

## Recurrent Urinary Tract Infection in Adults in Latvia: 2014 Observational Study

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### Abstract

Antimicrobial resistance is a growing worldwide problem. Urinary tract infection (UTI) is not an exception. Therefore, it is crucial to regularly update the bacterial flora spectrum data and the efficacy of the recommended empiric treatment to make timely and appropriate amendments where necessary.

This observational study was comprised in July-November 2014, when family physicians across Latvia submitted the anonymous patient data on recurrent UTI treatment in their practice. Anonymous patients' electronic data files were received, 113 of those met the inclusion criteria and were further analyzed.

Bacterial flora spectrum in Latvian adult recurrent UTI population was fairly consistent with data from other European countries, with *Escherichia coli* identified in 66 (58.41%) cultures, of those as monoculture in 55 (58.51%) and as combined culture in 11 (11.70%) cases. Combined cultures without *Escherichia coli* were obtained in 28 (29.79%) cases.

Sensitivity against Nitrofurantoin derivatives (NFDs) was present in 88 cases (91.49% of total cultures); *Escherichia coli* resistance against NFDs was found in only 4 cases (6.06% of *Escherichia coli* cultures).

The current first-choice empiric treatment of recurrent UTI by NFDs may stay unchanged. Particular NFD used in Latvia (Furamag<sup>®</sup>) is safe, well-tolerated and effective first-line UTI treatment choice.

**Keywords:** Urinary tract infection; Adults; Nitrofurantoin derivatives; Furamag<sup>®</sup>; Recurrent UTI; *Escherichia coli*; Resistance

### Background

Antimicrobial resistance is a growing worldwide problem. Urinary tract infection (UTI) is not an exception – according to European data, resistant *Escherichia coli* strains annually account to 32.500 cases with 5.100 deaths and 358.000 hospitalization days [1].

Therefore, it is crucial to regularly update the bacterial flora spectrum data and the efficacy of the recommended empiric treatment to make timely and appropriate amendments where necessary.

In Latvia, the novel nitrofurantoin derivate (NFD) is used as a standard empiric first-choice treatment for UTI (Furamag<sup>®</sup>).

NFDs are well-reputed as effective in low concentrations and against resistant bacteria; resistance against NFDs develops slowly and never reaches high degree; NFDs have wide activity range and are commonly used in treating urinary tract infections (UTI) both in adults and children.

First NFD were synthesized more than 60 years ago and were effectively used for treating UTI since then. However, those have side-effects, including frequent gastrointestinal disturbances, which effectively reduced NFD use especially in pediatrics.

NFDs act due to their specific furan aromatic ring, thus all NFDs has identical antimicrobial activity (but not identical bioavailability) [2,3]. The cross-resistance of NFDs is well-known and proved [4,5]. This allows the use of commercially available standard NFDs diagnostic disks for all NFDs.

The novel NFD, Furamag<sup>®</sup> (*Furaginum solubile* = potassium N-(5'-nitro-2'-furylallylidene)-1-aminogidantoin with magnesium carbonate) was first synthesized in Latvia in 1979. When first tested clinically it showed no side effects, was three times less toxic than Nitrofurantoin, and at the same time its bioavailability was three times higher than of Furazidin. Furamag<sup>®</sup> came commercially available in 1986 and since then became the first-line choice for empiric treatment of UTI both

in adults and children in former socialist European states. Its use in pediatrics has been sufficiently explored earlier [6,7].

### Objectives

Update the bacterial flora spectrum for recurrent UTI in Latvian adult population. Evaluate the efficacy of the currently recommended empiric UTI treatment.

### Study Design

The study was comprised in July-November 2014, when family physicians across Latvia were asked to submit the anonymous patient data on recurrent UTI treatment in their practice. During the above period, anonymous patients' electronic data files were received and analyzed.

The data were extracted and recorded as follows:

First visit: age and sex documentation; complaints documentation; obtaining and documenting urinalysis; obtaining and documenting urine culture (clean catch); empiric treatment initiation with Furamag<sup>®</sup> 50 mg twice daily, continued towards the second visit with a minimum of a seven full days.

Second visit after a minimum of a seven full days: complaints

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documentation; obtaining and documenting urinalysis; side effects documentation.

### Inclusion Criteria

Anonymous outpatient medical records; patients' age over 18 years; patients with recurrent UTI defined as three UTI episodes per year or two UTI episodes with interval of 6 months or shorter. UTI was defined as a combination diagnosis based primarily on complains (symptoms) and confirmed by positive laboratory tests (urinalysis and/or culture) as further described.

### Methods and Documentation

Complains were documented as: disuria (present/absent); flank, abdominal or back pain (present/absent); fever (present/absent).

Urinalysis was documented: WBC count below 25 WBC/mcl as negative; proteinuria with values below 0.25 g/l as negative; nitrite test results as positive/negative; pH within values 5 to 7 as normal.

Urine cultures (BACTEC system) were documented as: positive/no growth; flora identification; CFU count, where values  $5 \times 10^4$  and above accounted as positive; flora sensitivity against NFD (sensitive/resistant), using standard commercially available Nitrofurantoin disks.

