116.	Rodriguez-Bano J, Alcala JC, Cisneros JM, Grill F, Oliver A, Horcajada JP, et al. Community infections caused by extended-spectrum β -lactamase-producing Escherichia coli. Arch Intern Med. 2008;168:1897-902.

117.	Titelman E, Iversen A, Kalin M, Giske CG. Efficacy of pivmecillinam for treatment of lower urinary tract infection caused by extended-spectrum β -lactamase-producing Escherichia coli and Klebsiella pneumoniae. Microb Drug Resist. 2012;18:189-92.

118.	Soraas A, Sundsfjord A, Jorgensen SB, Liestol K, Jenum PA. High rate of per oral mecillinam treatment failure in community-acquired urinary tract infections caused by ESBL-producing Escherichia coli. PLoS One. 2014;9:e85889.

119.	Jansaker F, Frimodt-Moller N, Sjogren I, Dahl Knudsen J. Clinical and bacteriological effects of pivmecillinam for ESBL-producing Escherichia coli or Klebsiella pneumoniae in urinary tract infections. J Antimicrob Chemother. 2014;69:769-72.

120.	Nicolle LE, Mulvey MR. Successful treatment of ctx-m ESBL producing Escherichia coli relapsing pyelonephritis with long term pivmecillinam. Scand J Infect Dis. 2007;39:748-9.

121.	O'Kelly F, Kavanagh S, Manecksha R, Thornhill J, Fennell JP. Characteristics of gram-negative urinary tract infections caused by extended spectrum β lactamases: pivmecillinam as a treatment option within South Dublin, Ireland. BMC Infect Dis. 2016;16:620.

122.	Lampri N, Galani I, Poulakou G, Katsarolis I, Petrikkos G, Giamarellou H, et al. Mecillinam/clavulanate combination: a possible option for the treatment of community-acquired uncomplicated urinary tract infections caused by extended-spectrum β -lactamase-producing Escherichia coli. J Antimicrob Chemother. 2012;67:2424-8.

123.   Lund F, Tybring L. 6 -amidinopenicillanic acids--a new group of antibiotics. Nat New Biol. 1972;236:135-7.

124.   Nicolle LE. Pivmecillinam in the treatment of urinary tract infections. J Antimicrob Chemother. 2000;46:35-9.

125.   Roholt K, Nielsen B, Kristensen. Pharmacokinetic studies with mecillinam and pivmecillinam. Chemotherapy. 1975;21:146-66.

126.   Dewar S, Reed LC, Koerner RJ. Emerging clinical role of pivmecillinam in the treatment of urinary tract infection in the context of multidrug-resistant bacteria. J Antimicrob Chemother. 2014;69:303-8.

127.   Baines SD, O'Connor R, Huscroft G, Saxton K, Freeman J, Wilcox MH. Mecillinam: a low-risk antimicrobial agent for induction of Clostridium difficile infection in an in vitro human gut model. J Antimicrob Chemother. 2009;63:838-9.

128.   Sullivan A, Edlund C, Svenungsson B, Emtestam L, Nord CE. Effect of perorally administered pivmecillinam on the normal oropharyngeal, intestinal and skin microflora. J Chemother. 2001;13:299-308.

129.   Sullivan A, Fianu-Jonasson A, Landgren BM, Nord CE. Ecological effects of perorally administered pivmecillinam on the normal vaginal microflora. Antimicrob Agents Chemother. 2005;49:170-5.

130.   Anderson JD, Adams MA. Urinary excretion of mecillinam by volunteers receiving film-coated tablets of pivmecillinam hydrochloride. Chemotherapy. 1979;25:1-4.

131.   Park JT, Strominger JL. Mode of action of penicillin. Science. 1957;125:99-101.

132.   Grunberg E, Cleeland R, Beskid G, DeLorenzo WF. In vivo synergy between 6 β -amidinopenicillanic acid derivatives and other antibiotics. Antimicrob Agents Chemother. 1976;9:589-94.

133.   Cho H, Uehara T, Bernhardt TG. B -lactam antibiotics induce a lethal malfunctioning of the bacterial cell wall synthesis machinery. Cell. 2014;159:1300-11.

134.   Tipper DJ. Mode of action of β-lactam antibiotics. Pharmacol Ther. 1985;27:1-35.

135.   Sauvage E, Kerff F, Terrak M, Ayala JA, Charlier P. The penicillin-binding proteins: structure and role in peptidoglycan biosynthesis. FEMS Microbiol Rev. 2008;32:234-58.

136.   Hanberger H, Nilsson LE, Svensson E, Maller R. Synergic post-antibiotic effect of mecillinam, in combination with other β -lactam antibiotics in relation to morphology and initial killing. J Antimicrob Chemother. 1991;28:523-32.

137.   Neu HC. Synergistic activity of mecillinam in combination with the β -lactamase inhibitors clavulanic acid and sulbactam. Antimicrob Agents Chemother. 1982;22:518-9.

138.   Thomas K, Weinbren MJ, Warner M, Woodford N, Livermore D. Activity of mecillinam against ESBL producers in vitro. J Antimicrob Chemother. 2006;57:367-8.

139.   Sougakoff W, Jarlier V. Comparative potency of mecillinam and other β -lactam antibiotics against Escherichia coli strains producing different β -lactamases. J Antimicrob Chemother. 2000;46:9-14.

140.   Wootton M, Walsh TR, Macfarlane L, Howe RA. Activity of mecillinam against Escherichia coli resistant to third-generation cephalosporins. J Antimicrob Chemother. 2010;65:79-81.

141.   Kahlmeter G. An international survey of the antimicrobial susceptibility of pathogens from uncomplicated urinary tract infections: the ECO.SENS Project. J Antimicrob Chemother. 2003;51:69-76.

142.   Thulin E, Thulin M, Andersson DI. Reversion of High-level Mecillinam Resistance to Susceptibility in Escherichia coli During Growth in Urine. EBioMedicine. 2017;23:111-8.

143.   Norwegian Directorate of Health. Fastlegestatistikk, fjerde kvatral 2017. [General practitioners statistics, 4th quarter 2017]. 2018. [cited 04.03.19] Available at: https://helsedirektoratet.no/statistikk-og-analyse/fastlegestatistikk#fastlegestatistikk-2017

144.   Morken T, Myhr K, Ragnes G, Hunskår S. Legevaktorganisering i Norge. Rapport fra Nasjonal Legevaktregister 2016. [Out-of-hours care in Norway. Report from National registry on Emergency Primary Health Care 2016]. Report nr.4-2016. Bergen: National Centre for Emergency Primary Health Care, Uni Research Helse, 2016.

145.   Grude N, Tveten Y, Kristiansen BE. Urinary tract infections in Norway: bacterial etiology and susceptibility. A retrospective study of clinical isolates. Clin Microbiol Infect. 2001;7:543-7.

146.   Bergans T BJ, Digranes A et al. . Susceptibility testing of bacteria and fungi. Reports from "The Norwegian Working Group on Antibiotics". Scand J Infec Dis 1997;103:1-36.

147.   The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 9.0, 2019 [Cited 04.03.19] Available from: http://www.eucast.org. .

148.   The Norwegian Institute for Public Health. The Norwegian Prescription Database. 2017. [cited 25.11.18] Available from: http://www.norpd.no

149.   Social science statistics. 2017. [cited 20.03.2017] Available from: http://www.socscistatistics.com/tests/chisquare/Default.aspx

150.   Hooton TM, Roberts PL, Cox ME, Stapleton AE. Voided midstream urine culture and acute cystitis in premenopausal women. N Engl J Med. 2013;369:1883-91.

151.   Stamm WE, Counts GW, Running KR, Fihn S, Turck M, Holmes KK. Diagnosis of coliform infection in acutely dysuric women. N Engl J Med. 1982;307:463-8.

152.   Heisey DM. The Abuse of Power AU - Hoenig, John M. Am Stat. 2001;55:19-24.

153.   Hjemås G, Vold B. På randen av samhandling. [On the verge of co-operation]. Statistics Norway. 2011 [Cited 04.03.19] Available from: https://www.ssb.no/helse/artikler-og-publikasjoner/paa-randen-av-samhandling.

154.   Jeppesen N, Frimodt-Moller C. Serum concentrations and penetration into prostate of mecillinam and ampicillin. Curr Med Res Opin. 1984;9:213-8.

155.   Cordoba G, Holm A, Sorensen TM, Siersma V, Sandholdt H, Makela M, et al. Use of diagnostic tests and the appropriateness of the treatment decision in patients with suspected urinary tract infection in primary care in Denmark - observational study. BMC Fam Pract. 2018;19:65.

156.   Cheng G, Dai M, Ahmed S, Hao H, Wang X, Yuan Z. Antimicrobial drugs in fighting against antimicrobial resistance. Front Microbiol. 2016;7:470.

157.   Davenport M, Mach KE, Shortliffe LMD, Banaei N, Wang TH, Liao JC. New and developing diagnostic technologies for urinary tract infections. Nat Rev Urol. 2017;14:296-310.

158.   Lindback H, Lindback J, Melhus A. Inadequate adherence to Swedish guidelines for uncomplicated lower urinary tract infections among adults in general practice. APMIS. 2017;125:816-21.

159.   Hallsworth M, Chadborn T, Sallis A, Sanders M, Berry D, Greaves F, et al. Provision of social norm feedback to high prescribers of antibiotics in general practice: a pragmatic national randomised controlled trial. Lancet. 2016;387:1743-52.

160.   Vellinga A, Galvin S, Duane S, Callan A, Bennett K, Cormican M, et al. Intervention to improve the quality of antimicrobial prescribing for urinary tract infection: a cluster randomised trial. CMAJ. 2016;188:108-15.

161.   Schön G, Hedin K, Sundqvist M. Pivmecillinam in the treatment of ESBL-producing Escherichia coli. Clin Microbiol Infect. 2011;17:S443.

162.   Craig WA. Basic pharmacodynamics of antibacterials with clinical applications to the use of β-lactams, glycopeptides, and linezolid. Infect Dis Clin North Am. 2003;17:479-501.

163.   Kerrn MB, Frimodt-Moller N, Espersen F. Urinary concentrations and urine ex-vivo effect of mecillinam and sulphamethizole. Clin Microbiol Infect. 2004;10:54-61.

164.   Jensen KS Henriksen A, Frimodt-Moeller N. Pivmecilliam: Estimation of adequate dosage for susceptible and ESBL-producing E. coli by Monte Carlo PK/PD simulation. Abstracts of the 18nd European Congress of Clinical Microbiology and Infectious Diseases, Barcelona, Spain, 2008 Abstract P1255. [Cited 04.03.19] Available from: https://www.pkpdsim.candorsim.dk/p-ECCMID2008.html

165.   Pinart M, Kranz J, Jensen K, Proctor T, Naber K, Kunath F, et al. Optimal dosage and duration of pivmecillinam treatment for uncomplicated lower urinary tract infections: a systematic review and meta-analysis. Int J Infect Dis. 2017;58:96-109.

166.   Anesi JA, Lautenbach E, Nachamkin I, Garrigan C, Bilker WB, Omorogbe J, et al. The role of extended-spectrum cephalosporin-resistance in recurrent community-onset Enterobacteriaceae urinary tract infections: a retrospective cohort study. BMC Infect Dis. 2019;19:163.

167.   Pinault L, Chabriere E, Raoult D, Fenollar F. Direct identification of pathogens in urine using a specific MALDI-TOF spectra database. J Clin Microbiol. 2019. doi: 10.1128/JCM.01678-18. [Epub ahead of print]

168.   Dortet L, Poirel L, Nordmann P. Rapid detection of extended-spectrum-β -lactamase-producing enterobacteriaceae from urine samples by use of the ESBL NDP test. J Clin Microbiol. 2014;52:3701-6.

169.   Podnecky NL, Fredheim EGA, Kloos J, Sorum V, Primicerio R, Roberts AP, et al. Conserved collateral antibiotic susceptibility networks in diverse clinical strains of Escherichia coli. Nature Commun. 2018;9:3673.

170.   Langdon A, Crook N, Dantas G. The effects of antibiotics on the microbiome throughout development and alternative approaches for therapeutic modulation. Genome Med.2016;8:39.

171.   Whiteside SA, Razvi H, Dave S, Reid G, Burton JP. The microbiome of the urinary tract--a role beyond infection. Nat Rev Urol. 2015;12:81-90.

172.   Bolocan AS, Callanan J, Forde A, Ross P, Hill C. Phage therapy targeting Escherichia coli-a story with no end? FEMS Microbiol Lett. 2016;363(22).

173.   Storek KM, Auerbach MR, Shi H, Garcia NK, Sun D, Nickerson NN, et al. Monoclonal antibody targeting the β -barrel assembly machine of Escherichia coli is bactericidal. Proc Natl Acad Sci U S A. 2018;115:3692-7.

174.   Schreiber HLt, Conover MS, Chou WC, Hibbing ME, Manson AL, Dodson KW, et al. Bacterial virulence phenotypes of Escherichia coli and host susceptibility determine risk for urinary tract infections. Sci Transl Med. 2017;9(382).

175.   Ejrnaes K, Stegger M, Reisner A, Ferry S, Monsen T, Holm SE, et al. Characteristics of Escherichia coli causing persistence or relapse of urinary tract infections: phylogenetic groups, virulence factors and biofilm formation. Virulence. 2011;2:528-37.

176.   Huttner A, Gambillara V. The development and early clinical testing of the ExPEC4V conjugate vaccine against uropathogenic Escherichia coli. Clin Microbiol Infect. 2018;24:1046-1050.

177.   Naber KG, Cho YH, Matsumoto T, Schaeffer AJ. Immunoactive prophylaxis of recurrent urinary tract infections: a meta-analysis. Int J Antimicrob Agents. 2009;33:111-9.

Paper I

Bollestad M, Grude N, Lindbaek M. A randomised controlled trial of a diagnostic algorithm for symptoms of uncomplicated cystitis at an out-of-hours service. Scand J Prim Health Care 2015;33:57-64.

ORIGINAL ARTICLE

A randomized controlled trial of a diagnostic algorithm for symptoms of uncomplicated cystitis at an out-of-hours service

MARIANNE BOLLESTAD[1,3], NILS GRUDE[2,3] & MORTEN LINDBAEK[3]

[1]*Out-of-hours Service, Oslo Municipality Norway,* [2]*Department of Medical Microbiology, Vestfold Hospital Trust, Tønsberg, Norway,* [3]*The Antibiotic Centre for Primary Care, University of Oslo, Norway*

Abstract

Objective. To compare the clinical outcome of patients presenting with symptoms of uncomplicated cystitis who were seen by a doctor, with patients who were given treatment following a diagnostic algorithm. *Design.* Randomized controlled trial. *Setting.* Out-of-hours service, Oslo, Norway. *Intervention.* Women with typical symptoms of uncomplicated cystitis were included in the trial in the time period September 2010–November 2011. They were randomized into two groups. One group received standard treatment according to the diagnostic algorithm, the other group received treatment after a regular consultation by a doctor. *Subjects.* Women (n = 441) aged 16–55 years. Mean age in both groups 27 years. *Main outcome measures.* Number of days until symptomatic resolution. *Results.* No significant differences were found between the groups in the basic patient demographics, severity of symptoms, or percentage of urine samples with single culture growth. A median of three days until symptomatic resolution was found in both groups. By day four 79% in the algorithm group and 72% in the regular consultation group were free of symptoms (p = 0.09). The number of patients who contacted a doctor again in the follow-up period and received alternative antibiotic treatment was insignificantly higher (p = 0.08) after regular consultation than after treatment according to the diagnostic algorithm. There were no cases of severe pyelonephritis or hospital admissions during the follow-up period. *Conclusion.* Using a diagnostic algorithm is a safe and efficient method for treating women with symptoms of uncomplicated cystitis at an out-of-hours service. This simplification of treatment strategy can lead to a more rational use of consultation time and a stricter adherence to National Antibiotic Guidelines for a common disorder.

