Empirical treatment of acute uncomplicated cystitis in women: drug choice and treatment costs

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Introduction: According to the guidelines of The European Association of Urology, the following are considered as first choice drugs in the treatment of acute uncomplicated urinary tract infections (UTIs): fosfomycin trometamol, pivmecillinam and nitrofurantoin. Cotrimoxazole and/or trimethoprim can be considered as drugs of first choice in areas with known E. coli resistance rates of <20%. The aim of the present study was to determine the drug of first choice for the empirical treatment of UTIs in primary health care in our community and to determine the treatment cost differences. Results: Out of 500 medical records of women older than 18 years reviewed in two units of family medicine, 115 (23%) had at least one uncomplicated urinary tract infection in the period January 2010 to May 2013. Empirical treatment for them was chosen based on the official guide (3/7), physician’s own experience (2/7) or a recommendation of a colleague (2/7). UTIs were most commonly treated during 7.3 days with ciprofloxacin (46/115), which is not officially recommended as a first-line drug. This is also longer than the recommended three day course. The annual cost for ciprofloxacin was 2.5 times higher compared to the nitrofurantoin officially recommended as the first choice drug and 3.5 times higher compared to cotrimoxazole which is the second most commonly prescribed drug. Conclusion: It is necessary to increase awareness of the importance of following therapeutic guides, as well as the availability of therapeutic guides in primary medical practice.

Key words: Acute uncomplicated urinary tract infections, women, empirical treatment, therapeutic guide

Cytisitis

Introduction

Acute uncomplicated urinary tract infections (UTIs) due to their frequency represent a serious public health problem. They occur mostly among women, without structural and functional abnormalities within the urinary tract, without kidney diseases or comorbidity (1, 2). The clinical symptoms of the disease and a dipstick test are in most cases sufficient to diagnose acute uncomplicated cystitis. A positive dipstick test (leukocyte esterase or nitrite) is associated with a high probability of bacteriuria (80%).
A positive nitrate test is highly specific for UTI, but it occurs in only 25% of patients with UTI (3). Negative tests do not exclude bacteriuria and are associated with a bacteriuria probability of around 20% (4). So, if the dipstick test is negative despite the existence of clinical findings suggestive of a UTI, it is necessary to perform urine microscopy (3). The predominant cause of UTIs is bacteria *Escherichia coli* (70-95% cases) (1, 2). The second most common cause is *Staphylococcus saprophyticus* (5-10% cases) and occasionally *Enterobacteriaceae* such as *Proteus mirabilis* and *Klebsiella spp.* (1). Thanks to the predictability of causes and to the monitoring of their sensitivity, the current management of acute uncomplicated cystitis is usually empirical, without using a urine culture or susceptibility testing to guide therapy (1). Antibiotic therapy is recommended because clinical success is significantly more likely in women treated with antibiotics compared with placebo (5). The choice of an antibiotic for therapy should be guided by a spectrum of antibiotics and susceptibility patterns of the aetiological uropathogens, efficacy for the particular indication in clinical studies; tolerability, adverse effects, cost and availability (5). According to these principles fosfomycin trometamol, 3g in a single dose, pivmecillinam 400mg for 3 days, or nitrofurantoin 100mg twice a day for 5 days, are considered as drugs of first choice (5). Cotrimoxazole 160/800mg twice a day for 3 days, or trimethoprim 200mg for 5 days should only be considered as drugs of first choice in areas with known *E. coli* resistance rates of <20% (5). Alternative antibiotics are ciprofloxacin 250mg twice a day, extended-release ciprofloxacin 500mg once a day, levofloxacin 250mg once a day, norfloxacin 400mg twice a day, and ofloxacin 200mg twice a day, each as a 3-day course (5). However, the adverse effects of these drugs have to be considered. Routine post-treatment urinalysis or urine cultures in asymptomatic patients are not indicated. In women whose symptoms do not resolve by the end of the treatment, and in those whose symptoms resolve but reoccur within 2 weeks, urine culture and antimicrobial susceptibility tests should be performed. For therapy in this situation, one should assume that the infecting organism is not susceptible to the agent originally used and retreatment with another agent for 7-days (5) should be considered. Pharmacoeconomic analysis of the UTI treatment showed that health care costs are higher than the cost of the drug (3), which, however, does not diminish the importance of the drug price, especially in economically underdeveloped countries.

The objective of the present study was to determine the drug of first choice for the empirical treatment of UTI in primary health care in our community and to determine the treatment cost differences.

