



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 LINDBAEK³

¹Out-of-hours Service, Oslo Municipality Norway, ²Department of Medical Microbiology, Vestfold Hospital Trust, Tønsberg, Norway, ³The 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

Correspondence: Marianne Bollestad, Stavanger University Hospital, Pb. 8100 Forus, 4068 Stavanger, Norway. E-mail: mbollestad@hotmail.com

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- 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 \times 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?	<input type="checkbox"/>	<input type="checkbox"/>
Do you have –painful urination?	<i>mild</i> <input type="checkbox"/> <i>moderate</i> <input type="checkbox"/> <i>strong</i> <input type="checkbox"/>	<input type="checkbox"/>
-increased frequency of urination?	<i>mild</i> <input type="checkbox"/> <i>moderate</i> <input type="checkbox"/> <i>strong</i> <input type="checkbox"/>	<input type="checkbox"/>
-increased need to urinate?	<input type="checkbox"/>	<input type="checkbox"/>
-visible hematuria?	<input type="checkbox"/>	<input type="checkbox"/>
Are you pregnant or breastfeeding (infant under 1 month of age)?	<input type="checkbox"/>	<input type="checkbox"/>
Do you have diabetes or kidney disease?	<input type="checkbox"/>	<input type="checkbox"/>
Do you have -fever?	<input type="checkbox"/>	<input type="checkbox"/>
-reduced general condition?	<input type="checkbox"/>	<input type="checkbox"/>
-back/flank/stomach pain?	<input type="checkbox"/>	<input type="checkbox"/>
Do you have -increased vaginal secretion?	<input type="checkbox"/>	<input type="checkbox"/>
-itching/irritation?	<input type="checkbox"/>	<input type="checkbox"/>
-STRONG lower abdominal pain?	<input type="checkbox"/>	<input type="checkbox"/>
Have you had pain for more than 7 days?	<input type="checkbox"/>	<input type="checkbox"/>
Have you in the past 4 weeks had a urinary tract infection or used a urinary tract catheter?	<input type="checkbox"/>	<input type="checkbox"/>
Are you using antibiotics now?	<input type="checkbox"/>	<input type="checkbox"/>
Have you previously had an allergic reaction to penicillin?	<input type="checkbox"/>	<input type="checkbox"/>
Do you have esophageal passage problems?	<input type="checkbox"/>	<input type="checkbox"/>
Do you use the medication Probecid?	<input type="checkbox"/>	<input type="checkbox"/>
Temperature (<38° C)	<input type="checkbox"/>	<input type="checkbox"/>
	Delegated treatment	Doctor's consultation
Treatment chosen by support staff:	<input type="checkbox"/>	<input type="checkbox"/>

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

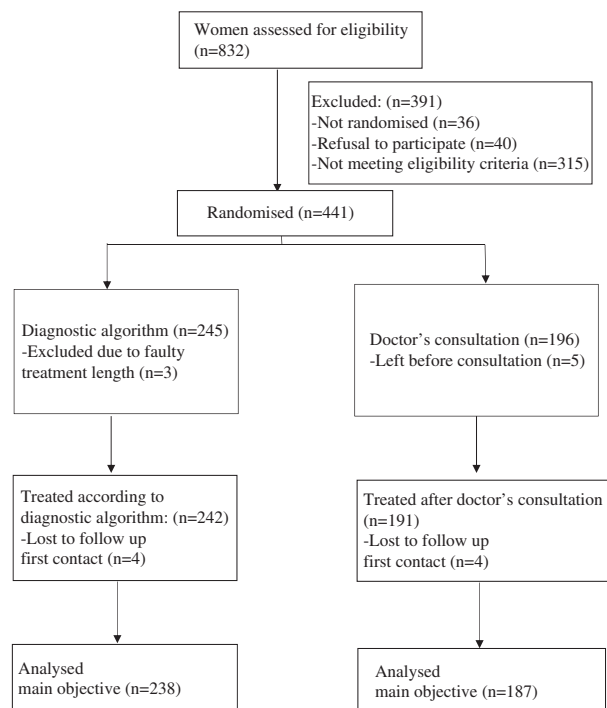


Figure 2. Trial flow chart: RCT of diagnostic algorithm for uncomplicated cystitis at an Out-of-hours service in Oslo, Norway.

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.

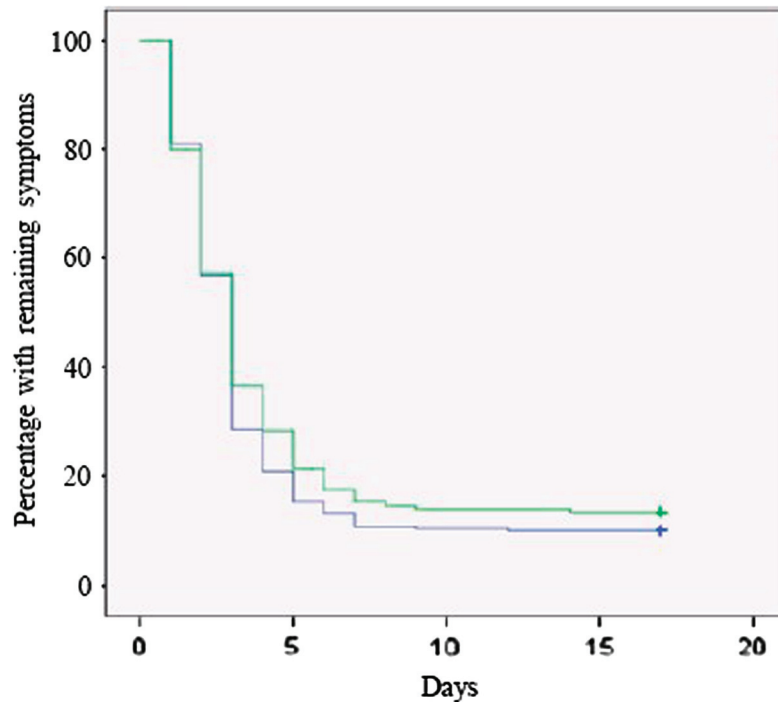


Figure 3. Symptom resolution: Percentage of patients with remaining symptoms versus number of days since the start of treatment, Kaplan–Meier plot. Blue line: Treated according to the diagnostic algorithm. Green line: Treatment chosen after a doctor’s consultation. P-value (log rank): 0.3.

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:			
<i>Escherichia coli</i> , n (%)	101 (77)	79 (78)	NS
<i>Staphylococcus saprophyticus</i> , n (%)	21 (16)	17 (17)	NS
Secondary pathogens:			
<i>Klebsiella species</i> , n (%)	3 (2)	2 (2)	NS
<i>Proteus mirabilis</i> , n (%)	4 (3)	0	NS
<i>Enterococcus faecalis</i> , n (%)	1 (1)	1 (1)	NS
<i>Enterobacter species</i> , n (%)	0	1 (1)	NS
Doubtful pathogens:			
<i>Streptococcus agalactiae</i> , n (%)	2 (2)	0	NS
<i>Pseudomonas species</i> , 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. ¹Non-significant bacteriuria, see Material and methods. ²All 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.

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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.

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