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Fosfomycin prophylaxis can reduce the risk of severe recurrent urinary tract infections requiring hospitalisation in children with complex urinary tract malformations

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ABSTRACT

Introduction: Urinary tract infections (UTIs) with resistant bacterial strains are one of the most troublesome problems in children with severe congenital anomalies of the kidney and urinary tract (CAKUT). We present the results of non-standard prophylactic treatment with fosfomycin of infants with complex urinary tract malformations.

Material and methods: It was a retrospective analysis of data of 5 male infants after urological interventions due to complex CAKUT. The frequency of UTIs, their aetiology and course, frequency and duration of hospitalisation due to UTIs, prophylaxis and treatment outcomes were analysed.

Results: The mean follow-up period was 16 months. Mean number of UTIs during observation was 5 (2–6). Infections with multi-drug resistant strains were observed in all patients before commencing fosfomycin prophylaxis, on average 21 days after urological procedure. Due to recurrent UTIs with highly resistant or reduced susceptibility strains, despite standard prophylaxis, we introduced fosfomycin in 50–70 mg/kg dose once a day for 4–9 months what reduced frequency of infections (3.6 vs. 1.0, $p = 0.01$), infections with decreased susceptibility strains (3.6 vs. 0.0, $p = 0.00006$) and need for hospitalisations (3.6 vs. 0.2, $p = 0.003$). Fosfomycin was introduced after 2–5 UTIs, at the mean age of 7 months, after mean of 4 months of ineffective standard prophylaxis. We didn't record any significant adverse effects of the treatment or bacterial resistance development.

Conclusions: In children with urinary tract malformations, and in particular with a history of urological interventions, in the case of recurrent UTIs with strains of reduced susceptibility to antibiotics, several months of non-standard prophylactic treatment with fosfomycin may be considered.

KEY WORDS:

infants, urinary tract infections, antibiotic prophylaxis, CAKUT.

INTRODUCTION

Children with urinary tract malformations are probably the most numerous group of patients in paediatric nephrological and urological practice. The clinical course depends on the severity and complexity of the defect. Children with urinary tract malformations are the most vulnerable to recurrent urinary tract infections (UTI) [1–3]. The recurrence of UTIs suggests a need for implementation of antibiotic prophylaxis. However, so far

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there is no consensus on which groups of children require prevention of urinary tract infection and whether it actually has long-term favourable health benefits for the children undergoing it [4, 5]. In the prophylaxis of infections, standard drugs include furazidin (available in Poland), nitrofurantoin, trimethoprim (including in combination with sulfamethoxazole), cefaclor, cefalexin, cefuroxime axetil, cefixime, ceftibuten and amoxicillin – in appropriately lower doses and considering the patient's age. The most common aetiological factor of UTIs is *Escherichia coli*, regardless of the age group and presence of CAKUT. However, one of the most troublesome problems in children with severe malformations is UTIs with resistant bacterial strains. They can cause frequent hospitalisations, requiring prolonged high generation and specific antibiotic therapy. Standard prophylaxis of infections in such cases may not be effective. The paper presents the results of non-standard prophylactic treatment with fosfomycin in a tertiary paediatric nephrology centre in central Poland.

MATERIAL AND METHODS

In the present study we analysed the course of urinary tract infections and the long-term effect of prophylactic treatment with fosfomycin in the first and second year of life in 5 boys with complicated congenital urinary tract malformations. Among the included patients, 2/5 (40%) were full term, and the mean birth weight was 3046 g (2500–3430 g). All had a malformation of the urinary tract of varying severity, 2/5 patients underwent prenatal interventions decompressing the urinary tract (vesico-amniotic shunting), and 4/5 (80%) patients had signs of renal failure after delivery. Due to successful surgical interventions releasing the urinary tract outflow, no patient was required to undergo renal replacement therapy. Each of the presented patients had surgical intervention on the urinary tract at some point in the neonatal period or infancy. Depending on indications the surgical procedures included cystoscopy with transurethral valve resections, endoscopic injections of bulking agents, urethrostomy or cystostomy creation.

The mean complete follow-up of the patients was 16 months (12–23 months), including 6 months (3–10 months) before implementation of fosfomycin.

