Research Article

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Features of Antibiotic Resistance in Uncomplicated Urinary Tract Infection in Children and Effectiveness of Immunoprophylaxis

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ABSTRACT

Background: *The relapsing course of urinary tract infections (UTI) is an important issue. Repeated courses of antibiotics contribute to selection of multi-resistant microorganisms. Obviously, a new way of prevention, such as vaccination, has to be introduced.*

Objectives: *The purpose of this study was to evaluate the effectiveness of oral vaccination with a complex of frozen lyophilized microorganisms — Escherichia coli, Enterococcus faecalis, Proteus mirabilis, Klebsiella pneumoniae, Pseudomonas aeruginosa, Propionibacterium acnes for the prevention of recurrent UTI in children.*

Methods: *The study involved 30 children aged 7 to 16 years with an uncomplicated course of UTI and a frequency of 3 or more episodes per year.*

The study found that pathogens of uncomplicated UTI were E. coli (66.7%), Enterobacter aer., Enterococcus faecalis, Enterococcus spp., Proteus mirabilis, Proteus vulgaris, S. hominis, Streptococcus haemolyticus. Several pathogens were observed in 10% of patients, the presence of polymycrobial microflora correlated with the frequency of UTI ($\chi 2 = 3.84$, $p<0.05$). The resistance of microflora to antibiotics decreased in the following order: aminoglycosides (4%), carbapenems (9%), cephalosporins (9%), fluoroquinolones (13%), protected penicillins (17%), macrolides (22%), penicillins (26%).

Results: *Evaluation of the oral vaccination effectiveness after 6 months showed a decrease of UTI rate (before vaccination: 3.55 (95% CI 2.91–4.18); after: 0.93 (95% 0.57–1.29) and also reduction of urinary syndrome signs (bacteriuria and leukocyturia). Side effects were not registered and 2/3 patients showed an improvement of their condition.*

Conclusion: *So, a multi-component vaccine can be a safe, effective alternative in prevention of UTI in children.*

Keywords

Urinary tract infections, Antibiotic resistance, Children, Bacterial lysate, Immunoprophylaxis.

Introduction

Recurrent course of urinary tract infection (UTI) remains an important problem which is proved by the data of infection recurrent cases rate in children of different age. During the period from 6 to 12 months, each third child in the younger age group and each fifth in the elder age group suffer from relapse of UTI.

There are certain difficulties in management of children suffering from recurrent infection of the urinary system [1].

First of all, it is a necessity of giving long term courses of antimicrobial therapy for treatment of urinary tract but on the other hand it can provoke microbial homeostasis disorder.

In addition, repeated courses of antibiotics contribute to selection of multiresistant microorganisms. Today the problem of antimicrobial resistance is considered to be a global threat [2,3].

Gram-negative and gram-positive bacteria demonstrate high resistance to antibiotics amoxicillin and clindamycin. Efficiency of the third generations of cephalosporins decrease due to high rate of producing extended spectrum beta-lactamase (ESBL) [4]. With time resistance of uropathogenic flora to vancomycin, nitrofurantoin, piperacillin-tazobactam increases [2].

The articles of recent years have a tendency to revise existing approaches to prevention of UTI recurrence. So, the US microbiological journal (2016) published the data that although use of AB-therapy demonstrates high effectiveness in treating UTI, but it is not enough effective for repeated episodes prevention [5].

The study conducted in a specialized Detroit Nephrology Hospital showed that using antimicrobial prophylaxis in children did not prolonged period between initial UTI and its first relapse, but the probability of occurrence of resistant pathogen causing relapse, increased 7.5 times [6].

Besides, there is evidence of antimicrobial resistance development with their long-term low-dose application [7], that proves the need in studying antibiotic-independent alternatives for the prevention UTI. In particular an opportunity of application of a number of drugs of different action and immunotherapy as well are discussed.

As for a possibility of immunoprophylaxis, an important role belongs to the adaptive immunity theory. So, the development of UTI as a result of experimental infection terminates in recovery with the next resistance to relapse as a result of the adequate immune reaction development. At the same time application of antibiotics leads to repeated relapses even with low-virulent flora due to immune response suppression.

In this regard, many studies as for effectiveness of immunoprophylaxis of UTI are carried out. Thus, the joint work of scientists from the UK and the Arab Emirates, devoted to assessing the possibility of non-antibacterial prevention of UTI in children, colonization of the urinary tract with Escherichia coli (*E. coli*) 83972 showed subjective benefits and fewer relapses requiring treatment. This allowed the authors to declare that non-pathogenic *E. Coli* is a candidate for the development of a live attenuated vaccine for the treatment and prevention of acute and recurrent UTI [8].

When evaluating safety and potency of vaccine containing O-antigens of four serotypes of *E. coli* (ExPEC4V), vaccination caused significant IgG-responses for all serotypes by the 30th day and the immune reactions remained up to 270 days [9].

In this regard it is becoming more apparent that using antibiotics for the prevention of UTI is not an optimal solution. It is necessary to study opportunities of immune system and mucosal immunity in response to vaccination [5].

It becomes extremely important to use new means of prevention, particularly vaccination.

The greater part of modern researches is dedicated to studying efficiency of monocomponent vaccines in UTI prevention [10]. At the same time, the spectrum of uropathogens is wide enough, which causes the need in stimulation of immune response in respect to different causative agents. In our opinion, application of complex vaccines for UTI recurrence prevention in children is very promising.

The aim of research was evaluation of efficiency of oral vaccine witch containing inactivated microorganisms as frozen freeze-dried form - *Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae, Propionibacterium acnes, Pseudomonas aeruginosa, Enterococcus faecalis* for prophylaxis of recurrent UTI in children.

Methods

Cohort overview and patients selection:

The study involved 30 children aged 7 to 16 years old with uncomplicated course of urinary tract infection and a documented frequency of UTI episodes from three or more times a year.

Pathology methods

Identification of uropathogens and assessment of their sensitivity to antibiotics were conducted by standard microbiological methods.

Vaccination assessment

A combination of purified lysates from 6 original patented highly purified inactivated bacterial strains, which are typical causative agents of urinary tract infection, was used for immunoprophylaxis.

1 capsule (250 mg) contains active ingredients:

- *Enterococcus faecalis lysatum cryodessicatum* (CCM7591) — 0.67 mg
- *Escherichia coli lysatum cryodessicatum* (SSM 7593) — 0.67 mg
- *Klebsiella pneumoniae lysatum cryodessicatum* (CCM 7589) — 0.67 mg
- *Propionibacterium acnes lysatum cryodessicatum* (CCM 7083) - 1.66 mg
- *Proteus mirabilis lysatum cryodessicatum* (SSM 7592) — 0.67 mg
- *Pseudomonas aeruginosa lysatum cryodessicatum* CCM (7590) — 0.67 mg

CCM — Catalog of Cultures of Microorganisms

Vaccination was carried out according to the scheme: taking the drug for 10 days, 1 capsule, followed by a break for 20 days — three times.

Evaluation of the effectiveness was carried out after 6 months from the start of vaccination based on analysis of UTI recurrence rate and features of the urinary syndrome.

Statistical analysis

The results are processed using medical statistics methods. After data collection, they were used for the statistical analysis. Descriptive data were presented as mean and standard deviation.

The χ^2 test was used for comparison of qualitative variable among different groups. P value less than 0.05 was considered statistically significant.

Results

The majority of the examined patients were in the younger age group (from 7 to 10 years old), in which the number of children with UTI decreased with age. A relatively even distribution of children according to age was observed in the elder group (11 to 16 years old). Gender characteristics of the patients corresponded to the generally accepted characteristics with the traditional predominance of girls (the ratio of boys:girls was 1:14).

The patients who participated in the study in the structure of urinary system infection were diagnosed: pyelonephritis (21 children) and cystitis (9 children).

The spectrum of the revealed uropathogens was analyzed in the course of work (Figure 1).

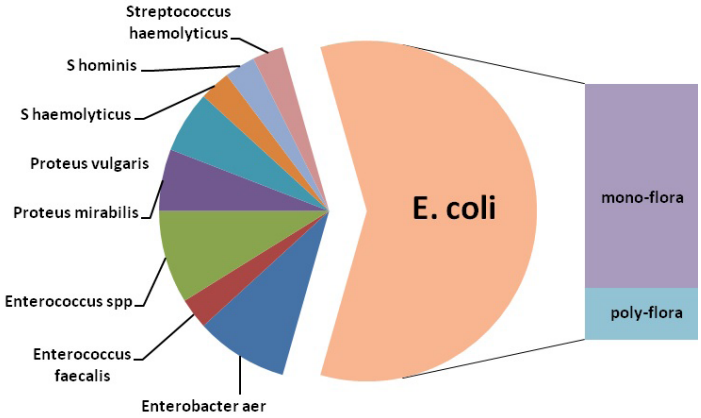

Figure 1: Spectrum of revealed uropathogens in children with uncomplicated forms of UTI (according to microbiological analysis of urine).

As the diagram shows, most frequently *E. coli* was inoculated (66,7%) in children with uncomplicated UTI. The next pathogens in frequency of occurrence were *Enterococcus spp* (10%) and *Enterobacter aer* (10%). *Enterococci* (13.3%), *Proteus* (13.3%), *Staphylococcus* (6.66%) and *Streptococcus* (3.33%) were also detected in the spectrum of uropathogens.

It should be noted that detection of one causative agent during bacteriological analysis was observed in 90% of patients, in the rest cases polyflora was revealed (the most common combination of *E. coli* and *Enterococcus*). The presence of polyvalent microflora was associated with the frequency of exacerbations of urinary system infection ($\chi^2 = 3.84$, $p<0.05$).

According to the results of antibiotic susceptibility pattern the susceptibility of uropathogens remained to antibacterial drugs of aminoglycosides, fluoroquinolones, cephalosporins and carbapenems group.

Taking into account the recurrent course of UTI, special attention was paid to the study of antibiotic resistance of the revealed uropathogens.

The level of resistance of uropathogenic microflora decreased in the following sequence: aminoglycosides (4%), carbapenems (9%), cephalosporins (9%), fluoroquinolones (13%), protected penicillins (17%), macrolides (22%), penicillins (26 %).

It is distinctive that high antibiotic resistance was observed in children who had previous repeated courses of antimicrobial therapy.

Obviously, the identified features of antibiotic resistance and reduced susceptibility of the extra-intestinal uropathogenic enteroflora to commonly used antibiotics has confirmed the need for non-antibacterial means during treatment and prevention of UTI in children.

Discussion

The spectrum of uropathogenic flora differs little according to various studies. The most common identified uropathogen are *Escherichia coli* (69%) and *Klebsiella spp.* (9.7%), *Pseudomonas aeruginosa* (6.7%), *Enterococcus spp.* (5.6%) and *Proteus spp.* (4.4%) [2].

The antibiotic susceptibility patterns of uropathogens among children revealed the following:
Escherichia coli (51.5%), *Klebsiella spp.* (16.8%) and *Enterococcus spp.* (9.9%) [3]. Slight variations in the spectrum of uropathogenic microflora, in our opinion, are stipulated by the nature of the course of infection of the urinary system and depend on the factors of its occurrence.

Analysis of *E. Coli* resistance showed that the observed children with uncomplicated UTI had increase in resistance not only to trimethoprim, but also to fluoroquinolones, aminoglycosides. Growth of resistance was detected for cephalosporins too. Reduced efficiency of cephalosporins is associated with ESBL production, which is typical for *E. coli* (69.2%) and *Klebsiella* (30.8%) [4]. Isolates of *Klebsiella* are also resistent to ciprofloxacin [5].

The revealed features reflect common trends as for antibiotic resistance of uropathogens too. The work "Long-term resistance trends of uropathogens and association with antimicrobial prophylaxis" demonstrates high indicators of resistance to amoxicillin, cotrimoxazole and ceftriaxone. Growth of resistance to nitrofurantoin, ceftriaxone and piperacillin-tazobactam are also established [2]. Resistance of uropathogens to aminoglycosides reaches 76.3%, and to fluoroquinolones 55.4% [4].

It seems the recurrent nature of the infection of the urinary system, the absence of the desired effect from the causal treatment is due not only virulent microflora, but also complex immunopathogenic mechanisms. Therefore, an alternative approach in the treatment of urinary tract infection is the stimulation of the patient's own immune mechanisms directed against the pathogenic flora, with

the help of oral administration of immunotherapy drugs.

Clinical studies have demonstrated the effectiveness of immunoprophylaxis of urinary system infection using a combination of 6 uropathogens lysates. Authors from 5 Medical Urology Centers in Prague showed in their study that vaccine therapy stimulated macrophages activity, increased the population of CD 4, increased the concentration of secretory IgA, increased the formation of protective molecules [11,12].

So, we considered it appropriate to evaluate the effectiveness of immunoprophylaxis with the use of bacterial lysates with urinary infection in children.

Against the background of the use of a complex drug developed taking into account the modern characteristics of uropathogenic microflora, and containing inactivated bacterial strains of the most common pathogens, a positive clinical and laboratory dynamics was observed (Figure 2).

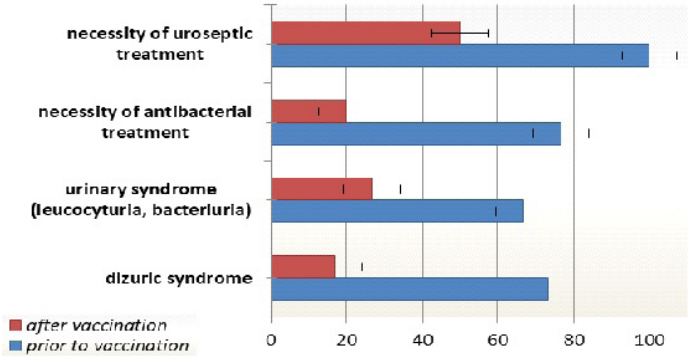

Figure 2: Evaluation of the effectiveness of immunoprophylaxis of urinary system infection in children.

Evaluation of effectiveness after 6 months from the start of vaccination showed: a decrease in the frequency of recurrences of UTI (Recurrence rate after treatment: before treatment: 3.55 (95% CI 2.91–4.18); after treatment: 0.93 (95% 0.57–1.29), as well as a decrease in manifestations of urinary syndrome in the form of bacteriuria and leukocyturia. It is important to note that the use of immunoprophylaxis has significantly reduced the use of antibacterial drugs and uroseptics.

It is also necessary to emphasize that no adverse events were registered during vaccination, and when subjectively assessing 2/3 of the patients showed an improvement of their condition.

Conclusion

The obtained data allowed making a conclusion that immunoprophylaxis can be a safe, acceptable and effective alternative in the prevention of UTI in children.

References

1. Brandström P, Hansson S. Long-term low-dose prophylaxis for young children. Pediatr Nephrol. 2015; 30: 425-432.
2. Bitsori M, Maraki S, Galanakis E. Long-term resistance trends of uropathogens and association with antimicrobial prophylaxis. Pediatr Nephrol. 2014; 29: 1053-1058.
3. Pouladfar G, Basiratnia M, Anvarinejad M, et al. The antibiotic susceptibility patterns among the population with urinary tract infection in Shiraz. Medicine Baltimore. 2017; 96: e7834.
4. Valerie P. O'Brien, Thomas J. Hannan, Hailyn V. Nielsen, et al. Drug and Vaccine Development for the Treatment and Prevention of Urinary Tract Infections. Microbiol Spectr. 2016.
5. Yunus Yilmaz, Zuhal Tekkanat Tazegun, Emsal Aydin, et al. Bacterial patterns of patterns of children in turkey. Iran Red Crescent Med J. 2016; 18: e26610.
6. Mattoo TK. Are prophylactic antibiotics indicated after a urinary tract infection. Curr Opin Pediatr. 2009; 21: 203-206.
7. Barclay J, Veeratterapillay R, Harding C. Non-antibiotic options for recurrent urinary tract infections in women. BMJ. 2017; 23; 359: j5193.
8. Kishor Tewary, Hassib Narchi. Recurrent urinary tract infections in children Preventive interventions other than prophylactic antibiotics. World J Methodol. 2015; 26; 5: 13-19.
9. Huttner A, Hatz C, van den Dobbelsteen G. Safety immunogenicity pathogenic pathogenic disease recurrent urinary tract infection a randomized, single-blind placebo-controlled phase 1b trial. Lancet Infect Dis. 2017; 17: 528-537.
10. Rebecca Forbes, Ased Ali, Alaa Abouhajar, et al. Alternatives to prophylactic antibiotics for women for urinary tract infection ALTAR study protocol for a multicentre pragmatic patient randomized non-inferiority trial. Trials 2018; 19: 616.
11. Miroslav Hanuš, Michaela Matoušková, Vlasta Králová. Immunostimulation with polybacterial lysate urivac® in preventing recurrent lower urinary tract infections. Ces Urol. 2015; 19: 33-43.
12. Taha Neto KA, Nogueira Castilho L, Reis LO. Oral vaccine OM-89 in the recurrent urinary tract infection prophylaxis a realistic systematic review with meta-analysis. Actas Urol Esp. 2016; 40: 203-208.