Key Words: *After-hours care, algorithms, amdinocillin (mecillinam), general practice, Norway, primary health care, urinary tract infection*

Introduction

Uncomplicated cystitis accounts for approximately 95% of all consultations related to urinary tract infections (UTIs) in primary health care [1].

Several strategies have been explored to increase adherence to antibiotic guidelines for the treatment of acute urinary tract infection with variable results [2,3]. No antibiotic treatment, symptomatic treatment by the use of NSAIDs, cutting back on treatment length, and wait-and-see prescriptions are methods that aim to decrease the overall use of antibiotics. These strategies have a combined interest in preventing further development of antibiotic resistance [4–9]. However, refraining from antibiotic treatment increases the length of arduous symptoms [10,11].

Norwegian guidelines for the treatment of symptoms of acute cystitis in women have concluded that treatment can be given without a urine dipstick test. For repeated episodes of symptoms of cystitis, treatment can be given without seeing a physician, the suggested procedure being telephone contact with the medical secretary. Women suffering from recurring cystitis should see a doctor for examination and a urine culture [12].

The out-of-hours service in Oslo uses a questionnaire to identify patients who qualify for a simplified routine of diagnosing and treating uncomplicated cystitis, the objective being a safe, time-, and cost-saving procedure.

Mecillinam is the antibiotic of choice in treating cystitis according to the diagnostic algorithm. This is

- Lower urinary tract infections in women are very common and account for a significant percentage of consultations in primary health care.
- A search in relevant medical literature has not revealed any previous studies assessing the use of a diagnostic algorithm as part of the treatment scheme.
- Our study demonstrated that the use of a diagnostic algorithm is a safe and efficient method for identifying women eligible for treatment without seeing a doctor.
- This simplification of treatment strategy can contribute to shorter waiting time for the patient, better adherence to antibiotic guidelines, and a more rational use of consultation time in outpatient clinics.

a Scandinavian agent. This choice is based on epidemiological findings of *Escherichia coli* (*E.coli*) as the predominating bacterial agent [13,14]. *E.coli* has a relatively low rate of resistance towards mecillinam [15–17]. It is also found to have a relatively low resistance driving effect, which has caused increased focus on the possibility of use in the context of the increasing load of multi-resistant bacteria [18,19].

Acute uncomplicated cystitis is a common disorder, but current diagnostic strategies in general practice show considerable variation. Population-based before-and-after studies have proved that use of a diagnostic algorithm significantly decreases the use of urine analysis, urine culture, and office visits. At the same time it also increases the number of patients receiving recommended antibiotics. Randomized controlled trials were sought to evaluate the use of a diagnostic algorithm in identifying women with uncomplicated cystitis [20–22].

The objectives of the study were:

- to compare the clinical outcome of patients presenting with symptoms of uncomplicated cystitis who were treated after a regular consultation by a doctor with patients who were given treatment following a diagnostic algorithm;
- to compare safety and rate of complications in the two groups.

Material and methods

Since 2007 the out-of-hours service in Oslo has used a diagnostic algorithm to identify patients with an uncomplicated cystitis. Inclusion and exclusion criteria were chosen based on established symptoms

and risk factors for complicated UTI. The study was preceded by a pilot investigation conducted for one week in June 2010, with the aim of identifying potential logistical challenges.

In the course of 14 months from September 2010–November 2011, 441 women in the age group 16–55 years were included. Patients eligible for inclusion were identified by use of a diagnostic algorithm as shown in Figure 1. Women presenting with dysuria and increased frequency of urination were included. Visible haematuria and increased urge for urination were also registered, but did not determine inclusion. Criteria for exclusion were relevant comorbidity (diabetes, kidney disease, and oesophageal passage problems), symptoms indicative of pyelonephritis or a complicated UTI, symptoms indicative of a sexually transmitted infection (STI), ongoing antibiotic/probenecid treatment, or a previous allergic reaction to penicillin. Temperature was measured and ongoing fever led to exclusion.

Included patients were randomized into two groups. The registering nurse completed the randomization process by drawing a number 1 or 2 from an envelope. The envelopes were generated by the study coordinator with an equal amount of numbers. We did not use block randomization. This may have contributed to the higher number of patients in one group; 242 patients were given diagnostic algorithm-based care versus 191 patients who were seen by a doctor (Figure 2).

The study group received pivmecillinam 200 mg × 3 for three days in accordance with the diagnostic algorithm. The control group was seen by a doctor who was not aware that the patient was included in the study.

Urine dipstick findings were evaluated in both groups along with a cultured urine sample taken on the day of presentation at the out-of-hours service.

In both groups the follow-up included a telephone call from the study coordinator one week after contact and two weeks after the treatment was ended. A total of 12 patients in the study group and 16 patients in the control group were lost during the follow-up. Four patients in each group were unreachable for the first phone call.

According to protocol, a urine sample was sent to the laboratory for evaluation one week after finishing treatment. The vast majority of samples were received during a time period of one to two weeks after treatment. All urine culture results were evaluated by both the study coordinator and the treating physician.

All urine samples were cultured according to established procedures for identification and resistance patterns at the Department of Medical Microbiology, at Oslo University Hospital, Ullevål.

Diagnostic algorithm: uncomplicated UTI

	Yes	No
Are you a woman aged 16-55 years?	☐	☐
Do you have –painful urination? *mild* ☐ *moderate* ☐ *strong* ☐		☐
-increased frequency of urination? *mild* ☐ *moderate* ☐ *strong* ☐		☐
-increased need to urinate?	☐	☐
-visible hematuria?	☐	☐
Are you pregnant or breastfeeding (infant under 1 month of age)? ☐		☐
Do you have diabetes or kidney disease?	☐	☐
Do you have -fever?	☐	☐
-reduced general condition?	☐	☐
-back/flank/stomach pain?	☐	☐
Do you have -increased vaginal secretion?	☐	☐
-itching/irritation?	☐	☐
-STRONG lower abdominal pain?	☐	☐
Have you had pain for more than 7 days?	☐	☐
Have you in the past 4 weeks had a urinary tract infection or used a urinary tract catheter?	☐	☐
Are you using antibiotics now?	☐	☐
Have you previously had an allergic reaction to penicillin?	☐	☐
Do you have esophageal passage problems?	☐	☐
Do you use the medication Probecid?	☐	☐
Temperature (<38° C)	☐	☐

	Delegated treatment	Doctor's consultation
Treatment chosen by support staff:	☐	☐

Figure 1. Diagnostic algorithm.

The uropathogens were quantified in colony-forming units/mL. Significant bacteriuria was defined according to current European guidelines for patients with symptoms of UTI as $\geq 10^3$ /mL for primary pathogens, $\geq 10^4$/mL for secondary pathogens, and $\geq 10^5$/mL for doubtful pathogens [23] (see Table II).

The statistical power of the data was based on symptom relief in 85% of the control group versus 75% in the group treated according to the diagnostic algorithm by day four, and a given power of 80% and a p-value of $< 5\%$ (two-sided test). Sample size calculation indicated that 250 patients in each group were needed.

SPSS18 manufactured by IBM was used for statistical analysis. Descriptive analysis of data was done. For the evaluation of the primary outcome measurement a Kaplan–Meier plot was performed.

Results

The main outcome measurement of the study was the number of days until symptomatic resolution in the two groups as shown in a Kaplan-Meier plot (Figure 3). By day four 188 of 238 (79%) in the group treated according to the diagnostic algorithm and 134 of 187 (72%) in the control group were free
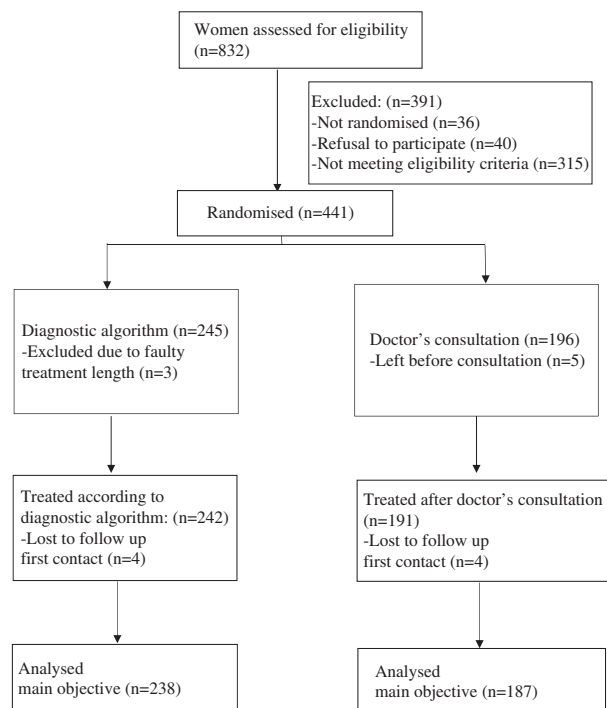
Figure 2. Trial flow chart: RCT of diagnostic algorithm for uncomplicated cystitis at an Out-of-hours service in Oslo, Norway.

of symptoms (p = 0.09). A median of three days until symptom resolution was found in both groups, log rank test p = 0.3.

Patient characteristics

Table I gives basic demographic data, including age and the country of origin. No significant differences between the two groups were found. Increased frequency of urination and pain on urination along with female sex and age were valued as absolute criteria of inclusion. The symptom scores did not reveal significant differences between the two groups.

Urine dipstick findings were evaluated; there were no significant differences in the number of patients who presented with a positive nitrate or leukocyte esterase test (see Table I). Bacteriological findings showed an insignificantly higher rate of growth of single-culture bacteria in the group seen by a doctor (Table II).

The value of the control urine samples was compromised by a group of patients who failed to deliver the samples. However, there was an insignificantly higher (p = 0.13) number of negative control urine samples in the group who had seen a doctor.

A majority of the patients included in the group seen by a doctor were diagnosed with uncomplicated cystitis and treated with mecillinam, which is the standard procedure for treatment according to the diagnostic algorithm. Of 191 patients, 186 were diagnosed with cystitis, two were diagnosed with pyelonephritis, one was diagnosed with bacterial vaginosis, two were diagnosed with cystitis and other illness (bacterial vaginosis and muscular pain), and in two patients no illness was found.

Table I. Baseline demographic and clinical characteristics of consecutive female patients presenting with symptoms of urinary tract infection at an out-of-hours service in Oslo, Norway.

	Diagnostic algorithm (n = 242)	Doctor's consult (n = 191)	p-value
Age, mean (SD), y	27 (8)	27 (8)	NS
Country of origin			
Norwegian, n, (%)	206 (85)	159 (83)	NS
Other European, n, (%)	25 (10)	27 (14)	NS
Outside Europe, n, (%)	9 (4)	4 (2)	NS
Unknown, n, (%)	2 (1)	1 (1)	NS
Patient-reported symptoms			
Painful urination			
Strong, n (%)	85 (35)	48 (25)	NS
Moderate, n (%)	126 (52)	111 (58)	NS
Mild, n (%)	31 (13)	32 (17)	NS
Increased frequency of urination			
Strong, n (%)	89 (37)	64 (34)	NS
Moderate, n (%)	132 (54)	110 (58)	NS
Mild, n (%)	21 (9)	17 (9)	NS
Increased need to urinate, n (%)	237 (98)	190 (99)	0.07
Macroscopic haematuria, n (%)	92 (38)	78 (41)	NS
Urinary dipstick findings	n = 160	n = 187	
Nitrate positive, n (%)	29 (18)	29(16)	NS
Leukocyte esterase positive n (%)	141(88)	164(88)	NS

Notes: Crosstabs analysis. Pearson's chi-square p-value. NS = non-significant. p < 0.15 stated.
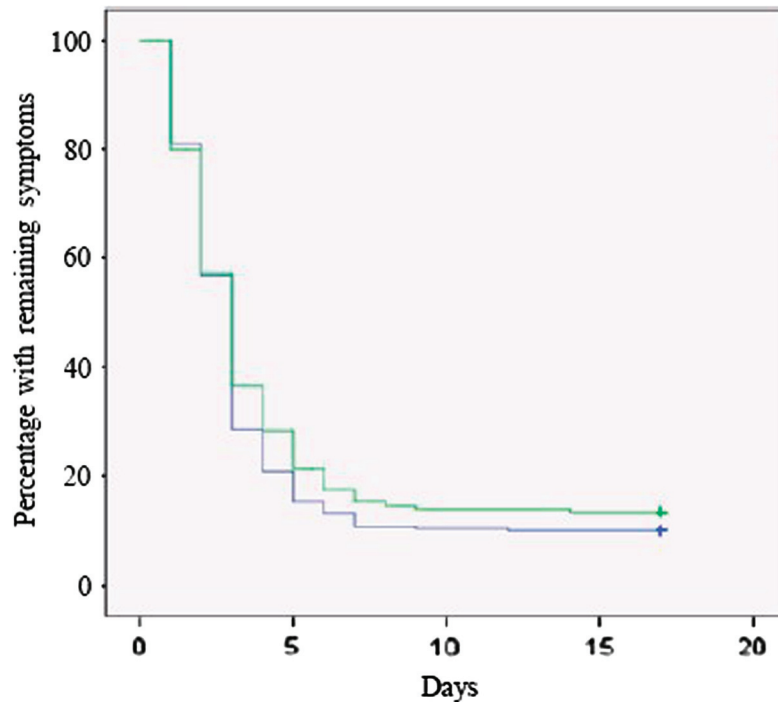
Figure 3. Symptom resolution: Percentage of patients with remaining symptoms versus number of days since the start of treatment, Kaplan–Meier plot. Blue line: Treated according to the diagnostic algorithm. Green line: Treatment chosen after a doctor's consultation. P-value (log rank): 0.3.

In the group seen by a doctor 80% were treated with mecillinam. Other antibiotics used were trimethoprim (13%) and nitrofurantoin (6%). Two patients (1%) were not given any antibiotic treatment.

During the follow-up period 12% of the patients treated according to the diagnostic algorithm contacted a doctor versus 18% in the group seen by a doctor (p 0.08). An alternative antibiotic regime was given to 11% in the group treated according to the diagnostic algorithm versus 16% in the group seen by a doctor.