**Methods**

This observational study was conducted in two family medicine units where 500 medical records of women older than 18 years were viewed. Criteria for inclusion in further analysis were a first uncomplicated urinary tract infection in the period January 2010 to May 2013 and prescribed empirical therapy. UTIs in pregnant women were excluded from the analysis. The effectiveness of empirical therapy has been evaluated based on the outcome of the disease in terms of improving or worsening clinical symptoms (occurrence of relapse and/or recidivism).

Recurrence, in form of relapse or recidivism is the return of clinical signs of disease. Relapse is the return of the clinical signs of disease two weeks after its apparent cessation, and recidivism is the return of the clinical signs of disease more than two weeks after its cessation.

The method of drug selection for empirical therapy was tested by a questionnaire...
with the simple question if the applied drug was chosen on the basis of the official guide, own experience or the recommendation of a colleague.

The data was collected in The Microsoft Office Excel database and statistically analysed by SPSS Statistic 17.0 for Windows. Descriptive statistical analysis presented as arithmetic mean, standard deviation (SD) and standard error of mean (SEM) values was performed. Frequencies were expressed as percentages. The differences in disease outcome after administration of three different therapeutic regimens were analyzed using the Chi-square test with p<0.05 considered to be statistically significant. Costs of treatments were calculated by the number of defined daily doses per 1000 women (DDD/1000).

Results

Out of the reviewed 500 medical records of women older than 18 years in the family medicine units, 115 (23%) women, average age of 55 years, were diagnosed with acute uncomplicated cystitis (N 30) and empirical therapy was conducted.

Empirical therapy was included immediately in 23 women (20%), while for the rest of them (80% cases) laboratory tests were performed (Table 1).

Three out of the seven physicians chose the applied drug on the basis of the official guide, two physicians on the basis of their own experience and two physicians on the basis of colleagues’ recommendations.

The most frequently prescribed drugs were as follows: ciprofloxacin from the group of fluoroquinolones, cotrimoxazole (37/115) and cephalexin from the group of cephalosporins I generation (10/115).

Length of treatment was an average 7.3 days except for nitrofurantoin 3 days.

The therapy was effective (with no relapse or recidive) in 80/115 women, while recurrence (relapse and/or recidive) of the

<table>
<thead>
<tr>
<th>Laboratory parameter</th>
<th>Mean</th>
<th>SEM</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedimentation rate (mm/h)</td>
<td>17.82</td>
<td>2.04</td>
<td>12.74</td>
</tr>
<tr>
<td>Leukocyte count in blood (x10^9/l)</td>
<td>6.53</td>
<td>0.36</td>
<td>1.45</td>
</tr>
<tr>
<td>Leukocyte count in urine</td>
<td>12.80</td>
<td>0.77</td>
<td>5.40</td>
</tr>
</tbody>
</table>

Table 1. Laboratory tests results

Figure 1. The contribution of drugs prescribed in the empirical treatment of acute uncomplicated cystitis
disease was recorded in 35 cases, of which relapse was recorded in 9 women (7.8%).

There was no statistically significant difference in disease outcome between the three most frequently prescribed antimicrobial regimes (Table 2).

Side effects were recorded in three cases; one case of eczema when using ciprofloxacin and cephalexin, and two cases of nausea when using cotrimoxazole. The side effects were of mild intensity. The frequency of cystitis per 1.000 women age over 18 years was 0.21 per day (DDD/1000). Based on this, the cost of the three most commonly used drugs were calculated (Table 3).

**Discussion**

The high frequency of UTIs demonstrated in our study is expected. UTIs are currently one of the most common diseases encountered in medical practice (6, 7). Diagnosing acute uncomplicated cystitis seems to be simple, and immediate therapy, without additional diagnostic testing, is quite conventional in many countries. However, as many as 40% of patients with suspected UTIs do not have an infection (8). To test whether the patient has a UTI at all, orientating indirect methods are often used to detect the bacteria or inflammation (dipsticks).

Those approaches imply high sensitivity; majority of cases of UTI are treated, but many false positives are erroneously treated as well. In this case, there is a risk of increasing the problem of microbial resistance (9).

Laboratory blood analysis for the purpose of diagnosing UTI is unnecessary and incurs an unnecessary cost, as showed by our study as well (Table 1). We have documented the mid-rate of sedimentation and the number of leukocytes in the blood to be within the physiological ranges, as expected. In case of doubt, when full clinical picture of urinary tract infection is not expressed, or in the case of a negative dipstick test, microscopic urine analysis is preferred. However, an accurate diagnosis and a maximum specific therapy can be achieved only by urine culture identifying infective agents and determining their number and sensitivity. Urine culture is a simple, accessible method that costs considerably less than the potential costs and damage of prescribing an antibiotic to which the bacteria is resistant. Niroshan Sivathasan N and Rakowski KR believe that there is no advantage in routine microscopic analysis of urine samples and taking urine culture (10). They suggest that urine culture should be performed on all patients with symptoms that suggest pyelonephritis, on women and men with regular recurrence and on all pregnant women if symptoms persist for more than 3 days despite the use of an antimicrobial, and if

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**Table 2. Disease outcomes after administration of the three most frequently prescribed antimicrobial regimes were not statistically different (p>0.05)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cured</th>
<th>Recurrent infection (relapse/recidive)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>30</td>
<td>4/12</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>26</td>
<td>2/9</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>9</td>
<td>1/0</td>
</tr>
</tbody>
</table>

**Table 3. Direct costs of different antimicrobial treatments**

<table>
<thead>
<tr>
<th>Monitoring sample/period</th>
<th>Price of drug treatment (KM)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ciprofloxacin</td>
</tr>
<tr>
<td>DDD</td>
<td>1.58</td>
</tr>
<tr>
<td>DDD/1000</td>
<td>0.32</td>
</tr>
<tr>
<td>DDD/1000/year</td>
<td>116.8</td>
</tr>
</tbody>
</table>

* Wholesale drug prices
either the nitrite or leukocyte esterase is negative (10). If the patient is nitrite positive and leukocyte esterase negative, starting antimicrobial therapy is recommended, and if the patient is leukocyte esterase positive and nitrite negative, it is believed that therapy should be started depending on the results of the microscopic examination of urine and urine culture (10).

The use of 11 different antimicrobials in the treatment of acute uncomplicated cystitis in our study confirms great doubt about drug selection. Although therapeutic guides significantly facilitate the work of healthcare providers, particularly those in primary health care, they are not used enough in the practice. Modern clinical guidelines identify, summarize and evaluate the highest quality evidence and most current data about prevention, diagnosis, prognosis, therapy including dosage of medications, risk/benefit and cost-effectiveness. They also define the most important questions related to clinical practice and identify all possible decision options and their outcomes (11). Healthcare providers are expected to know the medical guidelines of their profession and to decide whether or not to follow the recommendations of a guideline for an individual treatment. The guideline recommendations for the antibiotic treatment of UTI are often not implemented in practice. Fluoroquinolones are not recommended as drugs of first choice for uncomplicated urinary tract infections because of the development of resistance, but are, like in our study, still commonly prescribed for this purpose (Figure 1). Furthermore, the average length of treatment with ciprofloxacin of average 7.3 days is irrationally longer than the recommended three-day regime. It has been shown neither more effective in eradicating the infection, nor in preventing recurrence, but associated with significantly more adverse effects (10). National and international recommendations warn against the broad and uncritical use of fluoroquinolones for uncomplicated infections (12, 13). Nevertheless, a high frequency of prescribing fluoroquinolones was observed in the study performed in two ambulances in Croatia where the most frequently prescribed drug was norfloxacin (45.5% and 55% of patients) and the second option was cotrimoxazole (14, 15). Fluoroquinolones were too the drugs of choice in 78% and cotrimoxazole in 22% of cases in Switzerland (n=11,799 antibiotic prescriptions for outpatient UTI) (13). In a study including 1819 physicians in Germany, the most common antibiotics in the treatment of UTI were cotrimoxazole (61%) and fluoroquinolones (21%) (15).

The results of our study (Table 2), as well as a randomized treatment study have shown an equal effectiveness of cotrimoxazole, fluoroquinolones, fosfomycin trometamol, nitrofurantoin and pivmecillinam in the treatment of uncomplicated UTI (16). Considering this fact, the use of fluoroquinolones is recommended when there are contraindications to nitrofurantoin, cotrimoxazole and fosfomycin (17) and in communities with high resistance rates to them (greater than 10%-20%) (18).

One of the main reasons for adherence to the therapeutic guides in the choice of antibiotic therapy is the risk of developing resistance. In cases of relapse and/or recidivism occurrence, there is a great probability of resistance to a previously applied antimicrobial. Thus, the use of cotrimoxazole in the previous six months, and of fluoroquinolones in the previous 12 months is considered as an independent predictor of resistance (16).

Antibiotic sensitivity is a highly dynamic process and subject to local fluctuations and differences over time. The trend of development of resistance of Enterobacteriaceae and Gram-negative bacteria to beta-lactam antimicrobials and fluoroquinolones is alarming (19). Since 1988 there has been a documented high rate of resistance to cotrimoxazole.
This increase coincides with the increased use of cotrimoxazole in patients infected with human immunodeficiency virus (16).

In a Russian (2011) study, the most common uropathogen *E. coli* was the most sensitive to phosphomycin (99.3%), mecillinam (97.3%), nitrofurantoin (94.7%) and ciprofloxacin (87.4%) (20). Its lowest sensitivity was to ampicillin (42.1%) and cotrimoxazole (69.4%). Furthermore, the entire spectrum of bacterial urinary tract infections showed the highest sensitivity to phosphomycin (96.5%), nitrofurantoin (85.6%), ciprofloxacin (82.8%), cotrimoxazole (70.1%) and the lowest to ampicillin (44.3%) (20). Wagenlehner et al. (2011) indicate that the resistance of *E. coli* in Germany is the highest to ampicillin and cotrimoxazole (60% and 30%, respectively), to fluoroquinolones is almost 10% higher compared to previous years, while to fosfomycin, nitrofurantoin, and mecillinam is still below 10% (16). Araújo et al. (2011) indicated the minimum resistance of uropathogens to be to gentamicin (3.5%), ceftriaxone (5%) and norfloxacin (7.5%), while high resistance to ampicillin (64.7%) and cotrimoxazole (39.8%) was documented in Brazil (21).

Data on resistance obtained from local studies are very important for practice and the choice of antibiotics. Searching available databases on studies on resistance from our community has yielded a small number of these. According to the results of Uzunović-Kamberović in the Zenica-Doboj Canton (B&H), resistance rates of *E. Coli* and other coliforms isolated from patients with community-acquired urinary tract infections was significantly higher in men than in women. Specific age (0–6, 7–14, 15–19, 20–64, ≥65 years) resistance rates to nitrofurantoin were in the range of 15–63% and 2–12% in men and women, respectively. Resistance rates to ciprofloxacin in the two oldest age groups were 51% and 57% in men, and 11% and 17% in women (22). According to Institute of Microbiology and Virology, the Clinical Center of Banja Luka, most of bacteria causing intrahospital UTI, showed a high rate of resistance to ampicillin (72.3%), gentamicin (63.4%) and cotrimoxazole (68.3%) (23).

When it comes to our neighbors, Croatia, according to the research conducted by Andrešević et al. (2002), approximately half of the *E. coli* isolates were resistant to ampicillin, 15% to beta-lactam/beta-lactamase inhibitor combinations (24). About 24% of the isolates were resistant to cotrimoxazole, 13% to cefuroxime, 7% to gentamicin, 5% to ciprofloxacin, 4% to ceftazidime and none to imipenem (24): Similarly, in the other study the resistance rate of *E. coli* was 42.2% to amoxicillin, 20.6% to cotrimoxazole and 6.1% to norfloxacin (25).

Recommended drugs of first choice, fosfomycin trometamol and pivmecillinam are not available in our country, but nitrofurantoin is. Nitrofurantoin, as a first choice drug, in our study has been shown to be underused and used not long enough (Figure 3). However, it is needed to point out its advantages. Nitrofurantoin is characterized with low toxicity and an affordable price (26). It is bactericidal in urine at therapeutic doses, and its multiple mechanisms of action appear to have enabled it to retain potent activity against *E. coli*. According to the Croatian National Guideline, despite nearly 50 years of nitrofurantoin clinical application, *E. coli* is still highly (97%) sensitive to it. Its resistance is developing slowly. The consistent and high-level susceptibility of *E. coli* to nitrofurantoin may be influenced by the narrow spectrum of its activity (which is considered to be less selective for resistance), limited indication (treatment of acute cystitis), narrow tissue distribution (low or undetectable serum concentrations), and limited contact with bacteria outside the urinary tract (27). So, unlike fluoroquinolones and cephalosporins, a risk of bacte-
riological collateral damage in the form of selection of multiresistant pathogens or of increased risk of Clostridium difficile–associated colitis, have not been shown for nitrofurantoin so far. Severe adverse effects such as lung damage are generally not expected after treatment shorter than 6 months (16).

Although it is considered that the price of antibiotics participates only with 13% in the total cost of care for lower UTIs (3), having in mind the frequency of this disease and the economic situation in our country, the price should be taken into account in the choice of antibiotics. In this case, on one thousand of female residents, annual expenditures for DDD ciprofloxacin were 3.5 times higher compared to cotrimoxazole and 2.5 times compared to nitrofurantoin.

Conclusion

We concluded that it is necessary to increase awareness of the importance of the use of therapeutic guides as well as their availability in primary medical practice. Adherence to the therapeutic guides would reduce irrational and inadequate use of drugs, visits to a doctor and unnecessary financial expenses. Also, it is necessary to continuously monitor antibiotic resistance of UTI pathogens and introduce control measures in drug prescriptions.

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References

15. Velasco E, Noll I, Espelage W, Ziegelmann A, Krause G, Eckmanns TA. Survey of outpatient an-