The decision to use fosfomycin was made with caution by the treating team after all other therapeutic options in preventing recurrent urinary tract infections had been exhausted and after obtaining parental informed consent for off-label therapy. The perinatal characteristics of the study group are presented in part 1 of Table 1. The frequency of urinary tract infections, their aetiology and course, frequency and duration of hospitalisation due to urinary tract infections, type of urological intervention used in diagnosis and treatment, prophylaxis and treatment outcomes were analysed. Data on the potential side

effects described by the drug manufacturer in other age ranges were also collected. The data that were compared before and after the implementation of fosfomycin prophylaxis were: the number of total urinary tract infections, the number of infections requiring hospitalisation and the frequency of resistant or of reduced susceptibility bacterial strains. The paired Student's *t*-test was used to compare the groups; the result of $p < 0.05$ was considered significant.

RESULTS

During follow-up, patients had a mean of 5 UTI episodes [2–6]. Infections with highly resistant strains were observed in all patients, on average 21 days after urological surgery (2–34 days).

The first UTI after surgery, regardless of the time elapsed, was caused by highly or partially resistant strains. The first episode of UTI was full-blown in 3/5 patients, and the second episode in 4/5 patients. Subsequent infections were mildly symptomatic. The mean duration of treatment for the first episode of UTI was 13.6 days (12–22 days), the second episode 13.4 days (10–25 days), and the third episode 11 days (10–14 days), without statistical significance for the differences.

Fosfomycin in prophylaxis was introduced after an average of 3 infections with atypical strains (2–5 episodes), at the mean age of 7 months (4–11 months), for an average of 6 months (4–9 months), after an average of 4 months ineffective non-standard prophylaxis (2–6 months). Standard prophylaxis included nitrofurantoin or furazidin, co-trimoxazole, amoxicillin, cefaclor and cefuroxime axetil.

The mean dose of fosfomycin used in prophylaxis was 60 mg/kg (50–70 mg/kg) of body weight given in a single evening dose. No treatment complications, as described by the manufacturer in the summary of product characteristics, were observed. None of the children developed symptoms classified as common side effects of the drug, such as diarrhoea and dyspepsia.

The number of UTIs before the implementation of prophylaxis with fosfomycin differed significantly from the number of UTIs after its initiation – 3.6 vs. 1.0 on average, respectively, $p = 0.01$. The number of infections with resistant or of reduced sensitivity strains before and after the implementation of prophylaxis with fosfomycin was different – an average of 3.6 vs. 0.0, respectively, $p = 0.00006$. (Figure 1). Before the implementation of fosfomycin prophylaxis, patients required inpatient treatment 2–5 times, an average of 3.6 times; after implementation, only one patient was hospitalised for infection, requiring intravenous treatment ($p = 0.003$).

After introducing fosfomycin prophylaxis, no infection with resistant strains was observed in any case – patients had infections with fully sensitive strains of *Klebsiella pneumoniae*, *Enterobacter cloacae*, and *Klebsiella*