For those who made follow-up contact significant bacteriuria was found in 19% of urine specimens in the diagnostic algorithm group and 26% in the control group. For those who did not contact a doctor again 10% significant bacteriuria was found in both groups. There were no cases of severe pyelonephritis or hospital admissions during the follow-up period.

The trial ended when the time frame for inclusion as agreed with the out-of-hours service in Oslo was reached. We managed to reach the needed sample in the algorithm group, but not in the control group. This was due to practical problems with recruitment of patients and the time frame given.

Discussion

Main findings

Our study demonstrated that an algorithm-based diagnosis of acute uncomplicated cystitis correlated well with the diagnosis given after a blinded doctor's consultation. There was no significant difference between the two groups in the number of days until clinical cure or in the number of patients who again contacted a doctor during the follow-up period. Although we did not manage to include a sufficient number of patients in the comparison group to meet our power calculation, we conclude that algorithm-based handling of patients was equivalent to an ordinary consultation. This conclusion is strengthened by the fact that we found an insignificant tendency for shorter duration of symptoms in the algorithm group.

A strict adherence to the algorithm to identify inclusion and exclusion criteria is necessary in order to ensure safe use of the algorithm. No cases of serious pyelonephritis or hospital admission were reported in the two groups.

Strengths and weaknesses

The study has been carried out in a setting with a high number of unselected patients with uncomplicated cystitis. During the follow-up, nearly all patients were successfully contacted regarding clinical cure, but a follow-up urine specimen was more often not received. All follow-up contacts were made by the same clinician.

With a mean age of 27 years in our patient population, the study is less representative of the elderly segment of included patients. In a young study pop-

Table II. Bacteriological findings in urine samples of female patients presenting with symptoms of urinary tract infection at an out-of-hours service in Oslo, Norway.

	Diagnostic algorithm	Doctor's consultation	p-value
Urine samples taken at consultation, n	234	172	
Negative culture, n (%)[1]	102 (44)	71 (41)	NS
Single culture isolates, n (%)[2]	132 (56)	101 (59)	NS
Primary pathogens:			
Escherichia coli, n (%)	101 (77)	79 (78)	NS
Staphylococcus saprophyticus, n (%)	21 (16)	17 (17)	NS
Secondary pathogens:			
Klebsiella species, n (%)	3 (2)	2 (2)	NS
Proteus mirabilis, n (%)	4 (3)	0	NS
Enterococcus fecalis, n (%)	1 (1)	1 (1)	NS
Enterobacter species, n (%)	0	1 (1)	NS
Doubtful pathogens:			
Streptococcus agalactiae, n (%)	2 (2)	0	NS
Pseudomonas species, n (%)	0	1 (1)	NS
Control urine sample, n (% of total)	169 (78)	130 (76)	
Negative culture, n (%)[1]	150 (89)	117 (90)	0.13
Single culture isolates, n (%)[2]	19 (11)	13 (10)	NS

Notes: Crosstabs analysis. Pearson's chi-square p-value. NS = non-significant. p < 0.15 stated. Patients who did not deliver primary or control urine samples were excluded. [1]Non-significant bacteriuria, see Material and methods. [2]All species-specific percentage values are calculated for the total number of single-culture isolates.

ulation STIs are more common and it has been noted that adolescent females with symptoms of UTI could benefit from testing for both STI and UTI [24]. A Swedish study conducted in general practice found a prevalence of 4% of *Chlamydia trachomatis* among young women with symptoms of UTI; this is comparable to the prevalence of 3% in the general population of women in the same age group [25].

Symptoms of STIs determine exclusion in the diagnostic algorithm; however, it is possible that some patients had a co-infection or a primary STI. There were no patients in the control group diagnosed with an STI. In addition, equal symptomatic and bacteriological outcomes in the two arms make a significant number of STIs less probable.

It is noteworthy that the doctor who treated the control patients was able to consider the urine dipstick findings when choosing antibiotic treatment. One could speculate this this would result in the doctor choosing an alternative regimen to ensure an effect against non-nitrate-producing organisms. Our findings did not show such a change in treatment choice. It is possible that the treating physician did not consider the nitrate status of the urine dipstick findings.

Urine samples were spontaneous samples taken at the time of consultation, thus a number of women had not kept the urine in the bladder for at least four hours, which is regarded as necessary to demonstrate significant bacteriuria. This may explain why the studied population showed a lower percentage of significant bacteriuria than previous studies [15,26]. There was no significant difference between the

groups as to proportion of significant bacteriuria in the primary urine samples.

Whether it is feasible from a resistance point of view to keep mecillinam as the treatment of choice according to the diagnostic algorithm, or whether variation among the recommended treatment regimens would be more beneficial should be considered. In Norway recommended treatment regimens include mecillinam, nitrofurantoin, and trimethoprim. Ciprofloxacin is not a recommended agent for the treatment of uncomplicated cystitis in Norway [16].

Comparison with other studies

To the best of our knowledge this is the first randomized controlled study to assess whether an algorithm-based care is equivalent to doctor-based care in treating uncomplicated cystitis.

An article referring to a telephone-based nurse evaluation and treatment algorithm concluded that algorithm-based care could allow for successful management of uncomplicated cystitis. [27]

Previous studies have been performed to evaluate symptoms or a group of symptoms as a prognostic indicator of the presence of a UTI with variable findings.

A review article evaluated which data from the history and clinical findings gave significantly increased diagnostic precision with regard to acute uncomplicated cystitis. It was found that a combination of dysuria and increased frequency of urination without increased vaginal secretions gave a 96% chance of a UTI [28]. Another study found the prognostic value

of symptoms and clinical findings to be low in regard to how well they predicted a UTI [29].

Recently the results of a self-reporting questionnaire to assess UTIs and differential diagnosis was published and found to be applicable for clinical studies and practice for diagnosis of uncomplicated UTI. The study was, however, not a randomized controlled trial and could not provide a comparison with a control group for symptomatic and bacteriological outcome [30].

Implications/conclusion

This simplification of treatment strategy can give a shorter waiting period for the patient, better adherence to antibiotic guidelines, and more rational use of consultation time in outpatient clinics.

We conclude that our algorithm is a feasible and safe way to handle young women with symptoms of an acute cystitis, and that the strategy can be transferred to other out-of-hours services.

Ethical approval

The study is registered in Clinical trials (reference number: NCT01132131) and has been approved by the Regional Ethical committee (reference number: 2010/486).

Declaration of interest

There are no conflicts of interest in connection with the paper. The authors alone are responsible for the content and writing of the paper.

References

[1] Baerheim A. Empirical treatment of uncomplicated cystitis. Scand J Prim Health Care 2012;30:1–2.

[2] Arnold S, Straus S. Interventions to improve antibiotic prescribing practices in ambulatory care. Cochrane Database Syst Rev 2005;19:CD003539.

[3] Willems L, Denckens P, Philips H, Henriquez R, Remmen R. Can we improve adherence to guidelines for the treatment of lower urinary tract infection? A simple, multifaceted intervention in out-of-hours services. J Antimicrob Chemother 2012;67:2997–3000.

[4] Christiaens TC, De Meyere M, Verschraegen G, Peersman W, Heytens S, De Maeseneer JM. Randomised controlled trial of nitrofurantoin versus placebo in the treatment of uncomplicated urinary tract infection in adult women. Br J Gen Pract 2002;52:729–34.

[5] Høye S, Frich JS, Lindbæk M. Use and feasibility of delayed prescribing for respiratory tract infections: A questionnaire survey. BMC Fam Pract 2011;18:12–34.

[6] Bleidorn J, Gagyor I, Kochen MM, Wegscheider K, Hummers-Pradier E. Symptomatic treatment (ibuprofen) or antibiotics (ciprofloxacin) for urinary tract infections? Results from a randomized controlled pilot trial. BMC Med 2010;8:30.

[7] Little P, Moore MV, Turner S, Rumsby K, Warner G, Lowes JA et al. Effectiveness of five different approaches in management of urinary tract infection: Randomised controlled trial. BMJ 2010;340:c199.

[8] Katchman EA, Milo G, Paul M, Christiaens T, Baerheim, A, Leibovici L. Three days vs longer duration of antibiotic treatment in cystitis in women: Systematic review and meta-analysis. Am J Med 2005;118:1196–207.

[9] Skudal HK, Grude N, Kristiansen BK. Økende forekomst av antibiotikaresistens ved urinveisinfeksjoner [Increasing antibiotic resistance in urinary tract infections]. Tidsskr Nor Laegeforen 2006;126:1058–60.

[10] Little P, Merriman R, Turner S, Rumsby K, Warner G, Lowes JA, et al. Presentation, pattern and natural course of severe symptoms, and role of antibiotics and antibiotic resistance among patients presenting with suspected uncomplicated urinary tract infection in primary care: Observational study. BMJ 2010;340:b5633.

[11] Ferry S, Holm SE, Stenlund H, Lundholm R, Monsen TJ. Clinical and bacteriological outcome of different doses and duration of pivmecillinam compared with placebo therapy of uncomplicated lower urinary tract infection in women: The LUTIW project. Scand J Prim Health Care 2007;25:49–57.

[12] Flottorp S, Oxman AD, Cooper JG, Hjortdahl P, Sandberg S, Vorland LH. Retningslinjer for diagnostikk og behandling av akutte vannlatingsplager hos kvinner [Guidelines for diagnosis and treatment of acute urinary tract problems in women]. Tidsskrift Nor Laegeforen 2000;120:1748–53.

[13] Grude N, Tveten Y, Kristiansen BE. Urinary tract infections in Norway: Bacterial etiology and susceptibility. A retrospective study of clinical isolates. Clin Microbio Infect 2001;7:543–7.

[14] Jureen R, Digranes A, Bærheim A. Urinveispatogene bakterier ved ukompliserte nedre urinveisinfeksjoner hos kvinner [Urinary tract pathogens in uncomplicated lower urinary tract infections in women in Norway]. Tidsskr Nor Laegeforen 2003;123:2021–2.

[15] Grude N, Tveten Y, Jenkins A, Kristiansen BE. Uncomplicated urinary tract infections: Bacterial findings and efficacy of empirical antibacterial treatment. Scand J Prim Health Care 2005;23:115–19.

[16] Lindbæk M, Berild D, Eliassen KE, Fetveit A, Grude N, Hjortdahl P. Nasjonale faglige retningslinjer for antibiotikabruk i primærhelsetjenesten [National guidelines for use of antibiotics in primary health care]. Helsedirektoratet. 2013. Available at http://www.antibiotikasenteret.no/index.php/retningslinjer-for-antibiotikabruk (accessed October 2, 2014).

[17] Kahlmeter G, Poulson HO. Antimicrobial susceptibility of Escherichia coli from community-acquired urinary tract infections in Europe: The ECO-SENS study revisited. Int J Antimicrob Agents 2012;9:45–51.

[18] Monsen TJ, Holm S, Ferry BM, Ferry S. Mecillinam resistance and outcome of pivmecillinam treatment in uncomplicated urinary tract infection in women. APMIS 2014; 122:317–23.

[19] Dewar S. Emerging clinical role of pivmecillinam in the treatment of urinary tract infection in the context of multidrug-resistant bacteria. J Antimicrob Chemother 2014;69:303–8.

[20] Bent S, Saint S. The optimal use of diagnostic testing in women with acute uncomplicated cystitis. Am J Med 2002;113:20–8.

[21] Flottorp S, Oxman AD, Håvelsrud K, Treweek S, Herrin J. Cluster randomised controlled trial of tailored interventions to improve the management of urinary tract infections in women and sore throat. BMJ.2002;325:367.

[22] Grigoryan L, Trautner BW, Gupta K. Diagnosis and management of urinary tract infections in the outpatient setting: A review. JAMA 2014;312:1677–84.

[23] Aspevall O, Hallander H, Gant V, Kouri T. European guidelines for urinalysis: A collaborative document produced by European clinical microbiologists and clinical chemists under ECLM in collaboration with ESCMID. Clin Microbiol Infect 2001;7:173–8.

[24] Huppert JS, Biro F, Lan D, Mortensen JE, Reed J, Slap GB. Urinary symptoms in adolescent females: STI or UTI? J Adolesc Health 2007;40:418–24.

[25] Österberg E, Aspevall O, Grillner L, Persson E. Young women with symptoms of urinary tract infection: Prevalence and diagnosis of chlamydial infection and evaluation of rapid screening of bacteriuria. Scand J Prim Health Care 1996;14:43–9.

[26] Kahlmeter G. An international survey of the antimicrobial susceptibility of pathogens from uncomplicated urinary tract infections: The ECO.SENS Project. Clin Microbiol Infect 2003;51:67–76.

[27] Schauberger CW, Merkitch KW, Prell AM. Acute cystitis in women: Experience with a telephone-based algorithm. WMJ 2007;106:326–9.

[28] Stephen B, Nallamothu BK, Simel DL, Fihn SD, Saint S. Does this woman have an acute uncomplicated urinary tract infection? JAMA 2002;287:2701–10.

[29] Medina-Bombardo D, Jover-Palmer A. Does clinical examination aid in the diagnosis of urinary tract infections in women? A systematic review and meta-analysis. BMC Fam Pract 2011;12:111

[30] Alidjanov JF, Abdufattaev UA, Makhsudov SA, Pilatz A, Akilov FA, Naber KG, et al. New self-reporting questionnaire to assess urinary tract infections and differential diagnosis: Acute cystitis symptoms score. Urol Int 2014;92:230–6.

Paper II

Bacteriology in uncomplicated urinary tract infections in Norwegian general practice from 2001–2015

Marianne Bollestad, MD[1,2,3]*, Ingvild Vik, MD[4,5], Nils Grude, MD, PhD[6,7], Hege Salvesen Blix, MSc Pharm, PhD[8], Hanne Brekke, MD[9], Morten Lindbaek, MD[10]

[1]Infectious Diseases Resident & PhD Student, Department of General Practice, Antibiotic Centre of Primary Care, Institute of Health and Society, University of Oslo, Oslo, Norway; [2]Infectious Diseases Resident & PhD Student, Department of Emergency General Practice, Oslo Accident and Emergency Outpatient Clinic, City of Oslo Health Agency, Oslo, Norway; [3]Infectious Diseases Resident & PhD Student, Division of Medicine, Stavanger University Hospital, Stavanger, Norway; [4]GP & PhD Student, Department of General Practice, Antibiotic Centre of Primary Care, Institute of Health and Society, University of Oslo, Oslo, Norway; [5]GP & PhD Student, Department of Emergency General Practice, Oslo Accident and Emergency Outpatient Clinic, City of Oslo Health Agency, Oslo, Norway; [6]Consultant Microbiologist & Researcher, Department of General Practice, Antibiotic Centre of Primary Care, Institute of Health and Society, University of Oslo, Oslo, Norway; [7]Consultant Microbiologist & Researcher, Department of Medical Microbiology, Vestfold Hospital Trust, Toensberg, Norway; [8]Specialist in Hospital Pharmacy, Norwegian Institute of Public Health, Oslo, Norway; [9]Infectious Diseases Resident, Department of Medical Microbiology, Oslo University Hospital, Oslo, Norway; [10]Professor, Department of General Practice, Antibiotic Centre of Primary Care, Institute of Health and Society, University of Oslo, Oslo, Norway

Abstract

Background: Uncomplicated urinary tract infections in women are common, and urine samples from these patients are not routinely cultured. Empirical treatment is based on knowledge of resistance patterns for common uropathogens.

