



TREATMENT AND PROPHYLAXIS OF THE LOWER URINARY TRACT RECURRENT INFECTIONS IN WOMEN

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For citation: Kuzmin IV, Al-Shukri SKh, Slesarevskaya MN. Treatment and prophylaxis of the lower urinary tract recurrent infections in women. *Urologicheskie vedomosti*. 2019;9(2):5-10. <https://doi.org/10.17816/uroved925-10>

Received: 02.04.2019

Revised: 14.05.2019

Accepted: 19.06.2019

⊗ Treatment of 52 women with uncomplicated recurrent lower urinary tract infection aged 19 to 56 years (mean age – 34.4 ± 9.6 years) was performed. All patients were prescribed an antibacterial nitrofurantoin series drug Urofuragin™ (Furazidin) at a dose of 100 mg 3 times a day for 7 days. Treatment was started in the period of exacerbation of the disease. After the end of the treatment the postcoital antimicrobial prophylaxis (100 mg Urofuragin single dose) was prescribed. The dynamics of clinical and laboratory parameters were evaluated immediately after treatment, 2 and 12 weeks after its completion. Before treatment the bacteriological study of urine showed the presence of more than 10^3 CFU/ml in 38 (73.1%) out of 52 patients and in 29 patients *Escherichia coli* was detected. Positive dynamics of clinical and laboratory parameters were noted after the end of treatment. By 2 weeks after the end of treatment, 47 patients (90.4%) had no leukocyturia, 41 (78.8%) had no bacteriuria and at 12 weeks of follow-up same results were achieved in 45 (86.5%) and 40 (76.9%) out of 52 treated patients respectively. During the follow-up period of 12 weeks after the end of treatment, recurrence of lower urinary tract infection was observed only in 8 (15.4%) patients, which occurred on average 48.4 ± 14.1 days after the end of treatment. Tolerance to Urofuragin was satisfactory. Adverse events associated with the drug were noted in 12 (23.1%) patients but they did not lead to the drug withdrawal. The results of the study showed that Urofuragin is an effective antibacterial drug for treatment and prevention of recurrence of uncomplicated infections of the lower urinary tract.

⊗ **Keywords:** lower urinary tract infections; recurrent cystitis; Urofuragin; furazidin.

ЛЕЧЕНИЕ И ПРОФИЛАКТИКА РЕЦИДИВИРУЮЩЕЙ ИНФЕКЦИИ НИЖНИХ МОЧЕВЫХ ПУТЕЙ У ЖЕНЩИН

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Для цитирования: Кузьмин И.В., Аль-Шукри С.Х., Слесаревская М.Н. Лечение и профилактика рецидивирующей инфекции нижних мочевых путей у женщин // Урологические ведомости. – 2019. – Т. 9. – № 2. – С. 5–10. <https://doi.org/10.17816/uroved925-10>

Поступила: 02.04.2019

Одобрена: 14.05.2019

Принята к печати: 19.06.2019

⊗ Проведено лечение 52 женщин с неосложненной рецидивирующей инфекцией нижних мочевых путей в возрасте от 19 до 56 лет (средний возраст — $34,4 \pm 9,6$ года). Всем пациенткам назначали антибактериальный препарат нитрофуранового ряда Урофурагин™ (фуразидин) в дозе 100 мг 3 раза в день в течение 7 дней. Лечение начинали в период обострения заболевания. После окончания лечения рекомендовали проводить посткоитальную антибактериальную профилактику (100 мг Урофурагина однократно). Динамику клинических и лабораторных показателей оценивали непосредственно после окончания лечения и через 2 и 12 нед. До лечения бактериологическое исследование мочи показало наличие более 10^3 КОЕ/мл у 38 (73,1 %) из 52 больных, причем у 29 выявлена *Escherichia coli*. После окончания лечения отмечена положительная динамика клинических и лабораторных показателей. Ко 2-й неделе после окончания лечения лейкоцитурии не было у 47 (90,4 %), а бактериурии — у 41 (78,8 %) пациентки, а на 12-й неделе наблюдения — у 45 (86,5 %) и 40 (76,9 %) пациенток соответственно из 52 пролеченных. За период наблюдения 12 нед. после окончания лечения рецидив инфекции нижних мочевых путей наблюдали только у 8 (15,4 %) больных, который возникал в среднем через $48,4 \pm 14,1$ дня после окончания лечения. Переносимость Урофурагина была удовлетворительной. Нежелательные явления, связанные с препа-