TABLE 1. Group characteristics and clinical course

Part 1				Part 2											
Patient	Diagnosis	Kidney function in the neonatal period maximal creatinine concentration in the neonatal period [day]	Urological intervention [day]	1st infection: 1) age 2) symptoms 3) aetiology 4) time of treatment 5) applied therapy 6) CRP (N < 1.0 mg/dl)	Prophylaxis	2nd infection: 1) age 2) symptoms 3) aetiology 4) time of treatment 5) applied therapy 6) CRP (N < 1.0 mg/dl)	Prophylaxis	3rd infection: 1) age 2) symptoms 3) etiology 4) time of treatment 5) applied therapy 6) CRP (N < 1.0 mg/dl)	Prophylaxis	4th infection: 1) age 2) symptoms 3) aetiology 4) time of treatment 5) applied therapy 6) CRP (N < 1.0 mg/dl)	Prophylaxis	5th infection: 1) age 2) symptoms 3) aetiology 4) time of treatment 5) applied therapy 6) CRP (N < 1.0 mg/dl)	Prophylaxis	Follow-up
KM (m) G2, P2, 38 GA 3340 g, Apg 8/8	Multicystic dysplasia LK ureterocoele, PUV VUR 4 LK	Kidney insufficiency (Cr 1.98 mg/dl (3)	Cystoscopy with TUR and incision of ureterocoele (10)	1) 12 days 2) fever 3) *Klebsiella pneumoniae* ESBL (+)*** 4) 22 days 5) gentamycin + ampicillin 6) 4.89 mg/dl	Amoxicillin	1) 1 month 2) fever 3) *Klebsiella pneumoniae* ESBL (+)*** 4) 14 days 5) meropenem 6) 6.53 mg/dl	Cefaclor	1) 2 months 2) mild 3) *Enterococcus faecium** 4) 10 days 5) meropenem, vancomycin 6) < 0.5 mg/dl After treatment – vesicostomy	Cefuroxime axetil	1) 2 months 2) mild 3) *Enterobacter cloacae* * + *Candida* 4) 18 days 5) amikacin + fluconazole (treatment 21 days) 6) < 0.5 mg/dl	Cotrimoxazole	1) 7 months 2) mild 3) *Escherichia coli* *+ *Candida* 4) 14 days 5) meropenem + fluconazole 6) < 0.5 mg/dl After recovery – ureterostomy	Fosfomycin	Prophylaxis for 4 months. During this time 1× mild infection with *Klebsiella pneumoniae*
JP (m) G2, P2 34 GA 2500 g Apg 6/6/8/9	Urethral atresia, hypodysplastic kidneys and megaureters	Kidney insufficiency Cr 2.37 mg/dl (7)	Vesicostomy (11)	1) 1.5 months 2) mild 3) *Serratia marcescens** 4) 10 days 5) ceftazidime 6) 7.43 mg/dl	Cotrimoxazole	1) 3 months 2) fever, sepsis 3) *Escherichia coli* * 4) 15 days 5) ceftriaxone 6) 18,41 mg/dl	Cefepime, bilateral ureterostomies and prophylaxis change – cotrimoxazole	1) 6 months 2) mild 3) *Enterobacter cloacae* complex*** + *Candida* 4) 14 days 5) meropenem + fluconazole 6) 4 mg/dl	Fosfomycin	1) 8 months 2) mild 3) *Enterobacter cloacae* 4) 10 days 5) meropenem 6) < 0.5 mg/dl	Fosfomycin	1) 10 months 2) mild 3) *Enterobacter cloacae* 4) 14 days 5) ceftazidime 6) < 0.5 mg/dl	Fosfomycin	1) 10 months 3) *Enterobacter cloacae* ESBL (+)*** 4) 17 days 5) ciprofloxacin Return to fosfomycin and continuation for 3 months, no recurrence of severe UTIs – nitrofurantoin
FŁ (m) G2, P1 38 GA 3430 g Apg 10/10	VUR IV RK PUV	Normal kidney function	Cystoscopy with TUR and injection of bulking agent (5 m)	1) 5 months 2) fever 3) *Klebsiella pneumoniae* ESBL (+)*** 4) 10 dni 5) ceftriaxone 6) 13,46 mg/dl	Furazidine	1) 6 months 2) mild 3) *Klebsiella pneumoniae**** 4) 10 days 5) meropenem 6) 0.58 mg/dl	Furazidine	1) 10 months 2) mild 3) *Klebsiella pneumoniae* ESBL (+)*** 4) fosfomycin 5) 10 days 6) 1.12 mg/dl	Fosfomycin					Fosfomycin continued for 9 months, without UTIs – nitrofurantoin

TABLE 1. Cont.

Part 1				Part 2									
ML (m) G1, P1 35 GA 3200 g Apg 8/8/10/10	Bilateral hydronephrosis, megaureters PUV	Kidney insufficiency Cr 4.4 mg/dl (10)	Cystoscopy with TUR bilateral ureterostomies: right (12) and left (50)	1) 2 months 2) mild 3) *Klebsiella pneumoniae* ESBL (+)*** + *Enterobacter cloacae* ESBL (+)*** 4) 14 days 5) meropenem 6) 0.51 mg/dl	Furazidine	1) 4 months 2) fever 3) *Klebsiella pneumoniae* ESBL (+)*** + *Enterococcus faecium** 4) 14 days 5) meropenem + vancomycin 6) < 0.5 mg/dl	Fosfomycin						Fosfomycin continued for 4 months – without UTI; cultures from stomas with *Staphylococcus epidermidis* without inflammation in urine
BC (m) G2, P2 33 GA 2760 g Apg 6/6/6	Hypodysplastic kidneys Lung hypoplasia	Kidney insufficiency Cr 1.88 mg/dl (6)	Cystoscopy with TUR (3)	1) 18 days 2) fever 3) *Staphylococcus** 4) 12 days 5) ampicillin + gentamicin 6) 3.45 mg/dl	None	1) 2.5 months 2) fever, sepsis 3) *Escherichia coli* ESBL (+)*** 4) 14 days 5) meropenem 6) 15.76 mg/dl	Cotrimoxazole	1) 3 months 2) mild 3) *Escherichia coli* ESBL (+)*** 4) 10 days 5) meropenem 6) 0.96 mg/dl	Cotrimoxazole	1) 4 months 2) mild 3) *Escherichia coli* ESBL (+)*** 4) 14 days 5) meropenem 6) 2.81 mg/dl	Cefixime	1) 5 months 2) mild 3) *Escherichia coli* ESBL (+)*** 4) 14 days 5) meropenem 6) 3.34 mg/dl	Fosfomycin	Fosfomycin for 8 months – during that time catch-up growth and mild UTI-s with fully susceptible strains: *Klebsiella oxytoca* At 15 months – death due to severe RSV infection and generalized inflammatory response

G – pregnancy, P – delivery, GA – week of pregnancy/gestational age in weeks, PUV – posterior urethral valves, VUR – vesico-ureteral reflux, CRP – C-reactive protein; ***multi-drug resistant strain, *strain of decreased susceptibility.
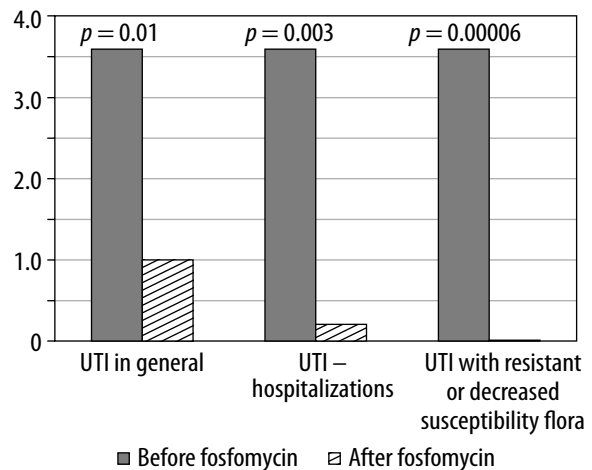

FIGURE 1. Change in the incidence of urinary tract infections, hospitalisations, and infections with resistant or decreased susceptibility strains before and after commencing prophylaxis with fosfomycin. The mean values are shown on the vertical axis

oxytoca. This is a significant change because infections with the multi-drug-resistant strains *Klebsiella pneumoniae* ESBL (+), *Enterobacter cloacae*, *Escherichia coli* ESBL (+) and with the medium susceptibility strains *Enterococcus faecium*, *Enterobacter cloacae*, *Escherichia coli*, *Serratia marcescens* were observed before the onset of treatment. Multi-drug resistant pathogens cultured from patients were sensitive only to drugs that could be used intravenously at hospital, without the possibility of using sequence therapy – *Klebsiella pneumoniae* ESBL (+) and *Enterobacter cloacae complex* were sensitive only to carbapenems, and *Escherichia coli* ESBL (+) only to meropenem. Although during the observation the sensitivity of selected pathogens to fosfomycin began to be assessed, this drug was not directly considered in the treatment of the patients. Antibiograms for pathogens of moderate sensitivity also indicated the inability to use an effective oral therapy.

After finally stopping the fosfomycin prophylaxis we did not observe any fosfomycin-resistant infection in the patients from the study group. The decision on the termination of fosfomycin prophylaxis was based on the clinical course.

The clinical course, considering the number of urinary tract infections, their aetiology, treatment time and the type of prophylaxis used, is presented in part 2 of Table 1. The sensitivity of the cultured pathogens with the division into highly-resistant, intermediate and sensitive is presented in Table 2.

DISCUSSION

In the paper we present 5 cases of patients in whom, due to recurrent infections of the urinary tract with highly resistant or of reduced susceptibility strains, it was decided to introduce non-standard procedures using a temporary prophylactic therapy with fosfomycin. Such

TABLE 2. Susceptibility of isolated pathogens divided into highly-resistant, intermediate and sensitive

Pathogen	ESBL	Amikacin	Amoxicillin + clavulanic acid	Ampicillin	Cefalexin	Cefepime	Cefotaxime	Ceftazidime	Ciprofloxacin	Colistin	Cefuroxime	Ertapenem	Gentamycin	Meropenem	Imipenem	Norfloxacin	Levofloxacin	Trimethoprim/ sulfamethoxazole	Fosfomycin	Nitrofurantoin	Linezolid	Quinupristin/ dalfopristin	Teicoplanin	Vancomycin
Klebsiella pneumoniae ESBL (+)***	Pos	I/R	R	R	R	R	R	R	R	–/S		S	R	S	S	R		R	S					
Klebsiella pneumoniae	Neg	S	S	R	S	S	S	S	S			S	S	S	S	S		S						
Enterococcus faecium*	Pos			R								S			R		R				S	S	S	S
Enterobacter dloacae complex***	Pos	I			R	R	R	R	R			S	R	S	S	R		R						
Enterobacter dloacae*	Neg	S					R	R	S	S		S	S	S	S	S		S	S					
Enterobacter dloacae	Neg	S				S	S	S	S			S	S	S		S		S						
Escherichia coli ESBL (+)***	Pos	I	R	R	R	R	R	I	R		R	R	R	S	S	R		R						
Escherichia coli *	Neg	S	S/R	R	S	S	S	S	S		S	S	S	S	S	S		R		S				
Serratia marcescens*	Neg	I	R	R	R	S	S	S	S			S	S	S		S		S						
Klebsiella oxytoca*	Neg	I	R	R		S		S			S	S	S	S	S	S		S						
Klebsiella oxytoca	Neg	S	S	R	S	S	S	S	S			S	S	S	S	S		S						

ESBL – strain producing extended-spectrum beta-lactamases, Pos – positive, Neg – negative, S – susceptible, R – resistant, I – intermittent susceptibility, R – resistant; ***multi-drug resistant strain, *strain of decreased susceptibility

management significantly reduced the frequency of infections in the study group, and significantly changed their nature to a milder one, and reduced the need for hospitalisation with the need for intravenous treatment.

Among the patients in the present study, the most common infection in the first episode was *Klebsiella pneumoniae* ESBL (+) (extended-spectrum beta-lactamases); none of the patients were infected with *Escherichia coli* initially. Importantly, in all patients, infection with highly resistant strains was preceded by urological surgery on the urinary tract. Therefore, it seems that children with urological interventions are at risk of treatment-resistant infection. This justifies an individual approach to further treatment of these children, including therapies beyond standard management.

There is still a debate about the relationship between UTIs, in particular full symptomatic (feverish course), with long-term complications, such as scarring of the renal parenchyma or the development of arterial hypertension and chronic kidney disease [6–9]. So far, the exact predictive value of the occurrence of infections for the development of the above-mentioned complications in the future is not established. Development of drug resistance of bacteria was observed more often among children given UTI prophylaxis; therefore the indications for prophylaxis should be narrowed down and based on reliable analyses of reliable studies [10, 11]. It has been suggested that girls with grade III and IV vesicoureteral reflux may benefit from prophylaxis, but some sources do not support the long-term benefits of such treatment [10, 11]. It therefore seems that the implementation of prophylaxis should be based on the clinical course of the disease, considering the shortest possible duration of its administration. In the present study, despite the use of standard prophylaxis, patients developed feverish, sometimes generalised infections with resistant strains, which resulted in the need for hospitalisation and prolonged intravenous treatment, which undermined the rationale for standard prophylaxis. For this reason, the possibility of optimising the procedure was considered, including the administration of the drug outside the registration indications, which brought the expected effect in the absence of significant complications.

Fosfomycin is a broad-spectrum antibiotic against Gram (+) and Gram (–) bacteria, including multidrug resistant organisms. It is characterised by good tissue penetration (skin, soft tissues, muscles, bones, lungs, central nervous system) [12]. Fosfomycin is excreted unmetabolized in the urine, through glomerular filtration. It has an excellent safety profile in children, even with prolonged use [13, 14]. In 2015, a systematic literature review was published reporting low toxicity and insignificant concerns about the safety profile of fosfomycin in the adult and paediatric population [15]. In the analysed reports, based on the data of 254 paediatric patients, 6 studies used fosfomycin from a single dose to a month-

ly intravenous treatment. The most frequently reported adverse events were nonspecific rash, peripheral phlebitis with intravenous administration, and gastrointestinal symptoms, but these occurred less frequently than with other antibacterial agents. No serious adverse events related to the administration of fosfomycin were reported [16]. Also, in the observation of our patients, there were no side effects of fosfomycin administration.

Experience with its use in children is still limited. The dosage of the oral formulation in children has not yet been fully established. Depending on the country of registration, daily doses administered in intravenous treatment range from 100 mg/kg to 400 mg/kg (higher doses in severe infections). From the age of 12 or > 40 kg body weight, the adult dose is recommended [17, 18]. In recent years, clinical trials have also been conducted to assess the safety and pharmacokinetics of oral fosfomycin in neonates. In the NeoFosfo study (NCT03453177), fosfomycin 100 mg/kg IV every 12 h for 48 h was used and then converted to oral treatment with the same dose. The study has achieved a pharmacokinetic model for the drug, but no definitive binding results are yet available on drug dosing [19].

Currently, the use of fosfomycin monotherapy is recommended only in UTIs with a fever-free course, with drug registration in Poland over the age of 5 [18]. Registration indications include acute uncomplicated bacterial cystitis, heavy asymptomatic bacteriuria, and prevention of urinary tract infections associated with surgery and transurethral diagnostic procedures. Due to its wide spectrum, fosfomycin should be considered in the case of infections with immunocompromised microorganisms, i.e. *Escherichia coli* ESBL (+) [20]. In a Spanish study, it was estimated that 1–4% of paediatric UTIs have this aetiology and may be related to recurrent infections [21]. Similar data are available in our centre – it was found that among UTIs caused by *Escherichia coli* 4.82% produce ESBL-type immunity (unpublished data). Interestingly, among the analysed *Klebsiella* spp. strains, which most often caused the first infection in our patients, almost half (48.57%) were producers of ESBL-type resistance.

At this point it should be mentioned that in 2020, the European Medicines Agency (EMA) recommended that fosfomycin medicines given intravenously should only be used to treat serious infections when other antibiotic treatments are not suitable [22]. Fosfomycin medicines given orally can be continued in treatment of uncomplicated bladder infections in women and adolescent girls. They can also be used to prevent infection in men who undergo a procedure whereby a tissue sample is taken from their prostate (biopsy). The EMA also recommended that intramuscular fosfomycin and fosfomycin granules for children (2 g) under 12 years of age should be suspended as there is no clear evidence that they are sufficiently effective for their currently authorised uses. We strongly agree with the above recommendations.

However, our study group was a specific one presenting an insufficient response for a typical approach; therefore it was necessary to try exceptional measures.

In the described children, we tried to determine the possibility of eradication of atypical strains, which contributed to the necessity of hospitalisation of patients and the use of prolonged treatment. After analysing the available data, which indicate the high effectiveness of periprocedural prophylaxis with fosfomycin and the possibility of using intermittent prophylaxis in women, an attempt was made to rum the off-label preventive treatment [23, 24]. During the preparation for such a procedure, antibiograms of cultured microorganisms, which showed the possible efficacy of fosfomycin, were considered. Determining the dose used in prophylactic treatment was problematic. As previously mentioned, the prophylactic therapy of UTIs in children is performed by administering a daily dose in the amount of 1/3 of the therapeutic dose. Literature data show that in adult women with recurrent UTIs, the dose of 3 g/7–10 days is used [24, 25]. However, the population presented in the study was significantly different – these were children with urinary tract malformations with impaired proper outflow of urine from the urinary tract, often with bladder dysfunction resulting from the presence of a bladder obstruction. It seems that in such cases intermittent prophylaxis might not bring the expected effect. The daily use of 1/3 of the daily dose was also supported by information from clinical trials in which daily treatment was extended to one month. In our observation, all children undergoing extended prophylaxis with fosfomycin eradicated the resistant strains and reduced the incidence of UTIs in general. If infections occurred during fosfomycin prophylaxis, they were caused by typical strains of normal drug susceptibility. Moreover, after the discontinuation of fosfomycin, the patients only experienced infections with the typical strains. The exception was a patient with urethral atresia (JP), in whom prophylaxis was discontinued only after 2 months and the infection with the highly resistant strains reoccurred. Afterwards fosfomycin was reintroduced for the next 3 months with a good outcome. This suggests that in the case of the most complex CAKUT a 2-month period of treatment could be insufficient to maintain good result.

The available pharmacodynamic data show that the urinary concentrations of fosfomycin above the minimum inhibitory concentration (MIC) are maintained 24–48 hours after an oral therapeutic dose [26]. The daily dose of 1/3 of the therapeutic dose of fosfomycin resulted in a very good clinical effect and eradication of resistant pathogens. Considering the pharmacokinetics of the drug, it can be hypothesized that the proposed dosage achieved the clinical goal, and the lack of side effects indirectly indicated a low risk of drug accumulation and its toxicity. In addition, no patient developed a fosfomycin-resistant strain, which also indicates the efficacy of the dose used. It cannot be ruled out, howev-

er, that it would be as effective and safe to give the full dose of the drug 7–10 days apart as it is used in adults. However, leaving patients with a significant impairment of the urine outflow without an effective urine sterilizing drug in the interval between doses – especially in the context of the JP patient data, in whom the shortened prophylactic treatment led to a recurrence of infection with highly resistant strains – seemed unjustified to us. A study to evaluate the efficacy of intermittent dosing could have many benefits for the clinical management of children with complex urinary tract defects.

From the clinical point of view, the procedure presented in the study seems to be effective – it made it possible to stop the chain of hospitalisations and the need for treatment with broad-spectrum antibiotics of activity reserved for the most severe infections. On the other hand, prolonged use of fosfomycin in prophylactic doses may in the future generate the risk of developing resistance to this antibiotic. Data from a decade ago, in the form of a review of 17 studies, indicated that 96.8% of *Escherichia coli* ESBL (+) strains were susceptible to fosfomycin [27]. However, in 2022 Spanish researchers published data highlighting the increased prevalence of fosfomycin-resistant *E. coli* strains among ESBL strains over the past decade [28]. It is believed that a significant increase in the frequency of its use in outpatient infections may play a key role in the development of resistance to fosfomycin. Therefore, as a drug with a safe profile of action, and at the same time a broad spectrum, it should be used with caution in order to remain effective and useful for as long as possible. This is in line with EMA recommendations about narrowing the indications for using fosfomycin.

Among the presented patients, it was also difficult to determine the duration of the therapy. Based on the reports on the increasing resistance to fosfomycin, it seems advisable to keep the therapy as short as possible [28]. In the observation of our patients, a minimum 3-month initial treatment period was adopted. In 1 patient, treatment with fosfomycin was initially discontinued after 2 months, which was associated with a rapid recurrence of infection with highly resistant strains. The remaining patients were treated for at least 4 months. The time was extended beyond 6 months for various reasons – from parents' reluctance to change treatment which guaranteed the child's well-being, to the effects of the COVID-19 pandemic period, in which it was difficult to maintain rigid check-ups deadlines. Ultimately, no complications were observed in any of the patients, even during 9 months of treatment, and the most visible effect was the absence of infections with atypical strains.

Our study had limitations. The results of our observation are promising, but they do not justify the wide implementation of the above-mentioned procedure in everyday practice. The main limitation of the study is the small study group. Based on the analysis of the clinical course of the disease in 5 children, no conclusive statistical results can be obtained. Moreover, due to the lack of registration of the drug in the indication of prophylaxis of UTIs in children (off-label use), it is difficult to determine the appropriate prophylactic dose and duration of drug use. The last point was guided by the clinical course. Due to the retrospective nature of the study, the concentration of the drug in the blood and urine of the children was not assessed. More extensive studies, including randomised clinical trials, in a group of children with complex defects of the urinary tract requiring urological intervention, would allow us to determine the appropriate dose and duration of treatment in prophylactic management.

CONCLUSIONS

In children with urinary tract malformations, and in particular with a history of urological interventions, in the case of recurrent infections of the urinary tract with strains with reduced susceptibility to antibiotics, several months of non-standard prophylactic treatment with fosfomycin may be considered. Such treatment appears to be safe, does not cause side effects and may reduce episodes of urinary tract infections requiring hospitalisation, thus improving the quality of life of patients and reducing health care costs.

DISCLOSURE

The authors declare no conflict of interest.

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