Aim: To evaluate the bacteriological findings and resistance patterns in urine samples from women with uncomplicated urinary tract infections, and to assess the relationship between antimicrobial use and resistance patterns from 2000–2015 in Norway.

Method: Bacteriology and resistance patterns were compared in 184 urine cultures from 2001, 406 urine cultures from 2010–2011 and 259 urine cultures from 2013–2015. Antibiotic use data from 2000–2015 were obtained from national databases.

Results: *Escherichia coli* (*E. coli*) was the main bacterial agent in 80% of the cultures. *Staphylococcus saprophyticus* (*Staph. saprophyticus*) represented 6–17%. For *E. coli*, susceptibility for mecillinam showed some variation but remained below 9%. There was negligible resistance to nitrofurantoin. Resistance to trimethoprim seemed to stabilise over the last 5 years at around 20%. Amoxicillin resistance had some variations, but remained stable around 30%. There was a steady rise in total consumption of selected antibiotics commonly used to treat urinary tract infections for the period 2000–2015.

Conclusion: Mecillinam and nitrofurantoin are both excellent first choices for empirical treatment of uncomplicated urinary tract infections. This study suggests that increasing resistance to trimethoprim challenges the rationale for its use as a first-line agent.

How this fits in

Empirical treatment for acute uncomplicated UTI is based on current resistance patterns and national guidelines. This study evaluated antibiotic use and bacteriological findings in uncomplicated UTIs in Norway from 2001–2015. This study found stable and high susceptibility to mecillinam and nitrofurantoin for *E. coli*. This study suggests that increasing resistance to trimethoprim challenges the rationale for its use as a first-line agent.

Introduction

Uncomplicated UTI is the most common infection in women presenting to primary health care.[1] Most women with symptoms of a UTI consult a doctor and are prescribed antibiotics.[2] Empirical treatment for uncomplicated UTI is based on current resistance patterns and national guidelines.[3] Treatment choices made in primary health care are important as they account for 85% of the total antibiotic use in Norway.[4]

E. coli is the most common pathogen isolated in community-acquired UTI.[5,6] Other pathogens commonly identified are *(Staph. saprophyticus, Klebsiella species (spp.), Enterococcus spp., Enterobacter spp.* and *Proteus mirabilis.*[7]

Current Norwegian guidelines recommend mecillinam, nitrofurantoin, and trimethoprim as empirical treatment options for uncomplicated UTI.[3] Previous studies have sought to determine resistance rates to empirical treatment regimes.[8,9]

Data from Belgium have suggested that species distribution is relatively stable, and that sensitivity to fosfomycin and nitrofurantoin remain at nearly 100%.[10,11] However, international data show increasing antimicrobial resistance to several recommended empirical treatment regimes.[12–14] Interestingly, Poland recently reported high overall resistance rates of the common uropathogens to first-line treatment regimes, including fosfomycin and nitrofurantoin.[12]

Current guidelines suggest the diagnosis may be given based on symptoms alone.[3,15] Since 2000 the Norwegian guidelines have recommended not to routinely culture urine samples from patients with acute uncomplicated UTI. This may lead to potential changes in resistance patterns going undetected and an overestimation of resistance rates.[16–18]

The aims of the study were:

- to evaluate the bacteriological findings and resistance patterns in urine samples from women with acute uncomplicated UTI in three cohorts in the time period 2001–2015 in Norway; and
- to assess the relationship between the use of antimicrobial agents in the treatment of UTI and resistance patterns in the time period 2000–2015 in Norway.

Method

The bacteriology and resistance patterns were compared in urine cultures collected from women with uncomplicated UTIs presenting in a general practice setting in three different time periods in Norway. Inclusion and exclusion criteria for the different studies have been published.[8,19–20] The material consisted of 184 urine cultures from 2001, 406 urine cultures from 2010–2011, and 259 urine cultures from 2013–2015.

The first study was performed in the county of Telemark in 2001. This study enrolled arbitrarily selected women presenting to the GP with symptoms of an uncomplicated UTI for which they received antibiotics.[8] Fresh midstream urine samples were sent to the local microbiology department in sterile containers with 1.6% boric acid. Significant bacteriuria was defined as pure or dominant growth of $\geq 10^4$ colony-forming units per millilitre (cfu/mL) for all pathogens. Antimicrobial susceptibility breakpoints were set according to the Norwegian Working Group on Antibiotics.[21]

The next two studies were performed at Oslo Accident and Emergency Outpatient Clinic (OAEOC), Department of Emergency General Practice. Sequential consulting women were enrolled in the time periods September 2010–November 2011 and April 2013–December 2015.

In the 2010–2011 study, inclusion criteria were determined by a diagnostic algorithm based on established symptoms and risk factors for complicated UTI. This study was conducted to validate a specific diagnostic algorithm and the results have been published.[19]

In the 2013–2015 study the same inclusion criteria were used to identify women with uncomplicated UTI. The data presented here are baseline data from the main centre of an ongoing multi-centre randomised controlled trial (NCT01849926) to assess ibuprofen versus mecillinam in the treatment of uncomplicated UTI.[20]

For the two latter studies a fresh midstream urine sample was sent to the Department of Microbiology at Oslo University Hospital, Ullevål, in sterile containers with 1.6% boric acid. The uropathogens were quantified in cfu/mL. Significant bacteriuria was defined according to current European guidelines as $\geq 10^3$/mL for primary pathogens, $\geq 10^4$/mL for secondary pathogens, and $\geq 10^5$/mL for doubtful pathogens.[22] Clinical breakpoints were taken from the European Committee on Antimicrobial Susceptibility Testing, which have remained unchanged since 2010.[23]

Data on antibiotic use were collected from two nationwide databases; the Norwegian drug wholesale statistics database and the Norwegian prescription database (NorPD).[24] The wholesale database logs sales of all medicines in Norway. NorPD contains a complete listing of all prescription drugs dispensed by pharmacies in Norway since 2004.

National resistance patterns were collected from The Norwegian Organization for Surveillance of Antimicrobial Resistance (NORM). From 2000 onwards, NORM has provided annual reports on the national usage of antimicrobial agents and the occurrence of resistance in Norway.[4] Data on resistance were compared to the total use (wholesales statistics) of selected antibiotics.

The results in this study represent a comparison done retrospectively and a power calculation was not performed. IBM SPSS statistics (version 23.0) was used for descriptive analyses of data. Comparison of aggregated data was done using a χ^2 calculator with a significance level of 0.05.[22]

Results

The three study populations all represented adult women, aged 15–65 years, with uncomplicated UTIs. There was a difference in age distribution between the first population and the two latter populations, with the first group representing an older cohort. The mean age in the two groups from the OAEOC was 27.1 years, whereas the first group had a mean age of 38.3 years. There was no statistically significant difference in age between the two groups from the OAEOC, but when each of the OAEOC groups were compared to the first group, the differences in age distribution were statistically significant with a *P*-value varying from *P* = 0.03 to *P*<0.01.

Table 1. Bacterial isolates from the three study cohorts

Microbe	2001 *n* (%)	2010–2011 *n* (%)	2013–2015 *n* (%)
E. coli	112 (82.4)[a]	180 (78.3)[a]	129 (81.6)[a]
Staph. saprophyticus	8 (5.9)[a]	38 (16.5)[a]	22 (13.9)[a]
Enterobacter spp.	0[a]	1 (0.4)[a]	4 (2.5)[a]
Enterococcus faecalis	3 (2.2)[a]	2 (0.9)[a]	1 (0.6)[a]
Klebsiella spp.	6 (4.4)[a]	5 (2.2)[a]	2 (1.3)[a]
Proteus spp.	5 (3.7)[a]	4 (1.7)[a]	0[a]
Staph. aureus	2 (1.5)[a]	0[a]	0[a]
No significant growth	48 (26.1)[b]	176 (43.3)[b]	101 (39.0)[b]
Total number of cultures with significant bacteriuria	136 (73.9)[b]	230 (56.7)[b]	158 (61.0)[ab]
Total number of cultures	184	406	259

[a]% of total number of cultures with significant bacteriuria. [b]% of total number of cultures.

Significant bacterial growth was found in 57–74% of all urine samples cultured. The main bacteriological agent in all three study populations was *E. coli,* ranging from 78% to 82%. The second most common isolate was *Staph. saprophyticus,* ranging from 6% to 17% (*Table 1*).

For trimethoprim there was a substantial increase in resistance from 2001 to 2010–2011, then a slight decrease from 2010–2011 to 2013–2015. There was a decrease in resistance to mecillinam in *E.coli* from 2001 to 2010–2011, followed by an increase from 2010–2011 to 2013–2015. There was an increase in resistance to amoxicillin for *Staph. saprophyticus* isolates from 2010–2011 to 2013–2015. There was no increase in resistance to nitrofurantoin for neither *E. coli* or *Staph. saprophyticus.* None of the changes in resistance rates were statistically significant (*Table 2*).

Wholesale statistics for commonly used antibiotics showed a steady rise in total consumption from 2000 until 2012. However, since 2012, there has been an overall reduction in antibiotic use (*Figure 1*). Data for the first choice antibiotics in the treatment of uncomplicated UTIs showed an increase in mecillinam consumption and a decrease for trimethoprim, while the use of nitrofurantoin and co-trimoxazole remained stable. Other treatment options for UTIs include amoxicillin/ampicillin and the quinolones ciprofloxacin and ofloxacin. For these drugs, there was a clear rise in consumption and a rise in resistance rates. However, the use has slightly decreased from 2012 onwards. Women used more antibiotics than men and the patterns of use were different. Women were more frequently prescribed mecillinam, while quinolones were more often prescribed for men (*Figure 2*).

This study looked specifically at the relationship between consumption and *E. coli* resistance rates, both in these and national data, for the two most commonly used antibiotics, trimethoprim and mecillinam. For trimethoprim, there was a reduction in use over the last 15 years. Trimethoprim resistance for *E. coli,* however, slightly increased (*Figure 3*). For mecillinam there was a clear rise in consumption during the study period, with a minimal decrease over the last 2 years. The resistance rates for *E. coli* showed some variation, but the overall trend was a slight increase in mecillinam resistance (*Figure 4*).

Discussion

Summary

E. *coli* was the dominant pathogen in all three populations. The prevalence of *Staph. saprophyticus* was higher in the 2010–2011 and 2013–2015 cohorts, which was expected as these two groups consisted of younger women.[25–26]

Table 2. Resistance to antibiotics commonly used to treat UTIs

Microbe	Antibiotic	2001 n (%) [95 % CI]	2010–2011 n (%) [95 % CI]	2013–2015 n (%) [95 % CI]
E. coli	Mecillinam	7 (6.3) [1.8 to 10.8]	4 (2.2) [0.1 to 4.3]	11 (8.5) [3.7 to 13.3]
	Nitrofurantoin	3 (2.7) [0.0 to 5.7]	0	0
	Trimethoprim	13 (11.6) [5.7 to 17.5]	38 (21.1) [15.1 to 27.1]	27 (20.9) [13.9 to 27.9]
	Co-trimoxazole	NA	39 (21.7) [15.7 to 27.7]	24 (18.6) [11.9 to 25.3]
	Sulphonamide	21 (18.8) [11.6 to 26.0]	NA	NA
	Amoxicillin	31 (27.7) [19.4 to 36.0]	63 (35.0) [28.0 to 42.0]	38 (29.5) [21.6 to 37.4]
	Ciprofloxacin	NA	NA	NA
Staph. saprophyticus	Mecillinam	NA	NA	NA
	Nitrofurantoin	0	0	0
	Trimethoprim	0	0	1 (4.5) [–4.2 to 13.2]
	Co-trimoxazole	NA	0	0
	Sulphonamide	0	NA	NA
	Amoxicillin	NA	4 (10.5) [0.8 to 20.2]	4 (18.2) [2.1 to 34.3]
	Ciprofloxacin	NA	NA	NA

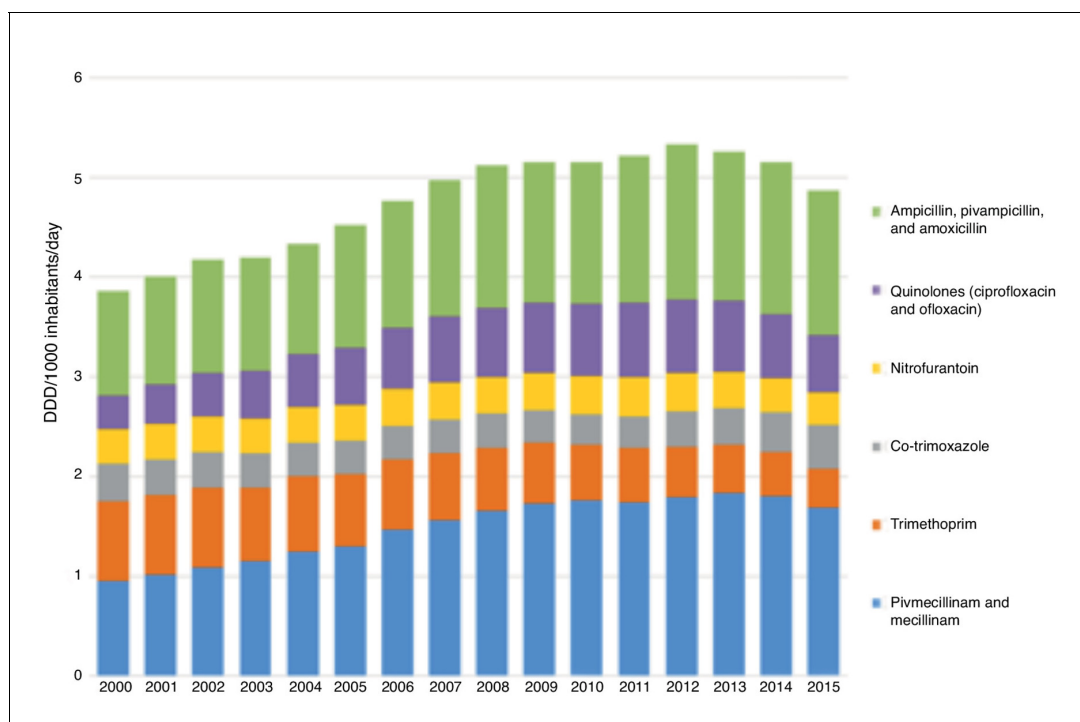NA = not applicable, isolate was not tested for this antibiotic.