ратом, отмечены у 12 (23,1 %) пациенток и ни в одном случае не стали причиной отмены препарата. Результаты исследования показали, что Урофурагин представляет собой эффективный антибактериальный препарат для лечения и профилактики рецидивов неосложненной инфекции нижних мочевых путей.

🔑 **Ключевые слова:** инфекции нижних мочевых путей; рецидивирующий цистит; Урофурагин; фуразидин.

INTRODUCTION

Lower urinary tract infections are among the most common diseases in women, with 20%–25% of women experiencing at least one episode of acute cystitis in their lifetime [1]. Cystitis occurs most frequently in patients aged from 25 to 30 years and over 55 years (during the postmenopausal period) [2, 3]. Lower urinary tract infections are defined as uncomplicated in the absence of any anatomic abnormalities of the bladder, in the presence of normal susceptible urine outflow from the bladder, and in the absence of serious comorbidity. Approximately 80% of affected patients experience uncomplicated lower urinary tract infections [4]. The most common cause of infection remains *Escherichia coli*, detected in 75% of cases, while less frequent causes include *Klebsiella spp.* and *Staphylococcus saprophyticus* and, even more rarely, other enterobacteria [1, 5]. The main pathogen and virulence factors of *E. coli* include the ability to adhere to urothelial cells using special villi, the pursuance of hyaluronidase activity (which causes damage to urothelial cells), and the possibility of active proliferation in the urine [6].

The relevance of lower urinary tract infections is determined not only by their high prevalence but also by their tendency for recurrence. Approximately every third woman with a history of acute cystitis will experience a recurrence of the disease within one year, and chronic recurrence can appear in 10% of cases [1]. Challenges in the treatment of recurrent lower urinary tract infections are associated primarily with the properties of uropathogens and the features of the local nonspecific reactions of the bladder mucosa. In most women, reinfection develops as a result of repeated colonization of the periurethral region by microorganisms of the intestinal group and their further penetration into the urethra and bladder [7].

The mainstay of treating uncomplicated lower urinary tract infections is antibiotics [8]. In recent years, due to the ongoing increases in antibiotic resistance patterns, new trends in the use of antibacterial drugs in the treatment of uncomplicated lower urinary tract infections have been noted, including, in particular, restrictions placed on the use of fluoroquinolones and cephalosporins. This is largely due

to the need to preserve drugs in these groups for the treatment of complicated urinary tract infections and other localized infections. First-line drugs for the treatment of uncomplicated lower urinary tract infections currently include nitrofurans and fosfomicin [1, 9]. According to the nonspecific mechanism of action, nitrofurans are close in nature to antiseptics, and this is why the resistance of pathogenic microorganisms develops relatively slowly; in addition, there is no cross-resistance with other classes of antibiotics [10]. Nitrofurans have been used for a long time, but in the last decade, have come to be used somewhat less frequently. This fact also seems to be important in relation to bacterial resistance because a decrease in the consumption of antibacterial drugs is accompanied by an increase in the sensitivity of pathogenic microorganisms to them.

A Russian study showed that, for complicated urinary tract infections, 93.7% and 95% of pathogen strains are susceptible to the nitrofurans nitrofurantoin and furazidone, respectively, while 94.7 and 96.8% of uncomplicated cases are susceptible to the same [5]. Furazidin is an analog of nitrofurantoin and acts on both Gram-positive and Gram-negative bacteria better than its original compound. Furazidin is effective in both acute and chronic urinary tract infections [11].

