ORIGINAL ARTICLE

A TEN-YEAR ANALYSIS OF CHANGES IN THE SENSITIVITY OF THE LEADING UROPATHOGEN TO ANTIBACTERIAL AGENTS IN CHILDREN WITH URINARY TRACT INFECTION IN THE NEPHROLOGY DEPARTMENT

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ABSTRACT

The aim: To study the prevalence of ABR among children with UTI over the past 10 years, with an assessment of the sensitivity of *E. Coli* to common antibiotics in dynamics.

Materials and methods: The study involved 1,044 children with UTI aged from 1 month to 18 years. Examination of patients and interpretation of the results was performed in accordance with the provisions of the Declaration of Helsinki of Human Rights. According to the design, the study included 3 comparison groups: Group 1 — children of the 2009 follow-up year (n = 337), Group 2 — of 2014 (n = 328) and Group 3 — of 2019 (n = 379).

Results: Escherichia coli is recognized as the leading uropathogen in all study groups: its percentage in Group 1 was 47 % (158/337), in Group 2 — 64 % (210/328) and in Group 3 — 66.5 % (252/379). The prevalence of antibacterial resistance of E. coli strains and the high dynamics of its growth are shown. So the level of resistance of E. Coli in 2019 was 70 ± 4.06 % (176/252). This was 11 % more compared to 2014 and 18.8 % more compared to 2009. The percentage of multiresistant strains tended to increase and amounted to 28 ± 9.97 % (70/252) among patients with UTI and 40 ± 9.12 % (70/176) in the structure of resistance in 2019. The relative risk of ABR increased by 1.6 times in 2019 compared to 2014 (RR_{2019} = 2.208 ± 0.207 [1.473;3.310], $p < 0.05$ vs RR_{2014} = 1.375 ± 0.209 [0.913;2.063]) and by 3 times compared to 2009 (RR_{2009} = 0.727 ± 0.209 [0.483;1.095]). Ampicillin and amoxicillin showed an equally low sensitivity level (3.5 ± 32.14 % (9/252)). Only every second child confirmed sensitivity to cefuroxime (53.6 ± 5.76 (135/252)). Ceftazidime and ciprofloxacin showed a relatively high sensitivity level — 77.4 ± 3.34 (195/252) and 83 ± 2.81 (209/252), and at the same time the rapidly growing resistance rates — almost twice as high over the past 5 years. Furazidin K showed a high sensitivity level of 85.7 ± 2.53% (216/252), the lowest level of overall resistance of 14.3 ± 15.15 % (36/252) and a slow rate of its formation. An unfavourable prognosis of an increase in the relative risk of ABR by 2.9-3.7 times in the next 5–10 years was determined among patients with UTI, provided that the existing diagnostic and treatment approaches are maintained.

Conclusions: The study results are important for understanding the clinical decision on the benefits of antibacterial therapy and optimizing its empirical choice for a patient with UTI.

KEY WORDS: urinary tract infection, children, *E. Coli*, antibiotic resistance

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INTRODUCTION

Selection of drug-resistant strains of pathogens is an integral part of modern antibacterial therapy [1]. Antimicrobial resistance is becoming a big risk to the global health of mankind [2].

Urinary tract infection (UTI), as one of the most common bacterial infections in children with an empirical antibiotic treatment strategy, is of particular multifaceted relevance [3]. Escherichia coli in childhood plays an important role as an infectious factor, as it is the cause of more than 80 % of all UTIs, bacteremia, foodborne infections, meningitis in newborns and other life-threatening conditions [4].

Recent studies have shown that up to half of *E. Coli* culture samples in children with urinary tract infections (UTI) are resistant to common antibiotics [5]. Researchers from the University of Bristol and Imperial College London studied antibiotic resistance in UTI caused by Escherichia coli and showed a growing level of its resistance to β-lactam antibacterial agents (ampicillin, amoxicillin, including protected by clavulanic acid) [6]. In other developed countries, a third of *E. Coli* samples were resistant to co-trimoxazole, and a quarter — to trimethoprim. In developing countries, resistance was even higher, probably due to the availability of over-the-counter antibiotics, according to the authors [7, 8]. Researchers point to the broad regular prescription of antibiotics by primary care physicians, which poses a high risk of resistance in children, which can persist up to 6-12 months after treatment [5, 9].