Figure 1 Total use of selected antibiotics commonly used to treat urinary tract infections in Norway (wholesale statistics).[a]
  [a]In 2000-2002, nalidixic acid and sulfathiazole were also used in Norway, however these two represented less than 0.3% of total use of antibiotics with the indication urinary tract.
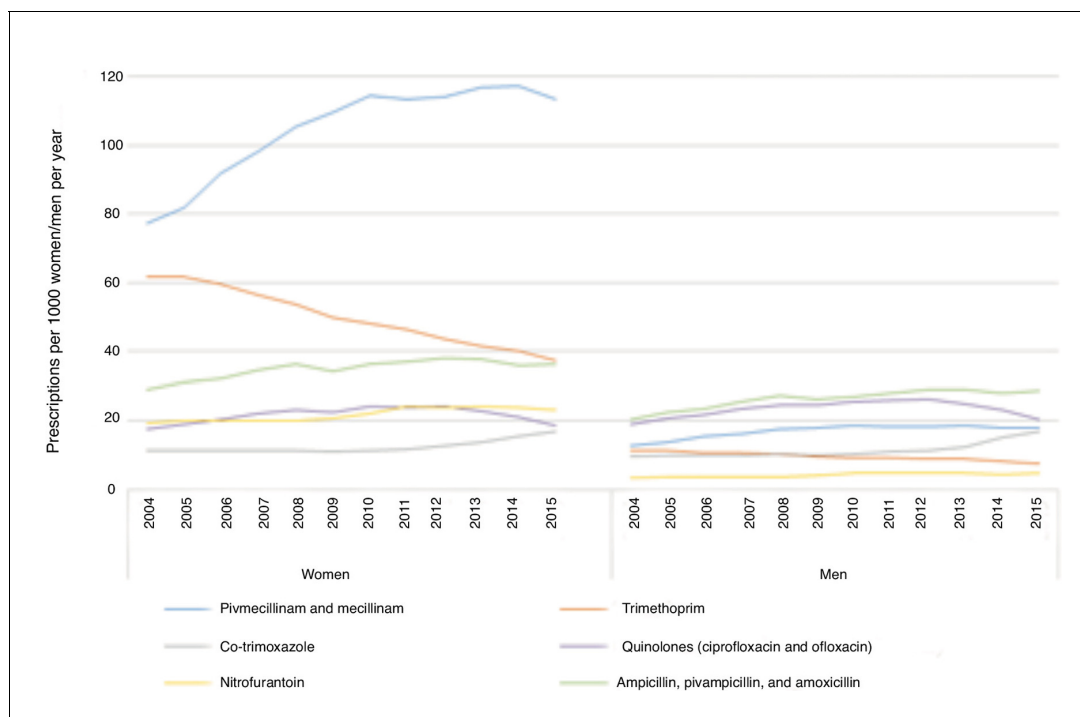

Figure 2 Distribution of use measured as number of prescriptions for selected antibiotics per 1000 women and men >20 years of age.
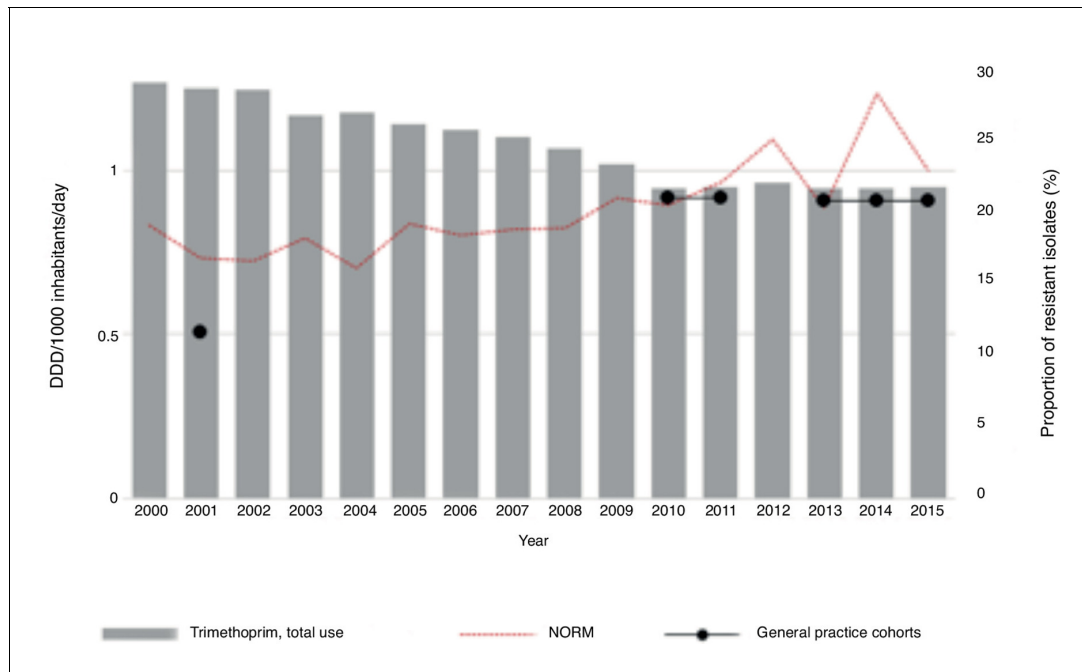
Figure 3 Total use of trimethoprim (wholesale statistics) and prevalence of resistant strains of *E.coli* isolates in urinary tract isolates from the national register (NORM) and the three different general practice cohorts.

This analysis showed that both *E. coli* and *Staph. saprophyticus* have been fully sensitive to nitrofurantoin over the last 5 years. Use of nitrofurantoin has remained stable and low during this 15-year
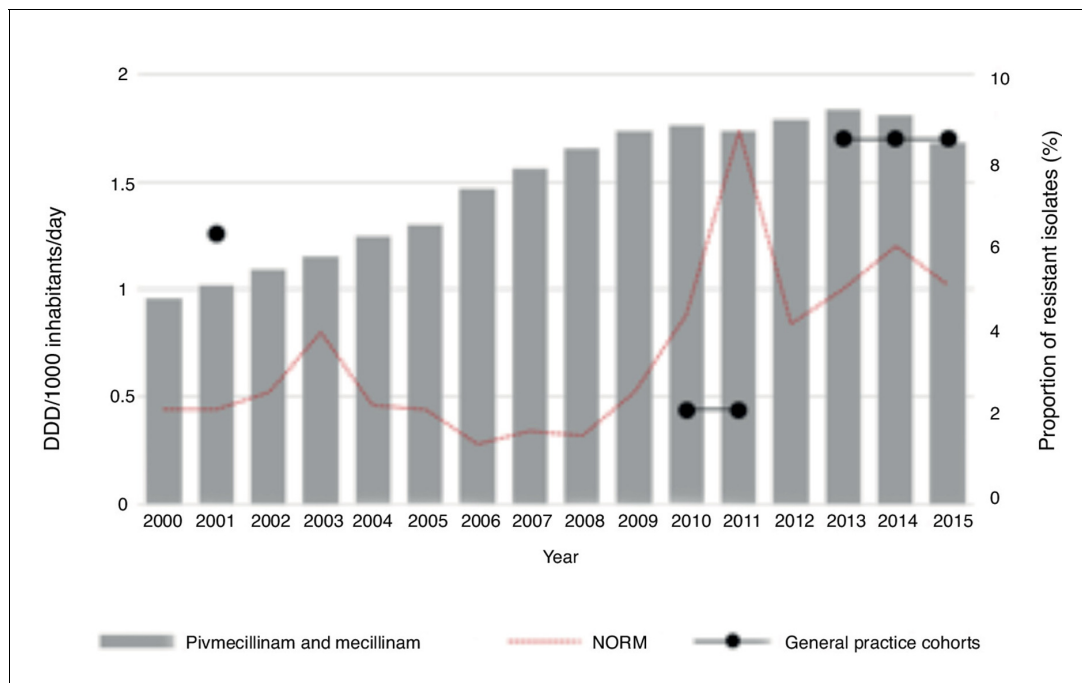

Figure 4 Total use of pivmecillinam and mecillinam (wholesale statistics) and prevalence of resistant strains of *E.coli* isolates in urinary tract isolates from the national register (NORM) and the three different general practice cohorts.

period. National numbers showed resistance rates of 1% for all urinary isolates of *E. coli* towards nitrofurantoin in 2015.[4]

Trimethoprim resistance increased from 2001 to 2011. However, during the last 5 years this trend has stabilised. These numbers were slightly lower than the national numbers, but the differences were marginal: 21% versus 23% in 2015 (Figure 3). Although the total use of trimethoprim has decreased, the resistance level has increased in the last 15 years. Even though these numbers are lower than the national numbers, the resistance rates exceed 20%. Norwegian guidelines suggest that antimicrobial agents should not be used empirically if resistance rates exceed 20%.[3]

There was some variation in the level of resistance to mecillinam in *E. coli*. In the current comparison there was a 'dip' in resistance for 2010–2011. This does not correspond with the findings in the national report, which showed a peak in the same period. In the study populations from 2001 and 2013–2015, there were higher resistance rates than the national rates. A possible explanation for this is that resistance to mecillinam in *E. coli* is difficult to measure and might have some geographical variations. These numbers differed somewhat from the national numbers, but both suggest quite stable and low levels of resistance. Despite a substantial rise in the use of mecillinam in Norway, there has not been a corresponding increase in the level of resistance to mecillinam for *E. coli*. This indicates that mecillinam has a low potential for inducing resistance.

For *E. coli* the resistance to amoxicillin also showed some variation, but remained high around 30%. Resistance levels were slightly lower in the current analysis than the national numbers, but again the observed differences were minimal: 30% versus 34% in 2015.

For amoxicillin, there was a marked increase in resistance in *Staph. saprophyticus*. Antibiotic resistance in *Staph. saprophyticus* is infrequent,[27] and resistance patterns for this bacteria are not included in national surveillance data. *Staph. saprophyticus* is not considered to be sensitive to mecillinam and susceptibility testing is therefore not routinely performed.[6]

Strengths and limitations

This analysis has three large general practice cohorts presenting with uncomplicated UTI. In Norway, urine from uncomplicated UTIs has not been routinely cultured in the last 20 years. This study evaluated if there has been a change in the distribution of bacterial isolates and resistance patterns in this population. Looking specifically at this group of patients is important as the national surveillance data represent a diverse population with more complicated infections. A 15-year comparison is a long period and provides confidence that this study's conclusions about the development of antibiotic resistance are accurate.

This study compared cohorts from Oslo and Telemark, which represents two of the 19 counties in Norway. Oslo County consist of the city of Oslo and surrounding suburbs. Telemark County consists of several municipalities and a few cities. Looking at the three cohorts together, there are data representing both an urban and a more rural population, reflecting the general Norwegian population. A limitation is that the two latter populations are similar and represent a younger population. The first dataset are from a more diverse population and this can cause some uncertainty when comparing the three groups. Other complicating factors are different procedures in the microbiological laboratories and changes in breakpoints in susceptibility testing. A weakness of this observational study is that a power calculation was not performed with regards to changes in resistance rates. Consequently, interpretation of significance levels is uncertain. All patients had to consent to participation, which might have resulted in selection bias.

Comparison with existing literature

Antimicrobial resistance is an international concern, and efforts are being made in many countries to achieve a better overview of consumption of antibiotics and national resistance rates.[28] Strategies to reduce antibiotic consumption include efforts to identify women with UTI who recover without antibiotics.[29] The topic of dusting off 'old' antimicrobials to treat UTIs has been raised.[30] Several European studies suggest that there is little resistance to mecillinam, fosfomycin, and nitrofurantoin, which the current study supports.[9–13,27] These three antibiotics all seem to be good first choice treatment options for many European countries.

Mecillinam is mainly used in the Scandinavian countries, but it should receive more attention in other European countries. *Staph. saprophyticus* is considered to be intrinsically resistant to

mecillinam, and extended spectrum beta-lactamase producing uropathogens are by definition resistant to mecillinam treatment, however smaller clinical studies have shown varying degrees of treatment effect.[6,31–32] Fosfomycin is widely used in some countries, for example Germany and Spain, but in Norway it is not marketed or readily available. According to data provided by NorPD, only 28 packages were prescribed to 19 patients in 2015. There is a rationale for Norway and the other Nordic countries to consider including fosfomycin as a first-line antibiotic treatment for uncomplicated UTI, replacing trimethoprim which has a resistance level of >20% in most European countries. Studies have shown high susceptibility rates for *Staph. saprophyticus* to fosfomycin.[33–34] Common European guidelines for the treatment of uncomplicated UTI might help to ensure good antibiotic stewardship.

The current analysis and other studies show that national surveillance numbers for resistance are somewhat higher than in urine cultured from patients with uncomplicated UTI.[11,35–36] *Staph. saprophyticus* has not been taken into account in the national surveillance of resistant microbes as it has been known to have very little resistance. In this comparison there was an increase in resistance to both amoxicillin and trimethoprim, and even though these numbers are small, they warrant increased monitoring. To keep track of the actual distribution of bacterial isolates and level of resistance it is important to keep a sentinel surveillance of bacterial agents causing uncomplicated UTIs. This is in line with what researchers from other countries have suggested.[11,36]

Implications for practice

Mecillinam and nitrofurantoin are both excellent first choices for empirical treatment of uncomplicated UTIs. This study suggests that increasing resistance to trimethoprim challenges the rationale for its use as a first-line agent. Norway might consider including fosfomycin as a first choice antibiotic for the treatment of uncomplicated UTI.

Sentinel surveillance of bacterial isolates from uncomplicated UTIs is necessary to ensure effective empirical treatment options.

References

1. Colgan R, Williams M. Diagnosis and treatment of acute uncomplicated cystitis. *Am Fam Physician* 2011; **84 (7):** 771–776.
2. Butler CC, Hawking MK, Quigley A, *et al.* Incidence, severity, help seeking, and management of uncomplicated urinary tract infection: a population-based survey. *Br J Gen Pract* 2015; **65(639):** e702–e707. doi: 10.3399/bjgp15X686965
3. Lindbaek M, Berild D, Eliassen KE, *et al.* Nasjonale faglige retningslinjer for antibiotikabruk i primærhelsetjensten. [National guidelines for use of antibiotics in primary health care] Helsedirektoratet. 2013. https://helsedirektoratet.no/retningslinjer/nasjonal-faglig-retningslinje-for-antibiotikabruk-i-primerhelsetjenesten (accessed 18 Sep 2017).
4. Simonsen GS, Magrete UA. Usage of Antimicrobial Agents and Occurence of Antimicrobial Resistance in Norway. Norwegian Surveillance System for Antimicrobial Drug Resistance. 2015. https://unn.no/Documents/Kompetansetjenester,%20-sentre%20og%20fagr%C3%A5d/NORM%20-%20Norsk%20overv%C3%A5kingssystem%20for%20antibiotikaresistens%20hos%20mikrober/Rapporter/NORM_NORM-VET-2015.pdf (accessed 2 Oct 2017).