To prevent a recurrence of uncomplicated lower urinary tract infections, *E. coli* lysate and herbal remedies are recommended. Antibacterial drugs are used both for long-term therapy and for prophylaxis following exposure to factors that may cause activation of the infection [12–14]. Since the recurrence of cystitis is most often associated with sexual intercourse, postcoital prophylaxis is widespread.

The aim of the study was to investigate the efficacy of the nitrofuran-type drug Urofuragin™ (furazidin; Adamed, Warsaw, Poland) in the treatment and recurrence prevention of uncomplicated lower urinary tract infection in women.

MATERIALS AND METHODS

We observed 52 women with uncomplicated recurrent lower urinary tract infection who were 19 to

56 years old (mean age: 34.4 ± 9.6 years). The study included women who had experienced at least two episodes of the disease within 6 months or three episodes within the year prior to the treatment and an additional acute episode at the time of treatment. The mean time from the previous episode of recurrent lower urinary tract infection was 3.0 ± 2.7 years and ranged from six months up to 12 years, and the average number of recurrences was 5.5 ± 1.7 times per year. The number of sexually active women was 40 (76.9%) out of 52, and 5 (9.6%) women were in menopause.

The exclusion criteria were complicated urinary tract infection, signs of acute or active-phase chronic pyelonephritis, pregnancy or lactation, the use of any antibacterial drugs within four weeks before inclusion in the study, hypersensitivity to furazidin or other drug components, chronic pelvic pain syndrome, overactive bladder, polyuria, renal or hepatic insufficiency, lactase, sucrose/isomaltase deficiency, lactose and/or fructose intolerance, and glucose-galactose malabsorption.

All patients were prescribed 100 mg of Urofuragin™ to be taken three times a day for seven days. After treatment, the patients received recommendations to help reduce the risk of a recurrence of their urinary tract infection. These recommendations included increasing their water intake and performing pre- and postcoital urine voiding. Postcoital antibacterial prophylaxis was recommended for sexually active patients in the form of 100 mg of Urofuragin™ to be taken after intercourse.

Patients were selected to participate in the study during screening visits. During this visit, a medical history was collected, complaints were assessed, a physical examination was conducted, and laboratory tests

including an urinalysis and midstream urine culture analysis were performed. To exclude sexually transmitted infections, polymerase chain reaction was used to detect *Chlamidia trachomatis*, *Mycoplasma genitalium*, and *Mycoplasma hominis* in scrapings from the urethra, vagina, and cervix. Symptoms were evaluated using a special questionnaire for the severity of cystitis symptoms [15]; a diary of urination; and the Pelvic Pain, Urgency, and Frequency Patient Symptom Scale (PUF Scale) questionnaire [16]. Clinical and laboratory parameters were evaluated immediately after treatment and at two and 12 weeks after treatment, respectively.

RESULTS

Before treatment, all patients had increased white blood cell counts in the urine, which was one of the inclusion criteria. Urine culture analysis showed results of more than 1,000 CFU/mL in 38 (73.1%) of 52 patients. Single uropathogens were detected in 35 (92.1%) among 38 patients with positive urine culture analysis, while two microorganisms were found in 3 (7.9%) patients. The most common etiological agent was *E. coli* in 29 patients (76.3% of all patients with a positive culture analysis and 55.8% of all patients). Additionally, *Enterococcus spp.* was isolated in three patients (7.9% and 5.8%, respectively), *S. saprophyticus* was isolated in two patients (5.3% and 3.8%), *Klebsiella pneumoniae* was isolated in two patients (5.3% and 3.8%), and *Staphylococcus aureus* and *Proteus mirabilis* were isolated in one patient each (2.6% and 1.9%).

Urofuragin™ treatment given for 7 days to limit lower urinary tract infection exacerbation was efficient in all 52 patients. Marked symptom regression was observed (Table 1). On day 7 after treatment,

Table 1

Dynamics of clinical parameters in the treatment and follow-up of patients with recurrent lower urinary tract infection, $M \pm \sigma$ ($n = 52$)

Таблица 1

Динамика клинических показателей в процессе лечения и последующего наблюдения пациенток с рецидивирующей инфекцией нижних мочевых путей, $M \pm \sigma$ ($n = 52$)

Parameter	Follow-up period			
	Before treatment	End of treatment (Day 7)	2 weeks after treatment	12 weeks after treatment
Cystitis symptom severity index, scores	$8.6 \pm 1.6^*$	0.7 ± 0.9	0.2 ± 0.4	0.4 ± 0.7
Urinary frequency per day, scores	$11.6 \pm 2.5^*$	6.3 ± 1.4	6.4 ± 1.2	6.1 ± 1.3
Total score by PUF Scale	$21.7 \pm 3.0^*$	–	0.6 ± 0.9	0.8 ± 1.1

Note. *There was a significant difference between parameters before and after treatment ($p < 0.001$).

Table 2

Dynamics of laboratory parameters in the treatment and follow-up of patients with recurrent lower urinary tract infection ($n = 52$)

Таблица 2

Динамика лабораторных показателей в процессе лечения и последующего наблюдения пациенток с рецидивирующей инфекцией нижних мочевых путей ($n = 52$)

Parameter	Follow-up period		
	Before treatment	2 weeks after treatment	12 weeks after treatment
Leucocyturia in urinalysis (> 10 WBCs per power field)	52 (100 %)	5 (9.6 %)	7 (13.5 %)
Positive urine culture	38 (73.1 %)	11 (21.1 %)	12 (23.1 %)

cystitis symptom severity index scores had decreased from 8.6 ± 1.6 points to 0.7 ± 0.9 points, while urinary frequency per day decreased from 11.6 ± 2.5 times to 6.3 ± 1.4 times ($p < 0.001$ in both cases). For the control examination at Weeks 2 and 12 after treatment, these parameters did not increase. For PUF Scale score at Weeks 2 and 12, these parameters differed significantly when compared with initial values.

After treatment, the observed dynamics in the clinical parameters were associated with positive changes in laboratory tests in all 52 patients. Two weeks after treatment, leukocyturia was only noted in five (9.6%) patients whereas it was present in all patients before treatment. Urine culture analysis results were positive in 38 (73.1%) patients before treatment but only in 11 (21.1%) patients two weeks after treatment. 12 weeks after treatment, no findings of leukocyturia were observed in 45 (86.5%) patients, and no bacteriuria was identified in 42 (76.9%) patients (Table 2).

During the 12-week follow-up period, the recurrence of lower urinary tract infection was observed in eight (15.4%) of the 52 women. Five patients attributed their relapse with sexual intercourse, two mentioned hypothermia, and one patient could not determine a possible cause. Recurrence occurred within 31 to 67 days after treatment (on average, at 48.4 ± 14.1 days). In most patients (84.6%), however, Urofuragin™ successfully prevented the recurrence of urinary tract infection during the 12-week follow-up period.

Urofuragin™ tolerance among the study participants was satisfactory. Adverse events of various levels of severity associated with the drug were registered in 12 (23.1%) patients. Indigestion symptoms (e. g., nausea, epigastric discomfort), drowsiness, and skin itch-

ing and dizziness were recorded in eight, two, and one patients, respectively. The noted adverse events did not provoke a withdrawal of the drug in any case.

CONCLUSION

In this study, Urofuragin™ was shown to be an effective antibacterial drug for the treatment and recurrence prevention of urinary infection in women and can be considered as one of the drugs of choice in this clinical situation.

REFERENCES

1. Урология. Российские клинические рекомендации / Под ред. Ю.Г. Аляева, П.В. Глыбочко, Д.Ю. Пушкаря. – М.: ГЭОТАР-Медиа, 2016. – 496 с. [Urologija. Rossijskie klinicheskie rekomendacii. Ed. by Yu.G. Aljaev, P.V. Glybochko, D.Yu. Pushkar. Moscow: GEOTAR-Media; 2016. 496 p. (in Russ.).]
2. Hooton TM. Clinical practice. Uncomplicated urinary tract infections. *N Engl J Med.* 2012;366(11):1028-1037. <https://doi.org/10.1056/NEJMcpr1104429>.
3. Перепанова Т.С. Неосложненная инфекция мочевых путей // Рациональная фармакотерапия в урологии: руководство для практикующих врачей / Под ред. Н.А. Лопаткина, Т.С. Перепановой. – 2-е изд. – М.: Литтерра, 2012. – С. 303–318. [Perepanova T.S. Neoslozhnennaja infekcija mochevyh putej. In: Racional'naja farmakoterapija v urologii: rukovodstvo dlja praktikujušhijh vrachej. Ed by N.A. Lopatkin, T.S. Perepanova. 2nd ed. Moscow: Litterra; 2012. P. 303-318. (In Russ.)]
4. Little P, Moore MV, Turner S, et al. Effectiveness of five different approaches in management of urinary tract infection: randomised controlled trial. *BMJ.* 2010;340: c199. <https://doi.org/10.1136/bmj.c199>.
5. Перепанова Т.С., Козлов Р.С., Дехнич А.В., и др. Эмпирический выбор антимикробных препаратов при неосложненной инфекции нижних мочевых путей: исследование резистентности возбудителей ДАРМИС // Экспериментальная и клини-

- ческая урология. – 2012. – № 2. – С. 78–83. [Perepanova TS, Kozlov RS, Dehnic AV, et al. The empirical choice of antibacterial treatment for uncomplicated urinary tract infection. DARMIS: clinical study of pathogens resistance. *Experimental and clinical urology*. 2012;(2):78-83. (In Russ.)]
6. Борисов В.В. Диагностика и терапия инфекций мочевыводящих путей. О чем следует помнить всегда (клиническая лекция). Часть 1 // Урологические ведомости. – 2017. – Т. 7. – № 3. – С. 52–59. [Borisov VV. Diagnosis and therapy of urinary infections. What should always remember (clinical lecture). Part 1. *Urologicheskie ведомosti*. 2017;7(3):52-59. (In Russ.)]. <https://doi.org/10.17816/uroved7352-59>.
 7. Перепанова Т.С., Хазан П.Л., Волкова Е.М., и др. Проблемы лечения рецидивирующей инфекции нижних мочевых путей [Медицинский портал для врачей] // Эффективная фармакотерапия. Урология и нефрология. – 2011. – № 3. – С. 38–43. [Perepanova TS, Hazan PL, Volkova EM, et al. Problemy lechenija recidivirujushhej infekcii nizhnih mochevyh putej [Meditsinskij portal dlya vrachej]. *Effektivnaja farmakoterapija. Urologiya i Nefrologiya*. 2011;(3):38-43. (In Russ.)]. Доступно по: <http://umedp.ru/upload/iblock/011/011c079c4a44c06082b107bb6074636a.pdf>. Ссылка активна на 15.05.2019.
 8. Wagenlehner FM, Weidner W, Naber KG. An update on uncomplicated urinary tract infections in women. *Curr Opin Urol*. 2009;19(4):368-374. <https://doi.org/10.1097/MOU.0b013e32832ae18c>.
 9. Аль-Шукри С.Х., Слесаревская М.Н., Кузьмин И.В. Применение фосфомицина при лечении неосложненной инфекции нижних мочевыводящих путей // Урология. – 2018. – № 5. – С. 153–159. [Al-Shukri SKh, Slesarevskaya MN, Kuz'min IV. Fosfomycin for treatment of uncomplicated lower urinary tract infection. *Urologiya*. 2018;(5):153-159. (In Russ.)]. <https://doi.org/10.18565/urology.2018.5.153-158>.
 10. Голуб А.В. Нитрофураны в терапии неосложненных инфекций мочевых путей [Медицинский портал для врачей] // Эффективная фармакотерапия. Урология и нефрология. – 2010. – № 3. – С. 30–34. [Golub AV. Nitrofurany v terapii neoslozhnennyh infekcij mochevyh putej [Meditsinskij portal dlya vrachej]. *Effektivnaja farmakoterapija. Urologiya i Nefrologiya*. 2010;(3):30-34. (In Russ.)]. Доступно по: <http://umedp.ru/upload/iblock/858/furamag.pdf>. Ссылка активна на 15.05.2019.
 11. Перепанова Т.С. Нитрофураны в урологической практике: все ли они одинаковы и почему мы возвращаемся к ним сегодня? // Экспериментальная и клиническая урология. – 2018. – № 3. – С. 91–101. [Perepanova TS. Nitrofurans in the urological practice: are they all the same and why are we getting back to them today? *Experimental and clinical urology*. 2018;(3):91-101. (In Russ.)]
 12. Вошула В.И., Вилюха А.И. Неосложненная инфекция мочевыводящих путей: длительный прием нитрофуранов для профилактики рецидивирования // Экспериментальная и клиническая урология. – 2014. – № 1. – С. 88–91. [Voschula VI, Vilyuha AI. Non-complicated urinary tract infections: long-term intake of nitrofurans for recurrence prevention. *Experimental and clinical urology*. 2014;(1):88-91. (In Russ.)]
 13. Пронкин Е.А. Неосложненные инфекции мочевыводящих путей у женщин — комплексная терапия // Урология. – 2018. – № 3. – С. 146–148. [Pronkin EA. Uncomplicated female urinary tract infections – comprehensive therapy. *Urologiya*. 2018;(3):146-148. (In Russ.)]. <https://doi.org/10.18565/urology.2018.3.146-148>.
 14. Слесаревская М.Н., Кузьмин И.В., Аль-Шукри С.Х. Фитолизин нефроCAPS в комплексном лечении женщин с хроническим рецидивирующим циститом // Урология. – 2018. – № 1. – С. 30–34. [Slesarevskaya MN, Kuzmin IV, Al-Shukri SKh. NefroCAPS phytolysin in complex management of women with chronic recurrent cystitis. *Urologiya*. 2018;(1):30-34. (In Russ.)]. <https://doi.org/10.18565/urology.2018.1.30-34>.
 15. Амдий Р.Э., Аль-Шукри С.Х., Кузьмин И.В., и др. Опыт применения канефрона при лечении острого неосложненного цистита у женщин // Урологические ведомости. – 2016. – Т. 6. – № 2. – С. 16–22. [Amdiy RE, Al-Shukri SKh, Kuzmin IV, et al. Use of Kanefron in treatment of acute uncomplicated cystitis in women. *Urologicheskie ведомosti*. 2016;6(2):16-22. (In Russ.)]. <https://doi.org/10.17816/uroved6216-22>.
 16. Аль-Шукри С.Х., Кузьмин И.В., Слесаревская М.Н., Игнашов Ю.А. Применение русскоязычной версии «Шкалы симптомов тазовой боли, urgencyности и частоты мочеиспускания» (PUF Scale) у больных с синдромом болезненного мочевого пузыря // Урологические ведомости. – 2017. – Т. 7. – № 2. – С. 5–9. [Al-Shukri SKh, Kuzmin IV, Slesarevskaya MN, Ignashov YuA. Use of the Russian version of pelvic pain and urgency/frequency patient symptom scale (PUF scale) in patients with the bladder pain syndrome. *Urologicheskie ведомosti*. 2017;7(2):5-9. (In Russ.)]. <https://doi.org/10.17816/uroved725-9>.

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