Side effects were documented as: any gastrointestinal disturbance (present/absent); photosensibilisation, including rash (present/absent); other (present/absent) with details, if present.

McNemar' test was used for evaluating categorical variables. IBM SPSS software (v.21) was used for data analysis.

### Results

113 medical files were found consistent with inclusion criteria and further analyzed. Females were represented in 103 cases (91.15%), males in 10 cases (8.85%). Age varied from 19 to 87 years.

First visit: dysuria was present in 107 (94.69%) cases; pain was present in 77 (68.14%) cases; fewer were present in 29 (25.66%) cases. First urinalysis showed WBC count over 25 WBC/mcl in 79 (69.91%) cases; proteinuria was positive in 19 (16.81%) cases; nitrite test was positive in 52 (46.02%) cases; pH within normal range was in 102 (90.27%) cases.

Second visit: dysuria was present in 6 (5.31%) cases; pain was present in 4 (3.54%) cases; fewer was absent in all cases.

Second urinalysis showed WBC count over 25 WBC/mcl in 11 (10.58%) cases; proteinuria was positive in 1 (0.96%) case; nitrite test was positive in 8 (7.69%) cases; pH within normal range was in 94 (90.38%) cases.

Cultures were positive in 94 (83.19%) cases, no growth found in 19 (16.81%) cases. *Escherichia coli* was identified in 66 (58.41%) cultures, of those as monoculture in 55 (58.51%) and as combined culture in 11 (11.70%) cases. Combined cultures without *Escherichia coli* were obtained in 28 (29.79%) cases.

Other flora was represented by: KES group (*Klebsiella*, *Enterobacter*, *Serratia*) in 13 (11.50%); *Morganella morganii* in 1 (0.88%); coagulase-negative *Staphylococcus* in 6 (5.31%); *Bacillus sp.* in 4 (3.54%); *Streptococcus sp.* in 4 (3.54%); B group Beta-hemolytic *Streptococcus* in 2 (1.77%); *Staphylococcus aureus* in 3 (2.65%); *Proteus sp.* in 4 (3.54%); *Enterococcus sp.* in 11 (9.73%); *Providencia rettgeri* in 1 (0.88%); and *Staphylococcus Saprophyticus* in 3 (2.65%) cases.

CFU count was positive ( $5 \times 10^4$  and over) in 77 (68.14%) cases.

Sensitivity against NFDs was present in 88 cases (91.49% of total cultures), *Escherichia coli* resistance against NFDs was found in only 4 cases (6.06% of *Escherichia coli* cultures).

Side effects: minor digestive-related complaints not requiring Furamag® discontinuation were recorded in 2 (1.77%) cases; no photosensibilisation or other side effects were recorded.

### Discussion

No incidence and prevalence data could be obtained due to study limitations, but published data list UTI among major healthcare problems, causing over 7 million of doctor visits annually [8] and 15% of all prescribed antibiotics in USA alone [9].

Globally, an estimated 150 million UTIs occur annually, resulting in over six billion dollars in direct healthcare expenditures. Predicted risk factors for UTI in the seven major markets (US, France, Germany, Italy, Spain, UK, and Japan), and a 10-year epidemiological forecast the increase of UTI incident cases with *E. coli* as most prevalent causative pathogen [10].

The concern of developing resistance to first-line antimicrobial agents, including fluoroquinolones, has become increasingly common in *Escherichia coli* [11]. The most recent European data suggest the avoidance of currently widely recommended fluoroquinolones, cotrimoxazole, or cephalosporins, and places nitrofurantoin derivatives and fosfomycin as first-choice antibiotics for the treatment of uncomplicated community-acquired cystitis [12,13].

Therefore, it is crucial to regularly update the bacterial flora spectrum data and the efficacy of the locally recommended empiric treatment to make timely and appropriate amendments where necessary.

Bacterial flora spectrum in Latvian adult recurrent UTI population showed no surprises and was fairly consistent with data even from geographically apart-standing regions, with *Escherichia coli* as a prevalent flora [14-17].

Nitrofurantoin derivative, in Latvian case Furamag® in particular, was clinically effective in all cases, even in those where culture was recorded as NFD-resistant. There was not a single case without any improvement in controlled parameters – Furamag® was clinically effective in all cases. This confirms unique multifactorial antibacterial activities of NFDs, which simultaneously inhibit protein synthesis, aerobic energy metabolism, DNA synthesis, RNA synthesis and cell-wall synthesis, thus ensuring antibacterial activity even against the seemingly resistant flora [18,19].

Furamag® tolerance was excellent, resulting only in 2 (1.77%) mild gastrointestinal events (not requiring the treatment discontinuation), which is fully comparable with earlier pediatric studies where side effect rate was even lower (1.2%). In comparison, up to 34% gastrointestinal intolerance for the Nitrofurantoin crystalline form and up to 13% for the Nitrofurantoin macrocrystalline form was reported [20].

### Conclusions

UTI patterns in Latvia are similar to those of other European countries.

The current first-choice empiric treatment may stay unchanged.

Furamag® is safe, well-tolerated and effective first-line UTI treatment choice, where available.

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