5. Foxman B. Urinary tract infection syndromes: occurrence, recurrence, bacteriology, risk factors, and disease burden. *Infect Dis Clin North Am* 2014; **28(1):** 1–13. doi: 10.1016/j.idc.2013.09.003

6. Monsen TJ, Holm SE, Ferry BM, *et al.* Mecillinam resistance and outcome of pivmecillinam treatment in uncomplicated lower urinary tract infection in women. *APMIS* 2014; **122(4):** 317–323. doi: 10.1111/apm.12147

7. Amna MA, Chazan B, Raz R, *et al.* Risk factors for non-Escherichia coli community-acquired bacteriuria. *Infection* 2013; **41(2):** 473–477. doi: 10.1007/s15010-012-0347-1

8. Grude N, Tveten Y, Jenkins A, *et al.* Uncomplicated urinary tract infections. Bacterial findings and efficacy of empirical antibacterial treatment. *Scand J Prim Health Care* 2005; **23(2):** 115–119. doi: 10.1080/02813430510015287

9. Gobernado M, Valdés L, Alós JI, *et al.* Antimicrobial susceptibility of clinical Escherichia coli isolates from uncomplicated cystitis in women over a 1-year period in Spain. *Rev Esp Quimioter* 2007; **20(1):** 68–76.

10. De Backer D, Christiaens T, Heytens S, *et al.* Evolution of bacterial susceptibility pattern of Escherichia coli in uncomplicated urinary tract infections in a country with high antibiotic consumption: a comparison of two surveys with a 10 year interval. *J Antimicrob Chemother* 2008; **62(2):** 364–368. doi: 10.1093/jac/dkn197

11. Heytens S, Boelens J, Claeys G, *et al.* Uropathogen distribution and antimicrobial susceptibility in uncomplicated cystitis in Belgium, a high antibiotics prescribing country: 20-year surveillance. *Eur J Clin Microbiol Infect Dis* 2017; **36(1):** 105–113. doi: 10.1007/s10096-016-2776-8

12. Stefaniuk E, Suchocka U, Bosacka K, *et al.* Etiology and antibiotic susceptibility of bacterial pathogens responsible for community-acquired urinary tract infections in Poland. *Eur J Clin Microbiol Infect Dis* 2016; **35(8):** 1363–1369. doi: 10.1007/s10096-016-2673-1

13. Malmartel A, Ghasarossian C. Epidemiology of urinary tract infections, bacterial species and resistances in primary care in France. *Eur J Clin Microbiol Infect Dis* 2016; **35(3):** 447–451. doi: 10.1007/s10096-015-2560-1

14. Delisle G, Quach C, Domingo MC, *et al.* Escherichia coli antimicrobial susceptibility profile and cumulative antibiogram to guide empirical treatment of uncomplicated urinary tract infections in women in the province of Québec, 2010-15. *J Antimicrob Chemother* 2016; **71(12):** 3562–3567. doi: 10.1093/jac/dkw302

15. Gupta K, Hooton TM, Naber KG, *et al.* International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis* 2011; **52(5):** e103–e120. doi: 10.1093/cid/ciq257

16. Hillier S, Bell J, Heginbothom M, *et al.* When do general practitioners request urine specimens for microbiology analysis? The applicability of antibiotic resistance surveillance based on routinely collected data. *J Antimicrob Chemother* 2006; **58(6):** 1303–1306. doi: 10.1093/jac/dkl432

17. Baerheim A, Digranes A, Hunskaar S. Are resistance patterns in uropathogens published by microbiological laboratories valid for general practice? *APMIS* 1999; **107(7):** 676–680. doi: 10.1111/j.1699-0463.1999.tb01458.x

18. Flottorp S, Oxman AD, Cooper JG, *et al.* Retningslinjer for diagnostikk og behandling av akutte vannlatingsplager hos kvinner. [Guidelines for diagnosis and treatment of acute urinary tract problems in women.] *Tidsskrift Nor Laegeforen* 2000; **120:** 1748–1753.

19. Bollestad M, Grude N, Lindbaek M. A randomized controlled trial of a diagnostic algorithm for symptoms of uncomplicated cystitis at an out-of-hours service. *Scand J Prim Health Care* 2015; **33(2):** 57–64. doi: 10.3109/02813432.2015.1041827

20. Vik I, Bollestad M, Grude N, *et al.* Ibuprofen versus mecillinam for uncomplicated cystitis — a randomized controlled trial study protocol. *BMC Infect Dis* 2014; **14:** 693. doi: 10.1186/s12879-014-0693-y

21. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 7.1. 2017; http://www.eucast.org/mic_distributions_and_ecoffs/ (accessed 2 Oct 2017).

22. Aspevall O, Hallander H, Gant V, *et al.* European guidelines for urinalysis: a collaborative document produced by European clinical microbiologists and clinical chemists under ECLM in collaboration with ESCMID. *Clin Microbiol Infect* 2001; **7(4):** 173–178. doi: 10.1046/j.1198-743x.2001.00237.x

23. Bergan T, Bruun JN, Digranes A, *et al.* Susceptibility testing of bacteria and fungi. Report from 'The Norwegian Working Group on Antibiotics'. *Scand J Infect Dis Suppl* 1997; **103:** 1–36.

24. The Norwegian Institute of Public Health. The Norwegian Prescription Database. Available from: www.norpd.no (accessed 23 Aug 2017).

25. Social Science Statistics. Chi square calculator. 2017; http://www.socscistatistics.com/tests/chisquare/Default.aspx (accessed 23 Aug 2017).

26. Adeghate J, Juhász E, Pongrácz J, *et al.* Does Staphylococcus saprophyticus cause acute cystitis only in young females, or is there more to the story? A one-year comprehensive study done in Budapest, Hungary. *Acta Microbiol Et Hung* 2016; **63(1):** 57–67. doi: 10.1556/030.63.2016.1.4

27. Lo DS, Shieh HH, Barreira ER, *et al.* High frequency of Staphylococcus saprophyticus urinary tract infections among female adolescents. *Pediatr Infect Dis J* 2015; **34(9):** 1023–1025. doi: 10.1097/INF.0000000000000780

28. Kahlmeter G. An international survey of the antimicrobial susceptibility of pathogens from uncomplicated urinary tract infections: the ECO.SENS Project. *J Antimicrob Chemother* 2003; **51(1):** 69–76.

29. Czaplewski L, Bax R, Clokie M, *et al.* Alternatives to antibiotics — a pipeline portfolio review. *Lancet Infect Dis* 2016; **16(2):** 239–251. doi: 10.1016/S1473-3099(15)00466-1

30. Gágyor I, Haasenritter J, Bleidorn J, *et al*. Predicting antibiotic prescription after symptomatic treatment for urinary tract infection: development of a model using data from an RCT in general practice. *Br J Gen Pract* 2016; **66(645):** e234–e240. doi: 10.3399/bjgp16X684361

31. El Sakka N, Gould IM. Role of old antimicrobial agents in the management of urinary tract infection. *Expert Rev Clin Pharmacol* 2016; **9(8):** 1047–1056. doi: 10.1080/17512433.2016.1189325

32. Søraas A, Sundsfjord A, Jørgensen SB, *et al*. High rate of per oral mecillinam treatment failure in community-acquired urinary tract infections caused by ESBL-producing Escherichia coli. *PloS one* 2014; **9(1):**e85889. doi: 10.1371/journal.pone.0085889

33. Jansåker F, Frimodt-Møller N, Sjögren I, *et al*. Clinical and bacteriological effects of pivmecillinam for ESBL-producing Escherichia coli or Klebsiella pneumoniae in urinary tract infections. *J Antimicrob Chemother* 2014; **69(3):** 769–772. doi: 10.1093/jac/dkt404

34. Maraki S, Samonis G, Rafailidis PI, *et al*. Susceptibility of urinary tract bacteria to fosfomycin. *Antimicrob Agents Chemother* 2009; **53(10):** 4508–4510. doi: 10.1128/AAC.00721-09

35. Keating GM. Fosfomycin trometamol: a review of its use as a single-dose oral treatment for patients with acute lower urinary tract infections and pregnant women with asymptomatic bacteriuria. *Drugs* 2013; **73(17):** 1951–1966. doi: 10.1007/s40265-013-0143-y

36. Chin TL, McNulty C, Beck C, *et al*. Antimicrobial resistance surveillance in urinary tract infections in primary care. *J Antimicrob Chemother* 2016; **71(10):** 2723–2728. doi: 10.1093/jac/dkw223

37. Christiaens TC, Digranes A, Baerheim A. The relation between sale of antimicrobial drugs and antibiotic resistance in uropathogens in general practice. *Scand J Prim Health Care* 2002; **20(1):** 45–49. doi: 10.1080/028134302317282743

Paper III

Bollestad M, Vik I, Grude N, Lindbaek M. Predictors of symptom duration and bacteriuria in uncomplicated urinary tract infection. Scand J Prim Health Care. 2018;3:1-9.

Taylor & Francis
Taylor & Francis Group

RESEARCH ARTICLE

Predictors of Symptom Duration and Bacteriuria in Uncomplicated Urinary Tract Infection

Marianne Bollestad[a,b,c], Ingvild Vik[a,b], Nils Grude[a,d] and Morten Lindbæk[a]

[a]The Antibiotic Centre of Primary Care, Department of General Practice, Institute of Health and Society, University of Oslo, Oslo, Norway; [b]Oslo Accident and Emergency Outpatient Clinic, Department of Emergency General Practice, City of Oslo Health Agency, Oslo, Norway; [c]Division of Medicine, Stavanger University Hospital, Stavanger, Norway; [d]Department of Medical Microbiology, Vestfold hospital trust, Toensberg, Norway

ABSTRACT

Objective: To identify baseline predictors of symptom duration after empirical treatment for uncomplicated urinary tract infection (UTI) and significant bacteriuria in a cohort of women treated for UTI.
Design: Prospective single-centre cohort study.
Setting: Outpatient clinic in Norway.
Patients: From September 2010 to November 2011, 441 women aged 16–55 years with symptoms of uncomplicated UTI were included.
Results: Dipstick findings of leukocyte esterase $1+$ (incidence rate ratio (IRR) 1.93, 95% confidence interval (CI) 1.23–3.01, $p < 0.01$) and microbe resistant to mecillinam treatment (IRR 1.41, 95% CI 1.07–1.89, $p = 0.02$) predicted longer symptom duration. More pronounced symptoms did not predict longer symptom duration (IRR 1.18, 95% CI 0.94–1.46, $p = 0.15$) or significant bacteriuria (odds ratio [OR] 1.16, 95% CI 0.72–1.88, $p = 0.54$). Leukocyte esterase $2+$ (OR 2.51, 95% CI 0.92–6.83, $p = 0.07$) or $3+$ (OR 2.40, 95% CI 0.88–6.05, $p = 0.09$) and nitrite positive urine dipstick test (OR 3.22, 95% CI 1.58–7.01, $p = <0.01$) were associated with bacteriuria.
Conclusion: More pronounced symptoms did not correlate with significant bacteriuria or symptom duration after empirical treatment for acute cystitis. One might reconsider the current practice of treating uncomplicated UTI based on symptoms alone.

KEY POINTS

- Treatment strategies for milder infectious diseases must consider ways of reducing antibiotic consumption to decelerate the increase in antibiotic resistance. Our findings suggest that more emphasis should be put on urine dipstick results and bacteriological findings in the clinical setting. One might reconsider the current practice of treating uncomplicated UTIs based on symptoms alone.

Introduction

Urinary tract infections (UTIs) are one of the most common bacterial infections encountered in the primary care setting. Most women experience at least one episode of acute uncomplicated cystitis in their lifespan [1, 2]. Women report diversity in symptom burden in relation to an episode of uncomplicated UTI [3].

Antibiotics prescribed in primary care account for around 85% of the total human antibiotic consumption in Norway [4]. Empirical treatment of UTIs is based on updated knowledge of antimicrobial resistance and national guidelines [5,6]. Refraining from treatment has been found to be inferior for both symptomatic and bacteriological cure of uncomplicated UTI [7–9]. However, a study of ibuprofen versus fosfomycin for the treatment of uncomplicated UTI found that two-thirds of women recovered without antibiotics [10]. Subgroup analysis of the patients found that five factors predicted the need for subsequent antibiotic treatment: urgency/frequency, impaired daily activities, and positive urine dipstick test results for erythrocytes, leukocyte esterase and nitrite [11].

Both national and international guidelines endorse the treatment of acute uncomplicated cystitis based on symptoms alone [5,12]. Studies have found diverging results in terms of how well symptoms predict the presence of a UTI using a positive urine culture for known uropathogens as the gold standard [7,13–15]. Women with a history of cystitis, frequent somatic symptoms, presence of bacteria resistant to the chosen antibiotic regime and severe symptoms at baseline are more likely to have symptoms of acute cystitis lasting longer than three days after the initiation of treatment [16].

Detection of leukocyte esterase and nitrites or erythrocytes and nitrites on the urine dipstick is considered to be moderately sensitive and specific for detecting a UTI when using a positive culture as the gold standard [14,17,18]. One study showed that a negative urine dipstick test for leukocytes and nitrites accurately predicted the absence of infection, as defined by standard microbiological parameters, but it did not predict the response to antibiotic treatment. Antibiotic treatment significantly reduces dysuria in women with a negative urine dipstick test [19].

Antibiotic resistance rates are increasing, and medical practice now focuses on developing new treatment strategies to reduce antibiotic use without comprising patient safety. New generations of drugs to combat microbial infections will probably not be a reality in the foreseeable future, and clinicians need alternative strategies to reduce antibiotic consumption [20].

It is of interest to identify which clinical and bacteriological factors, if any, predict longer duration of symptoms following empirical antibiotic treatment and the presence of bacteriuria. Further studies are needed to develop good clinical decision aids to identify those patients who are suitable for symptomatic treatment and/or delayed prescribing for uncomplicated UTI. This could lead to decreased antibiotic consumption and at the same time minimize the potential for prolonged patient discomfort.

The aims of this study were to identify:

- factors that predict significantly longer duration of symptoms in patients with uncomplicated UTI after empirical antibiotic treatment
- factors that predict significant bacteriuria in patients presenting with an uncomplicated UTI.

Material and methods

The analysed data were based on findings from a study assessing the use of a diagnostic algorithm to identify patients with uncomplicated UTI [21]. A prospective randomized study was performed during the 14 months from September 2010 to November 2011. Women between the ages of 16 and 55 years presenting with dysuria and increased frequency of urination were included. Visible haematuria and increased urinary urgency were also registered but were not used to determine inclusion. The exclusion criteria were significant co-morbidity including diabetes or kidney disease, pregnancy, breastfeeding (infant under one month of age), symptoms of pyelonephritis, symptoms of a sexually transmitted disease, symptoms lasting longer than seven days, use of a urinary catheter or diagnosed a urinary tract infection in the last four weeks, current use of antibiotics, known allergy to penicillin, oesophageal passage problems, use of the medication probenecid and fever ($>38^\circ$C) (Figure 1). The patients enrolled were randomized into two groups by drawing numbers from an opaque envelope. One group received treatment with mecillinam according to the standard diagnostic algorithm, and the control group was seen by a doctor who was unaware that the patient was identified as eligible for treatment according to the diagnostic algorithm.

The cardinal symptoms of acute uncomplicated UTI (painful urination and increased frequency of urination) were registered as mild, moderate or severe upon presentation to the study nurse.