So, on the one hand, children receive a disproportionately large number of antibiotics compared to other segments of the population, on the other hand, they are more vulnerable to immediate and long-term complications, such as renal scarring and renal impairment in inadequate treatment of UTI [10]. Constant monitoring of local microbial sensitivity is an absolute necessity for the correct empirical choice of antibiotic.

Table I. Dynamics of *E. coli* sensitivity in patients with UTI for the period 2009 - 2019.

Antibiotics	*Strains E.coli*	Years		
		2009 % ± 95% CI, (abs.)	2014 % ± 95% CI, (abs.)	2019 % ± 95% CI, (abs.)
Ampicillin	S	20±15,06 (34/168)	30,5±10,24* (64/210)	3,5±32,14* (9/252)
	MR	28,6±11,99 (48/168)	29,5±10,47# (62/210)	90,5± 2,01 * (228/252)
	R	51,4±7,41 (86/168)	40±8,3# (84/210)	6±24,59* (15/252)
Amoxicillin	S	23,2±13,79 (39/168)	4,3±32,04* (9/210)	3,5±32,14* (9/252)
	MR	32,1±11,17 (53/168)	36,7±8,91# (77/210)	26,6±10,28# (67/252)
	R	44,7±8,34 (76/168)	59±5,65* (124/210)	70±4,06* (176/252)
Cefuroxime	S	63,7± 5,73 (107/168)	56,2± 5,99# (118/210)	53,6± 5,76* (135/252)
	MR	14,2±18,58 (24/168)	34,8±9,29* (73/210)	27,4±10,07* (69/252)
	R	22,1±14,27 (37/168)	9±21,49* (19/210)	19 ±12,75# (48/252)
Ceftazidime	S	89,3±2,63 (150/168)	54,8± 6,16* (115/210)	77,4±3,34* (195/252)
	MR	6,6±28,65 (11/168)	38,1±8,64* (80/210)	8,3±20,52# (21/252)
	R	2,1±48,56 (4/168)	7,1±24,44# (15/210)	14,3±15,15* (36/252)
Ciprofloxacin	S	88,1±2,79 (148/168)	78,6 ±3,54# (165/210)	83±2,81# (209/252)
	MR	9,8±23,37 (16/168)	15,7±15,7# (33/210)	6±24,59# (15/252)
	R	2,1±48,56 (4/168)	5,7±27,54# (12/210)	11±17,5* (28/252)
Furazidine K	S	84,5±3,24 (142/168)	66,7±4,79* (140/210)	85,7±2,53# (216/252)
	MR	10,7±21,89 (18/168)	27,6±10,97* (58/210)	6,3±23,76# (16/252)
	R	4,8±33,91 (8/168)	5,7±27,54# (12/210)	8±21,07# (20/252)

Notes. S — sensitive strains, MR — moderately resistant, R — resistant, CI — confidence interval, p — statistical significance according to Pearson's chi-square test, compared to Group 1, * — $p < 0.05$, # — $p < 0.05$.

THE AIM

The aim was to study the prevalence of antibiotic resistance among children with UTI over the past 10 years, with an assessment of the sensitivity of *E. Coli* to common antibiotics in dynamics.

MATERIALS AND METHODS

The study involved 1,044 children with UTI aged from 1 month to 18 years, who were treated in the Paediatric Nephrology Unit of Kyiv City Children's Clinical Hospital No. 1 in 2009, 2014 and 2019 (interval up to 5 years).

According to the design, the study included 3 comparison groups: Group 1 — children of the 2009 follow-up year (n = 337), Group 2 — of 2014 (n = 328) and Group 3 — of 2019 (n = 379). The examination of patients and the management of the obtained data were consistent with the provisions of the Declaration of Helsinki of Human Rights.

Diagnosis of diseases was performed according to the unified clinical protocol No. 627 of the MOH of Ukraine of November 3, 2008 "On approval of the treatment protocol for children with urinary tract infections and

Table II. Dynamics of *E. coli* resistance in patients with UTI for 2009 - 2019

Strains E.coli	Years		
	2009 % ± 95% CI, (abs.)	2014 % ± 95% CI, (abs.)	2019 % ± 95% CI, (abs.)
Resistant	51,2±7,41 (86/168)	59±5,65# (124/210)	70±4,06* (176/252)
Monoresistant	25±13,13 (42/168)	32,4±9,8* (68/210)	42±7,26*(106/252)
Multiresistant	26,2±12,73 (44/168)	26,6±11,24# (56/210)	28±9,97# (70/252)

Notes. p — statistical significance according to Pearson's chi-square test, compared to Group 1, * — $p < 0.05$, # — $p < 0.05$.

tubulointerstitial nephritis". The generally accepted diagnostic methods for nephrological patients were applied. Among them: complete blood count and urinalysis, liver and renal tests with calculation of glomerular filtration rate (GFR), proteinogram, measurement of C-reactive protein, Nechiporenko test and Zimnitsky test, bacterial urine culture to determine the pathogen and its sensitivity using the disc dispersion method (DDM), ultrasound of the kidneys and bladder, voiding cystourethrography and excretory urography, if necessary.

Assessment of the distribution of the studied parameters using Pearson's chi-squared test confirmed the normal distribution. Statistical hypotheses were tested using the chi-square goodness of fit test. For fractional values, the 95 % confidence interval (CI) of the parameter distribution was calculated. The absolute and relative probability frequencies were calculated by the odds ratio (OR) with the calculation of the standard error under condition of 95 % CI. The threshold value for statistical significance was set at ≤ 0.05 [11].

Mathematical and statistical calculations were obtained using Microsoft Excel programs (Microsoft Office 2013 Professional Plus, license agreement (EULAID:O15_RTM_VL.1_RTM_RU) and STATISTICA 13.0 (StatSoftInc., Serial No. ZZS9990000099100363DEMO-L).

RESULTS

The leading uropathogen in all study groups was E. coli with a tendency to increase its specific gravity every 5 years. In Group 1 of patients (2009), the percentage of *E. Coli* was 47 % (158/337), in Group 2 (2014) — 64 % (210/328) and in Group 3 (2019) — 66.5 % (252/379).

The dynamics of changes in the sensitivity of Escherichia coli to a common range of antibiotics over the past 10 years with the statistical forecast of the distribution of parameters is shown in Table I. Among the studied classes of antibiotics there are representatives of β-lactams (ampicillin, amoxicillin, cefuroxime, ceftazidime, ciprofloxacin) and representative of nitrofurans (furazidin K).

As can be seen from Table I, in 2019, the sensitivity of E. Coli (in percentage of cases) to ampicillin and amoxicillin was equally low and amounted to 3.5 ± 32.14 (9/252), to cefuroxime — 53.6 ± 5.76 (135/252), to ceftazidime — 77.4 ± 3.34 (195/252), to ciprofloxacin — 83 ± 2.81 (209/252) and to furazidin K — 85.7 ± 2.53 (216/252). In turn, resistance values were as follows: to ampicillin — 6 ± 24.5 (15/252), to amoxicillin — 70 ± 4.06 (176/252), to cefuroxime —19 ± 12.75 (48/252), to ceftazidime — 14.3 ± 15.15 (36/252) and to furazidin K — 8 ± 21.07 (20/252). Moderately resistant strains to ampicillin — 90.5 ± 2.01 (228/252), to amoxicillin — 26.6 ± 10.28 (67/252), to cefuroxime — 27.4 ± 10.07 (69/252), to ceftazidime — 8.3 ± 20.52 (21/252), to ciprofloxacin — 6 ± 24.59 (15/252), to furazidin K — 6.3 ± 23.76 (16/252) were found.

Assessment of the prevalence of resistant Escherichia coli with the calculation of the percentage of monoresistant and multiresistant strains and the dynamics of changes every 5 years is shown in Table II.

The data in Table II showed that the overall level of resistant E. Coli strains at 95 % CI in 2009 was 51.2 ± 7.41 (86/168), in 2014 — 59 ± 5.65 (124/210) and in 2019 — 70 ± 4.06 (176/252). Moreover, in 2019, the monoresistant conditions in the total sample of UTI patients were 42 ± 7.26 (106/252) cases, multiresistant — 28 ± 9.97 (70/252).

The results of assessing the relative risk (RR) of resistance formation in patients with UTI during the indicated follow-up periods and its mathematical prognosis for the next 10 years are shown in Fig. 1.

As can be seen from the graph, the relative risk of antibiotic resistance in 2009 was RR = 0.727 ± 0.209 [0.483; 1.095], in 2014 — RR = 1.375 ± 0.209 [0.913/2.063], $p > 0.05$ and in 2019 — RR = 2.208 ± 0.207 [1.473;3.310], $p < 0.05$. According to the equation of the trend line, the relative risk of E. Coli resistance in 2024 will be RR = 0.7405*4-0.0443 = 2.918, and in 2029 — RR = 3.658 with a high statistical significance ($R^2 = 0.9948$).

DISCUSSION

The international community of nephrologists, urologists, infectious disease specialists (IDSA, EAU, AUA) identified the level of antibiotic resistance in the range of 10-20 % of strains, within which the empirical prescription of an antibacterial drug is possible [12]. If the culture test results are available, only the drugs with the sensitivity of microorganisms to these drugs should be prescribed [13]. The use of drugs with moderate resistance of the strains is also clinically justified, since it may not lead to patient recovery but may contribute to the recurrence or persistence of infection, the formation of resistance of microorganisms and other complications [14].

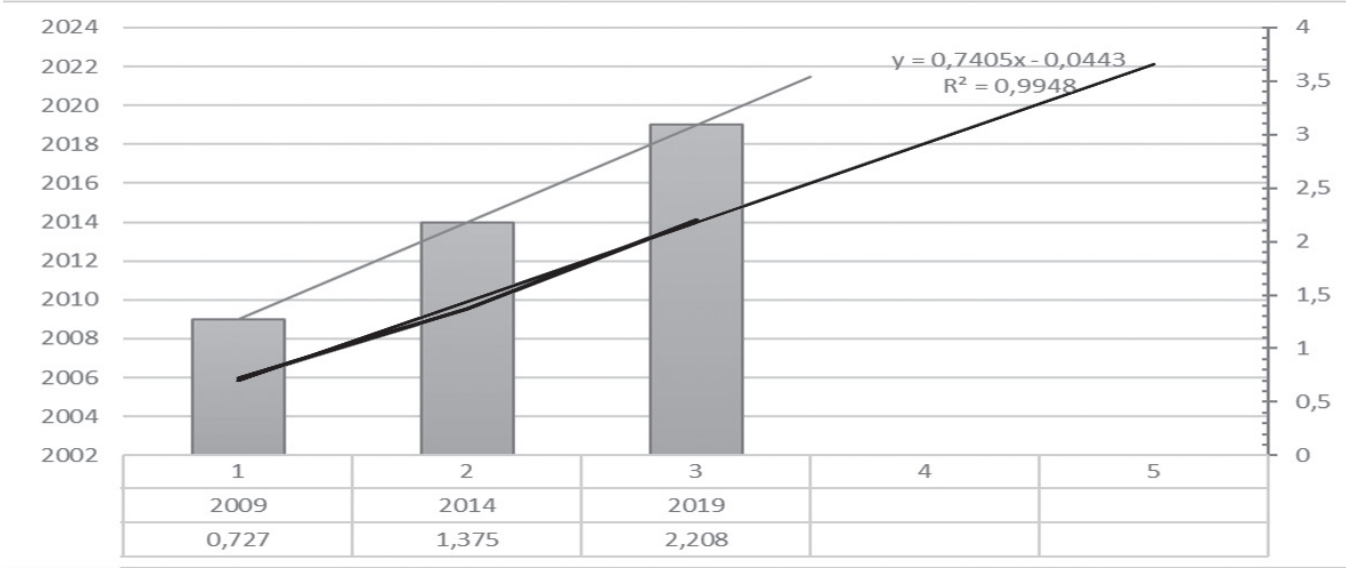

Fig. 1. Assessment and prognosis of the relative risk (RR) of antibiotic resistance in children with UTI
Notes. y = 0.7405x-0.0443 is the equation of the trend line to calculate the prognostic value in the following periods, where x is the number of the period; R^2 is coefficient of determination.

The results of our study showed that neither ampicillin nor amoxicillin can be the drugs of empirical choice in the treatment of UTI in children, which coincided with the studies of other authors [15]. But we also noted that cefuroxime cannot be a first-line drug without a culture test, since only every second child confirmed sensitivity to it (53.6 ± 5.76 (135/252)), while the level of overall resistance (R strains + MR strains) was 46.4 ± 6.64 (117/252). Relatively high sensitivity was shown for ceftazidime and ciprofloxacin in 2019 (77.4 ± 3.34 (195/252) and 83 ± 2.81 (209/252), respectively), while resistance to them grew quite rapidly — almost doubled in the last 5 years. Thus, overall resistance (R + MR) in 2019 for ceftazidime was 22.6 ± 11.44 (57/252), for ciprofloxacin — 17.0 ± 13.64 (43/252). A high sensitivity of 85.7 ± 2.53 (216/252) was determined for furazidin K as the representative of nitrofurans. With the best value of the overall resistance of strains in 2019 — 14.3 ± 15.15 (36/252) and the relatively slow formation of resistance. The value increase by 1.7 times over the past 10 years.

We found that the resistance level of E. Coli among children with UTIs has especially grown over the past 5 years, and compared to the 10-year period, the number of resistant strains has increased by 20 %. The percentage of multiresistant strains also tended to increase so that in 2019 almost every second child with resistance had multiresistant strains — 40 ± 9.12 (70/176). We statistically evaluated and determined the current adverse trends of ABR according to the relative risk analysis. In 2019 it increased by 1.6 times compared to 2014 (RR_{2019} = 2.208 ± 0.207 [1.473;3.310], p < 0.05 vs RR_{2014} = 1.375 ± 0.209 [0.913;2.063]) and by 3 times compared to 2009 (RR_{2009} = 0.727 ± 0.209 [0.483;1.095]). The mathematical equation of the trend line allowed us to determine the prognosis for ABR for the next 5-10 years if the existing diagnostic and therapeutic tactics of UTI are maintained. It was found that the relative risk of ABR progressively increased by 2.9-3.7 times. For comparison, RR_{2009} = 0.727 ± 0.209 [0.483; 1.095] and RR_{2029} = 3.658 with R^2 = 0.9948.

The study results are important for the management of paediatric UTI, both in primary health care and for optimal clinical decisions made by highly specialized doctors. Doctors should consider the effect of any use of antibiotics on further antimicrobial resistance and avoid their inadequate use. They should also adhere to data on local sensitivity and national recommendations, when the prescription of an antibacterial agent is indicated.

CONCLUSIONS

1. The antibacterial resistance of *E. Coli* strains is common among children with UTI and has high growth dynamics.
2. The resistance level of *E. Coli* was 70 ± 4.06% (176/252), which is 11 % more compared to 2014 and 18.8 % more compared to 2009.
3. The percentage of multiresistant *E. Coli* strains tended to increase and amounted to 28 ± 9.97 % (70/252) among patients with UTI and 40 ± 9.12 % (70/176) in the structure of resistance in 2019.
4. The relative risk of ABR in 2019 increased by 1.6 times compared to 2014 (RR2019 = 2.208 ± 0.207 [1.473;3.310], p < 0.05 vs RR2014 = 1.375 ± 0.209 [0.913;2.063]) and by 3 times compared to 2009 (RR2009 = 0.727 ± 0.209 [0.483;1.095]).
5. Ampicillin and amoxicillin cannot be the empirical choice in the treatment of UTI, because they show an equally low sensitivity (3.5 ± 32.14% (9/252)).
6. Cefuroxime cannot be a first-line drug without a culture test, since only every second child confirmed sensitivity to it (53.6 ± 5.76 (135/252)).

7. Ceftazidime and ciprofloxacin showed a relatively high sensitivity level — 77.4 ± 3.34 (195/252) and 83 ± 2.81 (209/252), respectively. At the same time, the rapidly growing resistance was recorded — almost doubled over the past 5 years.
8. Furazidin K showed a high sensitivity level of 85.7 ± 2.53% (216/252), the lowest level of overall resistance of 14.3 ± 15.15 % (36/252) and a slow rate of its formation.
9. The prognosis for the relative risk of ABR for the next 5-10 years is determined as an increase by 2.9-3.7 times if the existing diagnostic and therapeutic tactics of UTI are maintained.

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The Authors declare no conflict of interest.

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