The follow-up included a telephone call from the study co-ordinator one week after the primary contact and two weeks after the treatment was completed. The number of days until symptom resolution was recorded. Patients without symptom resolution at the two-week follow-up were registered as symptomatic for 15 days for the purpose of statistical analysis. Urine dipstick findings on the day of presentation were recorded. The Multistix 5 dipstick produced by Siemens Healthcare Diagnostics AS was used. The urine dipstick results were graded from 0 to 4 for erythrocytes, 0–3 for leukocyte esterase, and positive/negative for nitrite. A urine sample was sent to the laboratory for culturing on the day of presentation and one week after completing the treatment. The women were instructed to collect a midstream urine sample after spreading of the labia. The initial sample was taken upon presentation, regardless of bladder incubation time. For the follow-up sample the included patients were instructed to send a morning urine sample. The vast majority of samples were received within one to two weeks after treatment.

During the inclusion period, 832 consecutive women were screened for eligibility to enter the

Diagnostic algorithm: uncomplicated UTI

	Yes	No
Are you a woman aged 16–55 years?	☐	☐
Do you have		
-painful urination? *mild* ☐ *moderate* ☐ *strong* ☐		☐
-increased frequency of urination? *mild* ☐ *moderate* ☐ *strong* ☐		☐
-increased need to urinate?	☐	☐
-visible haematuria?	☐	☐
Are you pregnant or breastfeeding (infant under 1 month of age)?	☐	☐
Do you have diabetes or kidney disease?	☐	☐
Do you have -fever?	☐	☐
-reduced general condition?	☐	☐
-back/flank/stomach pain?	☐	☐
Do you have -increased vaginal secretion?	☐	☐
-itching/irritation?	☐	☐
-STRONG lower abdominal pain?	☐	☐
Have you had pain for more than 7 days?	☐	☐
Have you in the past 4 weeks had a urinary tract infection or used a urinary tract catheter?	☐	☐
Are you using antibiotics now?	☐	☐
Have you previously had an allergic reaction to penicillin?	☐	☐
Do you have oesophageal passage problems?	☐	☐
Do you use the medication Probecid?	☐	☐
Temperature (<38° C)	☐	☐

	Delegated treatment	Doctor's consultation
Treatment chosen by support staff:	☐	☐

Dark gray background: inclusion criteria
Light gray background: registered but did not determine inclusion
White background: exclusion criteria

Figure 1. Data were collected at Oslo Accident and Emergency Outpatient Clinic, Norway 2010–2011. The results have been previously published: http://www.tandfonline.com/doi/full/10.3109/02813432.2015.1041827 [20].

study; 391 were excluded primarily because they presented with one or more exclusion criteria. A total of 441 women were randomized to receive treatment in accordance with the diagnostic algorithm ($n = 245$) or treatment following a regular doctor's consultation ($n = 196$). A total of eight patients were excluded due to deviations from protocol leaving 242 in the diagnostic algorithm group versus 191 who received treatment following a doctor's consultation. The trial flow chart is included as a supplementary file. The cohort represents a young population with a mean age of 27 years [21].

All urine samples were cultured according to established procedures for identification of microbes with resistance patterns at the Department of Medical Microbiology, Oslo University Hospital, Ullevål. The uropathogens were quantified in colony-forming units (cfu)/mL. Significant bacteriuria was defined according to current European guidelines for patients with symptoms of UTI as $\geq 10^3$ cfu/mL for primary pathogens, $\geq 10^4$ cfu/mL for secondary pathogens and $\geq 10^5$ cfu/mL for doubtful pathogens [22]. Bacterial growth which did not meet the criteria for significant bacteriuria was registered as a negative culture.

Most patients included in this study were treated with a three-day regimen of mecillinam, dosage 200 mg TID for three days. Other treatment regimens were trimethoprim and nitrofurantoin, treatment length varied from three to 7 days.

The urine from 57% of patients exhibited significant bacterial growth. The most common pathogens were Escherichia coli (E. coli) (77%) and Staphylococcus saprophyticus (S. saprophyticus) (16%) [21].

The number of days with symptoms of acute UTI before the patient sought health care was not registered, but it was less than seven days for all patients since longer duration of symptoms led to exclusion. A median of three days until symptom resolution was found in both groups ($p = 0.3$) [21].

Statistical methods

To identify factors predicting longer symptom duration, the traditional negative binomial (NB2) model was fitted to the count data. The NB2 model was selected to handle over-dispersed Poisson data. Over-dispersion of the data was confirmed with the Pearson dispersion statistic of 4.31, a value that exceeds 1 for equally dispersed Poisson data.

Selection of predictors into the final fitted model was based on the backward elimination method. We started with all possible predictors of longer system duration in the model and at each stage of model development, the predictor with the largest p-value was removed and the model refitted. We also estimated the Akaike Information Criterion (AIC), which we used to compare all subsequent models; the smaller the AIC, the better the model. Therefore, each subsequent step of modelling eliminated the least significant variable in the model until the AIC estimate was higher than in the previous step. However, at each stage of modelling, the variable age was retained in the model regardless of its predictive power.

For the purpose of analysis, the cohort was divided into three age groups: 16–22, 23–28, and ≥ 29 years.

To identify factors predicting significant bacteriuria sensitivity, specificity and positive predictive values (PPV) were first calculated.

Binary logistic regression models were also fitted to the data to identify predictors of significant bacteriuria. The analyses proceeded in two steps. Firstly, univariate logistic regression models were fitted to the data to identify significant predictors. Secondly, the significant predictors from the univariate analyses together with clinically relevant predictors were used to fit a multivariate logistic regression model.

To assess the accuracy and discriminative value of the final prediction model, sensitivity was plotted against the false-positive rate (1–specificity) over a range of cut-point values for the continuous linear score in the receiver-operating characteristic (ROC) space, and the area under the ROC curve (AUC) was calculated.

All statistical analyses were performed using SPSS 22, and significance was set at $p < 0.05$.

Results

More severe symptoms or the presence of significant bacteriuria were not significant predictors of longer symptom duration after empirical treatment. The presence of leukocyte esterase 1+ on the urine test strip and the significant growth of a microbe resistant to the given antibiotic predicted significantly longer symptom duration (Table 1).

The presence of nitrite on the urine dipstick gave a PPV of 0.81 for significant bacteriuria; this was the highest PPV found. The presence of leukocyte esterase of 2+ and 3+ was also associated with an increased PPV of significant bacteriuria but to a lesser degree. More severe symptoms did not predict significant bacteriuria (Table 2).

Logistic regression analysis showed that neither age nor more pronounced clinical symptoms upon presentation correlated with the presence of significant bacteriuria.

Urine dipstick positive for nitrite (OR 3.22, 95% CI 1.58–7.01, $p < 0.01$) was associated with an increased probability of significant bacteriuria (Table 3). Urine dipstick findings with a leukocyte esterase value of 3+ (OR 2.40, 95% CI 0.88–6.05, $p = 0.09$), or a leukocyte esterase value of 2+ (OR 2.51, 95% CI 0.92–6.83, $p = 0.07$) showed association with significant bacteriuria, but did not reach significance.

Table 1. Predictors of a longer duration of urinary tract symptoms after empirical antibiotic treatment.

	Univariate analyses			Multivariate analyses		
	IRR* (B)	95% CI	p	IRR (B)	95% CI	p
Two strong symptoms and urgency n = 89 (reference: weak symptoms n = 344)	1.12	0.92–1.37	0.27	1.18	0.94–1.46	0.15
Age, years (reference: 16–22)						
16–22 n = 151	1.0			1.0		
23–28 n = 146	1.05	0.87–1.28	0.60	1.04	0.83–1.29	0.76
≥29 n = 136	1.14	0.94–1.39	0.19	1.06	0.85–1.32	0.59
Leukocytes (reference: negative n = 44)						
3+ n = 121	0.82	0.61–1.10	0.19	1.22	0.80–1.86	0.37
2+ n = 129	0.86	0.64–1.14	0.30	1.18	0.78–1.80	0.43
1+ n = 55	1.27	0.91–1.75	0.16	1.93	1.23–3.01	<0.01
Leukocytes, all positive n = 305 (reference: negative n = 44)	0.92	0.70–1.20	0.53			
Nitrite positive n = 58 (reference: negative n = 289)	1.13	0.89–1.44	0.31			
Erythrocytes positive n = 294 (reference: negative n = 54)	0.82	0.64–1.05	0.11			
Negative urine dipstick n = 22 (reference: any positive dipstick finding n = 324)	0.86	0.60–1.23	0.41	0.65	0.38-1.12	0.12
Microbe susceptibility to given treatment (reference: sensitive n = 179)						
Resistant n = 47	1.51	1.16–1.97	<0.01	1.41	1.07–1.89	0.02
No susceptibility testing performed n = 187	1.02	0.85–1.21	0.86	0.92	0.75–1.12	0.40
Doctors' consultation n = 191 (reference: algorithm group n = 242)	1.12	0.95–1.31	0.18			
Significant bacteriuria n = 233 (reference: negative n = 173)	1.06	0.89–1.25	0.53			

*IRR = incidence rate ratio;
CI = confidence interval.
The predictors of longer duration of urinary tract symptoms after empirical antibiotic treatment were identified using the traditional negative binomial model. The data were collected at Oslo Accident and Emergency Outpatient Clinic, Norway, 2010–2011.

Table 2. Symptoms and signs that predicted significant bacteriuria in acute uncomplicated cystitis.

Symptoms and signs	Growth + (%) N = 233	Growth − (%) N = 173	Total (%) N = 406	Sensitivity	Specificity	PPV*
Pain at urination (all)	233 (100)	173 (100)	406 (100)			
Strong	77 (33)	54 (31)	131 (32)	0.33	0.69	0.58
Urinary frequency (all)	233 (100)	173 (100)	406 (100)			
Strong	81 (35)	65 (38)	146 (36)	0.35	0.62	0.56
Urgency (n = 405)°	228 (98)	172 (99)	400 (99)	0.98	0.58	0.57
Two strong symptoms and urgency	53 (23)	35 (20)	88 (22)	0.23	0.80	0.60
Age, years (all)	233 (100)	173 (100)	406 (100)			
16–22	73 (31)	67 (39)	140 (35)	0.31	0.61	0.52
23–28	80 (34)	57 (33)	137 (34)	0.34	0.67	0.58
≥29	80 (34)	49 (28)	129 (32)	0.34	0.72	0.62
Urine dipstick findings						
Leukocytes (n = 327)	192 (59)	135 (41)				
3+	75 (39)	40 (30)	115 (32)	0.39	0.70	0.65
2+	79 (41)	39 (29)	118 (36)	0.41	0.71	0.67
1+	25 (13)	27 (20)	52 (16)	0.13	0.80	0.48
Leukocytes, all positive	179 (93)	106 (79)	285 (87)	0.93	0.21	0.63
Negative	13 (7)	29 (22)	42 (13)			
Nitrite positive (n = 325)	44 (23)	10 (8)	54 (17)	0.23	0.93	0.81
Erythrocytes positive (n = 326)	174 (91)	103 (77)	277 (85)	0.91	0.23	0.63

*PPV = positive predictive value.
The sensitivity, specificity and PPV of symptoms and signs that predicted significant bacteriuria were identified using data collected at Oslo Accident and Emergency Outpatient Clinic, Norway, 2010–2011.
°1 patient did not respond.

Table 3. Predictors of the presence of significant bacteriuria in urine samples from women with diagnosed acute uncomplicated cystitis.

	Univariate analyses			Multivariate analyses		
	OR* (B)	95% CI	p	OR (B)	95% CI	p
Two strong symptoms and urgency, n = 89 (reference: weak, n = 344)	1.16	0.72–1.88	0.54			
Age, years						
16–22, n = 151 (reference)	1.00			1.00		
23–28, n = 146	1.29	0.80–2.07	0.30	1.35	0.75–2.40	0.31
≥29, n = 136	1.50	0.92–2.44	0.10	1.44	0.80–2.56	0.22
Urine dipstick findings						
Leukocytes (reference: negative, n = 44)	1.0			1.0		
3+, n = 121	4.18	1.96–8.93	<0.01	2.40	0.88–6.05	0.09
2+, n = 129	4.52	2.12–9.65	<0.01	2.51	0.92–6.83	0.07
1+, n = 55	2.07	0.88–4.84	0.10	1.38	0.46–4.19	0.57
Leukocytes, all positive, n = 305 (reference: negative, n = 44)	3.77	1.88–7.56	<0.01			
Nitrite positive, n = 58 (reference: negative, n = 289)	3.71	1.79–7.68	<0.01	3.22	1.58–7.01	<0.01
Erythrocytes positive, n = 294 (reference: negative, n = 54)	2.91	1.55–5.46	<0.01	1.40	0.60–3.25	0.45
Positive urine dipstick, 324 (reference: negative, n = 22)	9.18	2.63–32.02	<0.01	2.73	0.47–15.73	0.26

*OR = odds ratio;
 CI = confidence interval.
The predictors of the presence of significant bacteriuria were identified in a logistic regression analysis of data collected at Oslo Accident and Emergency Outpatient Clinic, Norway, 2010–2011.

Significant bacteriuria receiver operating characteristic curve area [with age]: 0.61 (95% CI: 0.55 - 0.67)
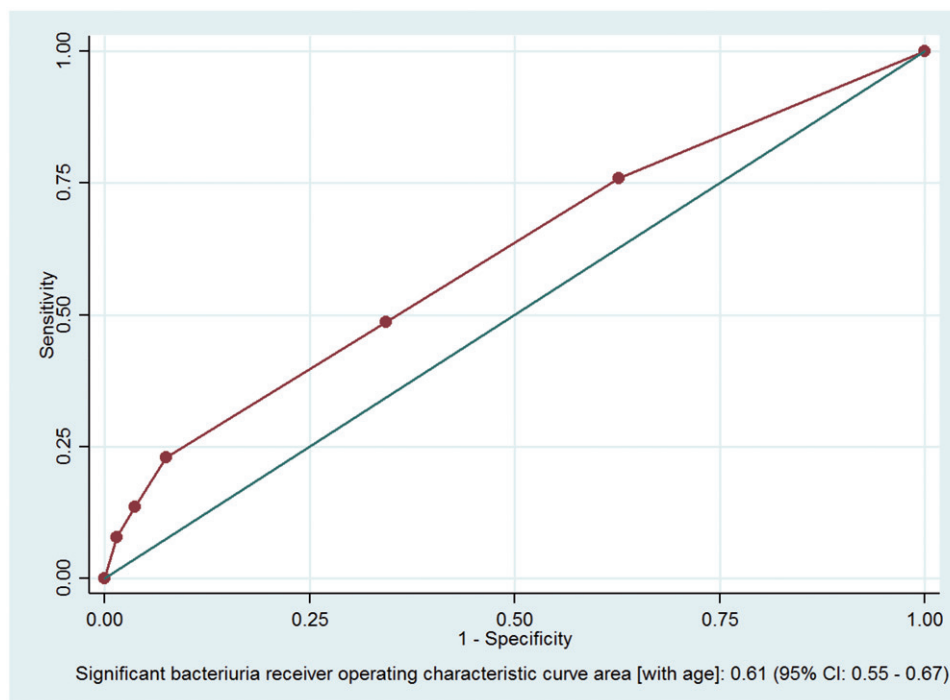
Figure 2. Correlations between the presence of leukocyte esterase, nitrite, age and significant bacteriuria. CI = confidence interval. Receiver-operator characteristic (ROC) analysis of the relationship between the presence of leukocyte esterase, nitrite, age and significant bacteriuria. The data were collected at Oslo Accident and Emergency Outpatient Clinic, Norway, 2010–2011.

The ROC analysis gave an AUC of the final model of 0.61 (95% CI 0.55–0.67) (Figure 2).

In our cohort, 59/347 (17.0%) of the registered urinary dipstick findings were nitrite positive. For five of the patients with a positive nitrite dipstick test, a urine culture was not performed. After exclusion of these patients, 42/54 (77.8%) of nitrite positive urine samples showed significant growth of a gram-negative uropathogen. For the remaining cultures, one showed no growth, two showed significant growth of *S. saprophyticus*, and the rest showed mixed bacterial growth.

We found that 176/180 (97.8%) of *E. coli* isolates were sensitive to mecillinam and 39/146 (26.7%) of the urine samples with significant growth of *E. coli* and registered urinary dipstick findings were nitrite positive.

Discussion

Statement of principal findings

Our study identified the presence of leukocyte esterase (2+, 3+) and nitrite on the urinary dipstick test as significant predictors of the presence of bacteriuria. Leukocyte esterase 1+ and microbial resistance to the given antibiotic was associated with longer symptom duration. The severity of symptoms at presentation was neither a significant predictor of the presence of bacteriuria nor longer symptom duration after adequate treatment.

Strengths and weaknesses of the study

The study included patients recruited from a large and relatively young population, and complete data were obtained from nearly all the included patients. Given the median age of 27 years in these subjects, the findings are representative of younger patient populations compared with those included in previously published studies, and do not represent the elderly population. Women aged ≤55 years represent around 50% of women presenting to the general practitioner with UTIs. The questionnaire did not identify a complete medical history or social and psychological factors that could have affected the reported symptoms. The study did not include a control group of untreated women with symptoms of uncomplicated UTI.

Findings in relation to other studies

Previous studies have shown varying results in terms of whether symptoms can be used to identify patients with an uncomplicated UTI [8,11,12]. Norwegian national guidelines suggest that antibiotic treatment should be given based on symptoms alone for women with suspected acute uncomplicated UTI [23].

Nitrite-positive urine dipstick was associated with significant bacteriuria. Gram-negative bacteria produce nitrite, and *E. coli* is by far the most common gram-negative uropathogen. A previous study of *E. coli* has identified specific virulence factor genes and phylogenetic groups of the microbe that increase the risk of persistence and relapse of UTI [24].

A relatively low percentage (26.7%) of patients who had significant growth of *E. coli* had a positive nitrite urinary dipstick test. A possible explanation for this finding is that the presence of nitrite on the urinary dipstick is associated with a more virulent isolate and can explain the association with prolonged symptom duration. Negative nitrite findings in the urinary dipstick test are also related to insufficient bladder time for conversion of nitrate to nitrite, decreased urine pH and low urinary excretion of nitrate.

The second most frequently isolated microbe was *S. saprophyticus*, which is considered to be intrinsically resistant to mecillinam treatment. However, a clinical effect has been shown for lower UTI in women where *S. Saprophyticus* as the bacterial agent. It is suspected that the observed effect of mecillinam treatment on microbes intrinsically resistant to treatment is related to the high concentration of mecillinam in urine and relatively low minimal inhibitory concentration of uropathogens [25].

Analysis of factors that might be associated with significant bacteriuria showed that detecting leukocyte esterase 2+ or 3+ on the urine dipstick was more clearly associated with significant bacteriuria than the detection of leukocyte esterase 1+. It is possible that in the cohort where leukocyte esterase 1+ was detected the symptoms did not represent an acute uncomplicated UTI and, if so, the antibiotics would have been expected to be less effective. In addition, the detection of leukocyte esterase 1+ on the urine dipstick was associated with longer symptom duration following empiric antibiotic treatment. We speculate that a possible treatment strategy for this group may be symptomatic relief combined with delayed prescribing.

In this study population, we found significant growth of uropathogens in 57% of the primary urine samples. Previous studies have suggested that for acute uncomplicated UTI, a value $\geq 10^2$ cfu/mL could signify significant bacterial growth, not $\geq 10^3$ cfu/mL as defined by current standards [22]. It is possible that cases of clinically relevant bacterial growth are missed and that use of polymerase chain reaction in testing for bacterial agents may improve the diagnostic precision [26].

Implications

More pronounced symptoms did not correlate with significant bacteriuria or longer symptom duration after empirical treatment for uncomplicated UTI. Our study identified dipstick findings and bacteriological

findings as clinically useful for identifying women with an expected longer duration of symptoms after empiric treatment and significant bacteriuria at presentation.

Future treatment strategies for milder infectious diseases must consider ways of reducing antibiotic consumption to decelerate the increase in antibiotic resistance, and several antibiotic-sparing treatment regimens have been proposed [10,27]. Our findings suggest that in clinical practice perhaps more emphasis should be put on urine dipstick results and bacteriological findings. In order to reduce unnecessary use of antibiotics, one might reconsider the current practice of treating uncomplicated UTI based on symptoms alone.

Ethics approval and consent to participate

The study is registered in Clinicaltrials.gov (reference number: NCT01132131) and was approved by the Regional Ethical Committee (reference number: 2010/486.) All patients provided written consent for participation.

Disclosure statement

The authors report no conflict of interest.

Notes on contributors

Marianne Bollestad, MD, is a PhD student at the Antibiotic Centre of Primary Care, Department of General Practice, Institute of Health and Society, University of Oslo, Oslo, Norway and pursuing a fellowship training program in Infectious Diseases at Stavanger University Hospital, Division of Medicine, Stavanger, Norway.

Ingvild Vik, MD, is a PhD student at the Antibiotic Centre of Primary Care, Department of General Practice, Institute of Health and Society, University of Oslo, Oslo, Norway and a general practitioner in training at the Department of Emergency General Practice, Oslo Accident and Emergency Outpatient Clinic, Oslo, Norway.

Nils Grude, MD, PhD, Consultant at Lab. for medical microbiology, Vestfold Hospital Trust, Tønsberg, Norway, and researcher at the Antibiotic Centre of Primary Care, Department of General Practice, Institute of Health and Society, University of Oslo, Oslo, Norway.

Morten Lindbæk, MD, general practice and leader of the Antibiotic Centre for Primary Care, Department of General Practice, Institute of Health and Society, University of Oslo, Oslo, Norway.

References

[1] Foxman B, Barlow R, D'Arcy H, et al. Urinary tract infection: self-reported incidence and associated costs. Ann Epidemiol. 2000;10:509–515.

[2] Schappert SM, Rechtsteiner EA. Ambulatory medical care utilization estimates for 2007. Vital Health Stat 13, Data from the National Health Survey. 2011;69:1–38.

[3] Malterud K, Baerheim A. Peeing barbed wire. Symptom experiences in women with lower urinary tract infection. Scand J Prim Health Care. 1999;17:49–53.

[4] Simonsen GS, Magrete UA. Usage of antimicrobial agents and occurrence of antimicrobial resistance in Norway. Norwegian Surveillance System for Antimicrobial Drug Resistance. Tromsø/Oslo. 2015. Date of access. www.antibiotikaresistens.no. June 6, 2017.

[5] Lindbaek M, Berild D, Eliassen KE, et al. Nasjonale faglige retningslinjer for antibiotikabruk i primaerhelsetjensten. [National guidelines for use of antibiotics in primary health care.] Helsedirektoratet. 2013. www.antibiotika.no. Date of access: June 6, 2017.

[6] Bollestad M, Vik I, Grude N, Blix HS, et al. Bacteriology in uncomplicated urinary tract infections in Norwegian general practice from 2001 to 2015. BJGP Open 2017. 2018;1:bjgpopen17X101145. doi: https://doi.org/10.3399/bjgpopen17X101145.

[7] Ferry SA, Holm SE, Stenlund H, et al. Clinical and bacteriological outcome of different doses and duration of pivmecillinam compared with placebo therapy of uncomplicated lower urinary tract infection in women: The LUTIW project. Scand J Prim Health Care. 2007;25:49–57.

[8] Ferry SA, Holm SE, Stenlund H, et al. The natural course of uncomplicated lower urinary tract infection in women illustrated by a randomized placebo controlled study. Scand J Infect Dis. 2004;36:296–301.

[9] Christiaens TC, De Meyere M, Verschraegen G, et al. Randomised controlled trial of nitrofurantoin versus placebo in the treatment of uncomplicated urinary tract infection in adult women. Brit J Gen Pract. 2002;52:729–734.

[10] Gagyor I, Bleidorn J, Kochen MM, et al. Ibuprofen versus fosfomycin for uncomplicated urinary tract infection in women: randomised controlled trial. BMJ. 2015;351:h6544.

[11] Gagyor I, Haasenritter J, Bleidorn J, et al. Predicting antibiotic prescription after symptomatic treatment for urinary tract infection: development of a model

using data from an RCT in general practice. Br J Gen Pract. 2016;66:e234–e240.

[12] Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis. 2011;52:e103–e120.

[13] Bent S, Nallamothu BK, Simel DL, et al. Does this woman have an acute uncomplicated urinary tract infection? JAMA 2002;287:2701–2710.

[14] Giesen LG, Cousins G, Dimitrov BD, et al. Predicting acute uncomplicated urinary tract infection in women: a systematic review of the diagnostic accuracy of symptoms and signs. BMC Fam Pract. 2010;11:78.

[15] Medina-Bombardo D, Jover-Palmer A. Does clinical examination aid in the diagnosis of urinary tract infections in women? A systematic review and meta-analysis. BMC Fam Pract. 2011;12:111.

[16] Little P, Merriman R, Turner S, et al. Presentation, pattern, and natural course of severe symptoms, and role of antibiotics and antibiotic resistance among patients presenting with suspected uncomplicated urinary tract infection in primary care: observational study. BMJ. 2010;340:b5633.

[17] Little P, Rumsby K, Jones R, et al. Validating the prediction of lower urinary tract infection in primary care: sensitivity and specificity of urinary dipsticks and clinical scores in women. Br J Gen Pract. 2010;60:495–500.

[18] Hooton TM. Clinical practice. Uncomplicated urinary tract infection. N Engl J Med. 2012;366:1028–1037.

[19] Richards D, Toop L, Chambers S, et al. Response to antibiotics of women with symptoms of urinary tract infection but negative dipstick urine test results: double blind randomised controlled trial. BMJ. 2005;331:143.

[20] Czaplewski L, Bax R, Clokie M, et al. Alternatives to antibiotics-a pipeline portfolio review. Lancet Infect Dis. 2016;16:239–251.

[21] Bollestad M, Grude N, Lindbaek M. A randomized controlled trial of a diagnostic algorithm for symptoms of uncomplicated cystitis at an out-of-hours service. Scand J Prim Health Care. 2015;33:57–64.

[22] Aspevall O, Hallander H, Gant V, et al. European guidelines for urinalysis: a collaborative document produced by European clinical microbiologists and clinical chemists under ECLM in collaboration with ESCMID. Clin Microbiol Infect. 2001;7:173–178.

[23] Flottorp S, Oxman AD, Cooper JG, et al. Retningslinjer for diagnostikk og behandling av akutte vannlatingsplager hos kvinner. [Guidelines for diagnosis and treatment of acute urinary tract problems in women.]. Tidsskr nor Laegeforen. 2000;120:1748–1753.

[24] Ejrnaes K, Stegger M, Reisner A, et al. Characteristics of *Escherichia coli* causing persistence or relapse of urinary tract infections: phylogenetic groups, virulence factors and biofilm formation. Virulence. 2011;2:528–537.

[25] Monsen TJ, Holm SE, Ferry BM, et al. Mecillinam resistance and outcome of pivmecillinam treatment in uncomplicated lower urinary tract infection in women. APMIS. 2014;122:317–323.

[26] Heytens S, De Sutter A, Coorevits L, et al. Women with symptoms of a urinary tract infection but a negative urine culture: PCR-based quantification of *Escherichia coli* suggests infection in most cases. Clin Microbiol Infect. 2017;23(9):647–652. Epub ahead of print.

[27] Høye S, Frich JC, Lindbaek M. Use and feasibility of delayed prescribing for respiratory tract infections: a questionnaire survey. BMC Fam Pract. 2011;12:34.

Appendix A Clinical registration form for the ESBL-UTI study

Registration form for clinical data

Name:

Date of birth:

Address:

Telephone number:

Comorbidity:
- ☐ Diabetes mellitus
- ☐ Urinary tract/kidney stone
- ☐ Immunosuppression
- ☐ Malignant disease of the urinary tract/kidney
- ☐ Pregnancy
- ☐ Malformation of urinary tract/kidney
- ☐ Use of urinary tract catheter in the last three months
- ☐ Admitted to hospital for more than two days in the last 90 days before sampling
- ☐ Undergone hemodialysis in the last 30 days before sampling
- ☐ Received iv chemotherapy in the last 30 days before sampling
- ☐ Undergone specialised medical treatment at home including catheter change in the last 30 days before sampling

Number of urinary tract infections in the last 30 days before current episode?

Date of first evaluation by a doctor for current episode:

Place of treatment:

Physician:

Duration (days) of symptoms before first evaluation by physician:

Symptoms:

Painful urination:	☐	YES	☐ NO
Frequent urination:	☐	YES	☐ NO
Hematuria:	☐	YES	☐ NO
Fever:	☐	YES	☐ NO
Reduced general condition:	☐	YES	☐ NO
Back/flank pain:	☐	YES	☐ NO
Abdominal pain:	☐	YES	☐ NO

Other:

Treatment given at first consultation:

Name:

Dosage:

Duration:

Number of days until symptom free or alternative treatment given:

**PLEASE FILL OUT THIS PAGE IF THE PATIENT HAS SEEN A DOCTOR AGAIN
IN THE FOLLOW-UP PERIOD:**
(If not, please skip this page)

Date of consultation:
Place of treatment:
Physician:

New antibiotic prescription:	☐ YES	☐ NO
Name:		
Dosage:		
Duration:		

Symptoms leading to consultation:

Painful urination:	☐ YES	☐ NO
Frequent urination:	☐ YES	☐ NO
Hematuria:	☐ YES	☐ NO
Fever:	☐ YES	☐ NO
Reduced general condition:	☐ YES	☐ NO
Back/flank pain:	☐ YES	☐ NO
Abdominal pain:	☐ YES	☐ NO
Other:		

PERSISTENT SYMPTOMS DURING FOLLOW-UP CONSULTATION?

☐ YES ☐ NO (registration complete)

Persistent symptoms at follow-up consultation

Painful urination:	☐ YES	☐ NO
Frequent urination:	☐ YES	☐ NO
Hematuria:	☐ YES	☐ NO
Fever:	☐ YES	☐ NO
Reduced general condition:	☐ YES	☐ NO
Back/flank pain:	☐ YES	☐ NO
Abdominal pain:	☐ YES	☐ NO

Other:

New antibiotic prescription: ☐ YES ☐ NO

Medicaments:

Dose:

Varighet: