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## ABSTRACT

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## RESULTS OF BACTERIOLOGICAL MONITORING OF URINARY TRACT INFECTIONS IN CHILDREN OF ZAPORIZHZHIA REGION IN 2023

**The aim of the study.** To investigate the structure of pathogens of acute urinary tract infections in children of Zaporizhzhia region in 2023 and their sensitivity to antibacterial agents.

**Materials and methods.** The analysis of the structure of pathogens in acute urinary tract infections and the determination of their sensitivity to antibiotics based on the results of bacteriological urine cultures of 322 children with acute urinary tract infections treated at the Zaporizhzhia Regional Children's Hospital in 2023 was performed. For each isolate, the multidrug resistance index was calculated, which allowed to judge the relative integral resistance of the isolated microorganisms to antibacterial drugs.

**Results.** It was established that the most common cause of urinary tract infections in children were gram-negative microorganisms (61.0%), including *Escherichia coli* (37.4%) and *Klebsiella pneumoniae* (10.8%) which were most often verified. Gram-positive bacteria were identified in 38.5% of patients, among which the *Enterococcus* bacteria (29.2%) predominated. High resistance of *Escherichia coli* to amoxicillin/clavulanate (31.5%), ciprofloxacin (30.1%), cefepime (20.1%), and ceftazidime (20.5%) was detected, including 29 (39.7%) multidrug-resistant isolates of *Escherichia coli*. The highest resistance of *Klebsiella pneumoniae* was found to amoxicillin/clavulanate (76.2%), cefepime (33.3%), ceftazidime (33.3%), ciprofloxacin (42.8%), and phosphamycin (28.6%). Multidrug resistance was shown by 76.2% of *Klebsiella pneumoniae* isolates. The highest susceptibility of *Enterococcus* bacteria was found to ampicillin (98.2%), linezolid (98.2%), vancomycin (100%), nitrofurantoin (100%), and tigecycline (100%). In no case microorganisms showed complete sensitivity to imipenem, and 17.9% of *Enterococcus* isolates were resistant to this antibiotic.

**Conclusions:** At the present stage, the dominance of gram-negative microflora among the pathogens of urinary system infections in children remains, among which *Escherichia coli* (37.4%) continues to be the leading pathogen. The growing role of *Enterococcus faecalis* (29.2%) as an etiologic factor of urinary tract infections in children was noted, which should be taken into account during the empirical use of antibiotics, especially if there is no effect within the first two days after the start of therapy.

**Key words:** urinary tract, infection, bacterial infection, antibacterial agents, antimicrobial resistance, children's health, children.

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## РЕЗУЛЬТАТИ БАКТЕРІОЛОГІЧНОГО МОНІТОРИНГУ ЗБУДНИКІВ ІНФЕКЦІЙ СЕЧОВИВІДНИХ ШЛЯХІВ У ДІТЕЙ ЗАПОРІЗЬКОЇ ОБЛАСТІ ЗА 2023 РІК

**Мета роботи.** Дослідити структуру збудників гострих інфекцій сечовивідної системи у дітей Запорізької області за 2023 рік та їх чутливість до антибактеріальних засобів.

**Матеріали та методи.** Аналіз структури збудників гострих інфекцій сечовивідної системи та вивчення їх чутливості до антибіотиків проводився за результатами бактеріологічних посівів сечі 322 дітей, хворих на гостру інфекцію сечовивідної системи, які знаходилися на лікуванні в КНП «Запорізька обласна дитяча лікарня» ЗОР протягом 2023 року. Для кожного ізоляту розраховували індекс множинної стійкості до антибіотиків (MAR), який дозволяв судити про відносну інтегральну резистентність виділених ізолятів мікроорганізмів до антибактеріальних препаратів.

**Результати.** Встановлено, що найбільш частою причиною розвитку інфекцій сечовивідної системи у дітей були грамнегативні мікроорганізми (61,0%), серед яких найчастіше верифікувалися *Escherichia coli* (37,4%) та *Klebsiella pneumoniae* (10,8%). Грампозитивні бактерії були ідентифіковані у 38,5% пацієнтів, серед яких переважали бактерії роду *Enterococcus* (29,2%). Виявлена висока резистентність *Escherichia coli* до амоксициліну/клавуланату (31,5%), ципрофлоксацину (30,1%), цефепіму (20,1%) та цефтазидіну (20,5%), в тому числі 29 (39,7%) ізолятів *Escherichia coli* виявилися мультирезистентними. Найбільшу резистентність *Klebsiella pneumoniae* встановлено до амоксициліну/клавуланату (76,2%), цефепіму (33,3%), цефтазидіну (33,3%), ципрофлоксацину (42,8%) та фосфаміцину (28,6%). Мультирезистентність проявляли 76,2% ізолятів *Klebsiella pneumoniae*. Найвищу чутливість бактерій роду *Enterococcus* встановлено до ампіциліну (98,2%), лінезоліду (98,2%), ванкоміцину (100%), нітрофурантоїну (100%) та тигецикліну (100%). В жодному разі мікроорганізми не проявляли повної чутливості до іміпенему, а 17,9% ізолятів *Enterococcus* були резистентними до даного антибіотику.

**Висновки:** На сучасному етапі зберігається домінування грамнегативної мікрофлори серед збудників інфекцій сечовивідної системи у дітей, серед яких провідним збудником продовжує виступати *Escherichia coli* (37,4%). Відмічено зростаючу роль

*Enterococcus faecalis* (29,2%) в якості етіологічного чинника інфекцій сечовивідної системи у дітей, що необхідно враховувати при проведенні емпіричної антибактеріальної терапії, особливо при відсутності ефекту її проведення протягом перших двох діб від її старту.

**Ключові слова:** сечовивідні шляхи, інфекція, бактеріальна інфекція, антибактеріальні засоби, резистентність до антимікробних препаратів, здоров'я дітей, діти.

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## ABBREVIATIONS

UTIs - urinary tract infections

ESBLs - extended-spectrum  $\beta$ -lactamases

MAR - multidrug resistance coefficient

## INTRODUCTION / ВСТУП

Among infectious diseases, urinary tract infections (UTIs) are one of the most common diseases caused by pathogenic microorganisms [1]. According to the literature, the main cause of UTIs in children (>90%) are *Escherichia coli*, *Klebsiella* and *Enterobacter*, so  $\beta$ -lactam antibiotics are recommended as first-line therapy [2, 3]. However, the most important problems associated with the treatment of UTIs are the emergence and spread of multidrug-resistant bacterial strains due to many different resistance mechanisms, which severely limits the therapeutic alternatives for clinicians [3]. Due to the increasing frequency of multidrug-resistant *Enterobacteriales* strains, extended-spectrum  $\beta$ -lactams are currently considered the first-line drugs for empirical antibiotic treatment of UTIs. However, recently, many countries have reported an increase in the number of *Enterobacteriales* producing extended-spectrum  $\beta$ -lactamases (ESBLs), and therefore clinicians face a dilemma regarding the choice of empirical antibiotics for pediatric UTIs [4, 5, 6]. Recent literature reports also indicate high levels of resistance of uropathogenic *E. coli* to fluoroquinolones, nitrofurantoin, trimethoprim-sulfamethoxazole, third-generation cephalosporins, and phosphomycin, ranging from 20–60%, 5–15%, 25–80%, and 10–66% and 10–15%, respectively [3, 7].

The ever-increasing prevalence of antibiotic resistance poses a threat to human health, especially among vulnerable populations in hospitals and emergency care facilities. Bacteria are rapidly developing new mechanisms of resistance to antimicrobial drugs [8]. The reasons for the growth of antimicrobial resistance are multifactorial. A key factor in the emergence of resistance is the inappropriate use of antibiotics, which leads to the overuse of

antimicrobials and inappropriate empirical therapy. Every year, there are fewer and fewer available antimicrobial drugs that are effective in the treatment of infectious diseases, including UTIs, and therefore the problem is getting worse [4, 8].

**The aim of the study.** To investigate the structure of pathogens of acute urinary tract infections in children of Zaporizhzhia region in 2023 and their sensitivity to antibacterial agents.

### Materials and methods.

We analyzed structure of pathogens and their antibiotic sensitivity based on the results of urine bacteriological cultures of 322 children with acute urinary tract infection treated at the Municipal non-commercial enterprise «Zaporizhzhia State Children's Clinical Hospital» of Zaporizhzhia Regional Council during 2023, including 50 children diagnosed with acute pyelonephritis, 24 children with acute cystitis, and 248 children with unspecified urinary tract infection.

The material for the study was a midstream portion of morning free-flow urine after a thorough external genital toilet. The material was delivered to the local laboratory in sterile, hermetically sealed containers.

Inclusion criteria: 1) children aged 4 to 18 years (mean age was  $10.3 \pm 1.1$  years); 2) clinical picture of an acute urinary tract infection; 3) yielded pathogens at titers  $>10^5$  CFU/ml.

In all the patients, the diagnosis was confirmed by anamnesis, clinical laboratory tests, X-ray, microbiological examination and ultrasound scan of the urinary system. The uropathogens were inoculated on ready to use media plates: blood agar Columbia (Biomerie, France), selective chocolate agar (Biomerie, France). Determination of the types of gram-positive and gram-negative bacteria and their sensitivity to antibiotics was performed on a bacteriological analyzer

VITEK 2 COMPACT (Biomerie, France) using AES software: Global CLSI-based+Phenotypic software and was additionally determined by the disc diffusion method. Antibiotic susceptibility was taken into account in accordance with the SLSI and EUCAST tables. Interpretation of the results was based on the EUCAST Version 13.0, 2023 control points [9]. According to the EUCAST recommendations [9], ceftazidime was used as a marker antibiotic of the cephalosporin series of the III generation and cefepime of the IV generation to determine the sensitivity of bacteria of the genus *Enterobacteriales*. The generally accepted indicators "sensitive", "moderately sensitive" and "resistant" were used to characterize microorganisms.

Multiple antibiotic resistance (MAR) index was calculated for each isolate and interpreted according to P. Krumperman (1983) [10] using the formula:  $MAR = a/b$ , where MAR = the multidrug resistance coefficient, a = the number of antibiotics to which the isolate under study was resistant, and b = the total number of antibiotics tested for this isolate. This indicator made it possible to assess the relative integrated resistance of microbial strains to the antibacterial drugs used in the study. A MAR value above 0.2 is considered to indicate that the isolated strain originates from a high-risk source where antibiotics are frequently used. A MAR value of 0.2 or

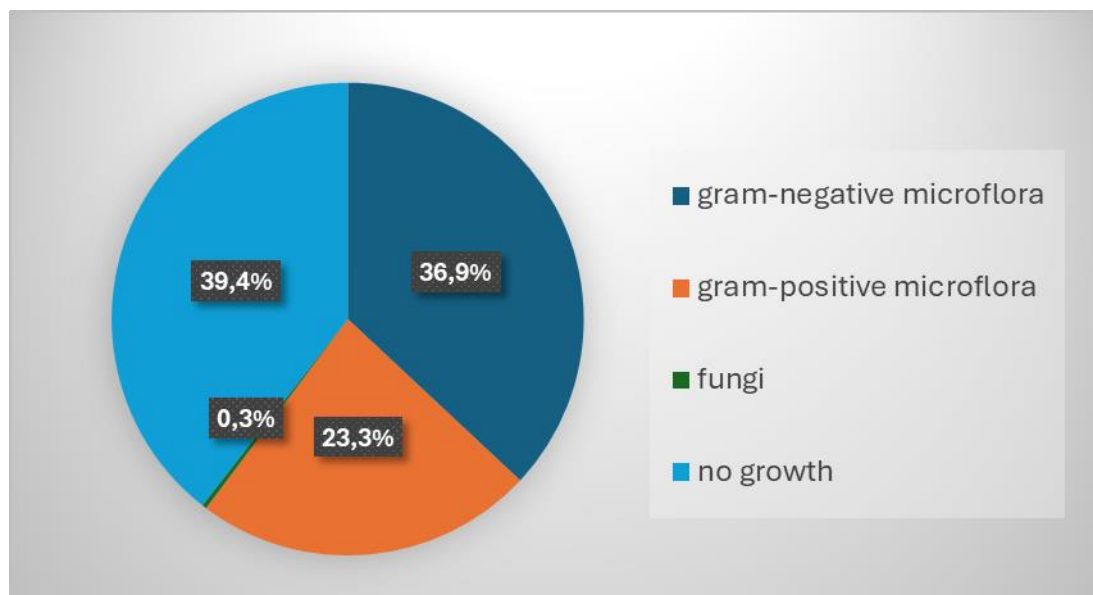
less indicates that the strain originates from sources where antibiotics are rarely or not at all used [11].

Mathematical analysis and statistical processing of data were performed on a computer using the licensed software package Statistica for Windows 13.0, serial number JPZ8041382130ARCN10-J with the determination of arithmetic mean (M), standard deviation ( $\sigma$ ) and mean errors (m). Student's t-test and Fisher's angular transformation were used to evaluate differences in the compared groups. Differences were considered significant at  $p < 0.05$ .

All studies conducted complied with the ethical standards of the Institutional and National Research Committee and the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

#### RESULTS/РЕЗУЛЬТАТИ

According to the results of urine bacteriological cultures of 322 patients with urinary tract infections, etiologically significant microorganisms were isolated in 195 (60.6%) patients (Fig. 1), including all children with acute pyelonephritis (50 (100%) children), 21 (87.5%) of 24 children with acute cystitis and 124 (50.0%) of 248 children with unspecified urinary tract infections.



**Figure 1 – Results of bacteriological examination of urine in children with urinary tract infections**

The absence of microbial growth in the urine in 127 (39.4%) cases was explained by the patients' self-taking of antibacterial drugs before hospitalization.

The analysis of the isolated pathogens revealed that the most common cause of urinary tract infections in children was gram-negative microorganisms, accounted

for 61.0% of all isolated cultures, among which mostly verified *Escherichia coli* – 37.4% (Table 1).

*Klebsiella pneumoniae* and *Pseudomonas aeruginosa* took the second and third places among gram-negative pathogens, accounting for 10.8% and 5.1%, respectively. Other gram-negative pathogens were found in a few cases.

Table 1.

## Etiologic structure of acute urinary tract infections in children of Zaporizhzhia region

Group of microorganisms	The absolute number of strains	% of the number of all isolated strains
Gram-negative microorganisms		
<i>Escherichia coli</i>	73	37,4
<i>Klebsiella pneumoniae</i> ss. <i>pneumoniae</i>	21	10,8
<i>Proteus mirabilis</i>	8	4,1
<i>Acinetobacter baumannii</i>	2	1,0
<i>Enterobacter cloacae</i>	3	1,5
<i>Morganella morganii</i> ss. <i>morganii</i>	1	0,5
<i>Pseudomonas aeruginosa</i>	10	5,1
<i>Providencia rettgeri</i>	1	0,5
Total	119	61,0
Gram-positive microorganisms		
<i>Enterococcus faecalis</i>	56	28,7
<i>Enterococcus faecium</i>	1	0,5
<i>Staphylococcus epidermidis</i>	3	1,5
<i>Staphylococcus aureus</i> ss. <i>aureus</i>	2	1,0
<i>Staphylococcus haemolyticus</i>	3	1,5
<i>Staphylococcus</i> , coagulase negative	3	1,5
<i>Corynebacterium amycolatum</i>	1	0,5
<i>Streptococcus agalactiae</i>	6	3,1
Total	75	38,5
Fungi		
<i>Candida albicans</i>	1	0,5

Among the gram-positive bacteria identified in 75 (38.5%) patients, bacteria of the genus *Enterococcus* (29.2%) prevailed. Bacteria of the genus *Staphylococcus* were isolated in 11 (5.5%) cases and *Streptococcus agalactiae* in 6 (3.1%) children. In 1 (0.5%) case, *Corynebacterium amycolatum* was isolated and in 1 (0.5%) case, *Candida albicans* was verified as the etiologic agent.

Given that the most common pathogens of urinary tract infections in hospitalized patients were *Escherichia coli*, *Klebsiella pneumoniae* and bacteria of the genus *Enterococcus*, at the next stage of our work we investigated the frequency of detection these microorganisms, taking into account the nosological form of UTI in children (Fig. 2).

As shown in Fig. 2, in the structure of isolated microorganisms *Escherichia coli* was significantly more

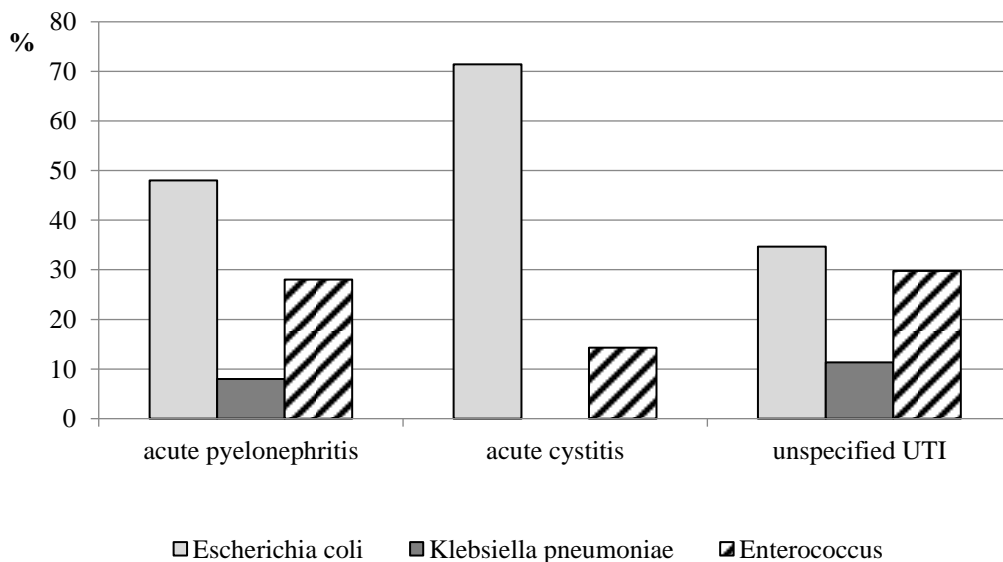
often the etiologic agent of acute cystitis (71.4%) than acute pyelonephritis (48.0%,  $p < 0.05$ ) and acute unspecified UTI (34.7%,  $p < 0.05$ ). At the same time, bacteria of the genus *Enterococcus* were 2 times more likely to be the causative agents of unspecified UTI (29.8%) and acute pyelonephritis (28.0%) than acute cystitis (14.3%,  $p < 0.05$ ). It should be noted that no cases of acute cystitis caused by *Klebsiella pneumoniae* were reported, while in acute pyelonephritis this uropathogen was verified in 8% of cases, and in unspecified UTI – in 11.3% of cases.

The susceptibility analysis of these microorganisms to antibiotics revealed high antibiotic resistance of *Escherichia coli* to amoxicillin clavulanate (31.5%), ciprofloxacin (30.1%), cefepime (20.1%) and ceftazidime (20.5%) (Table 2).

Table 2.

Antibiotic susceptibility of *Escherichia coli* isolated from children with acute urinary tract infections (%)

Antibiotic	Sensitive strains	Moderately sensitive strains	Resistant strains
Amoxicillin clavulanate	68,5	0	31,5
Amikacin	89,1	0	10,9
Cefepime	63,0	16,4	20,5
Ceftazidime	71,2	8,3	20,5
Meropenem	93,2	4,1	2,7
Phosphamycin	91,8	0	8,2
Ciprofloxacin	43,8	26,0	30,1
Trimethoprim-sulfamethoxazole	91,8	0	8,2
Nitrofurantoin	97,3	0	2,7



**Figure 2 – Frequency of *Escherichia coli*, *Klebsiella pneumoniae* and *Enterococcus* bacteria detection depending on the nosological form of urinary tract infections in children**

The low susceptibility of the isolated strains to ciprofloxacin (43.8%) and insufficiently high susceptibility to  $\beta$ -lactam antibiotics (63.0–71.2%) were noteworthy. In all cases, the isolated microorganisms were highly sensitive to meropenem (93.2%), phosphamycin (91.8%), and trimethoprim-sulfamethoxazole (91.8%).

It should be noted that among the 73 identified *Escherichia coli* isolates, only 14 (19.2%) of them did not show resistance to any tested antibiotic, 13 (17.8%) isolates were moderately sensitive to individual antibacterial drugs, while 46 (63.0%) isolates were resistant to antibiotics, including 29 (39.7%) strains were multidrug-resistant and showed

resistance to 2–7 antibiotics simultaneously (Fig. 3). The MAR index of the *Escherichia coli* sample averaged  $0.17 \pm 0.02$  units.

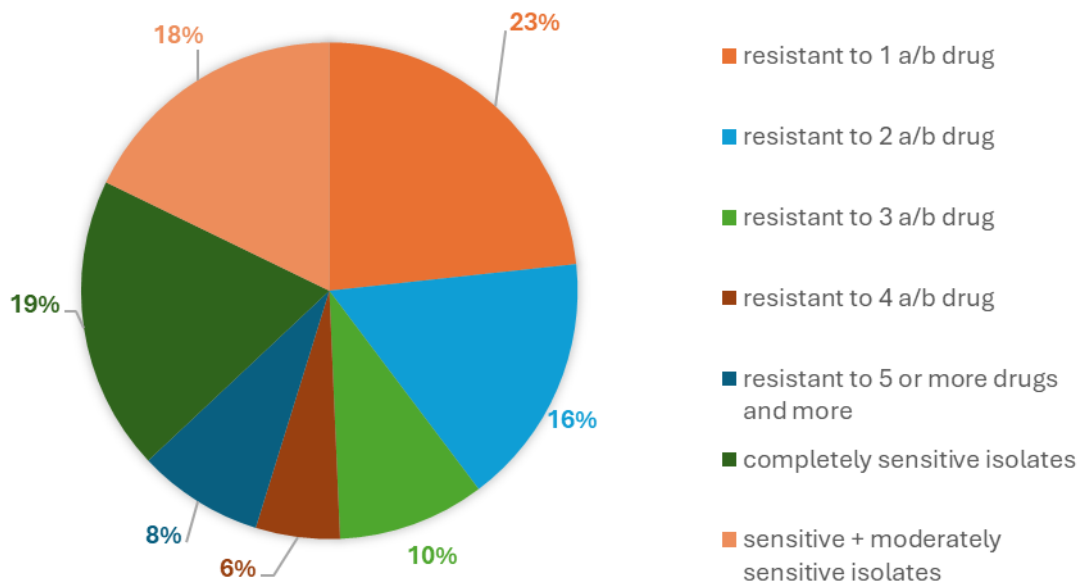
The study of *Klebsiella pneumoniae* susceptibility to antibacterial drugs demonstrated that the vast majority of bacteria were capable of cephalosporin synthesis, which led to high resistance of microorganisms to amoxicillin/clavulanate (76.2%) (Table 3). In 33.3% of cases, the isolated *Klebsiella pneumoniae* isolates were resistant to cefepime and ceftazidime. Resistance to ciprofloxacin was noted in 42.8% of isolates and insensitivity of *Klebsiella pneumoniae* to phosphamycin was registered in 28.6% of cases. The lowest activity against *Klebsiella*

*pneumoniae* isolates was found for ciprofloxacin (33.3%). High sensitivity of the isolates was shown only to amikacin (90.5%). Only 1 (4.8%) isolate of *Klebsiella pneumoniae* was sensitive to all antibiotics tested, and 3 (14.3%) isolates showed moderate

sensitivity of the uropathogen to one of the drugs. The majority of *Klebsiella pneumoniae* isolates (80.9%) were antibiotic-resistant, and the majority of them showed multidrug resistance (Fig. 4).

**Table 3.**  
**Antibiotic susceptibility of *Klebsiella pneumoniae* isolates from children with acute urinary tract infections (%)**

Antibiotic	Sensitive strains	Moderately sensitive strains	Resistant strains
Amoxicillin clavulanate	23,8	0	76,2
Amikacin	90,5	0	9,5
Cefepime	33,3	33,3	33,3
Ceftazidime	47,6	19,0	33,3
Meropenem	76,2	9,5	14,3
Phosphamycin	71,4	0	28,6
Ciprofloxacin	33,3	23,8	42,8
Trimethoprim-sulfamethoxazole	81,0	0	19,0



**Figure 3 – Antibiotic resistance profiles of *Escherichia coli* isolates from children with acute urinary tract infections**

The MAR index of *Klebsiella pneumoniae* averaged  $0.35 \pm 0.06$  units. The proportion of isolates with a MAR index of more than 0.2 was 76.2%, which is 1.9 times more frequent than among *Escherichia coli* isolates ( $p < 0.05$ ), while the MAR index of less than 0.2 was 23.8%, indicating that a greater proportion of isolates probably originated from a high-risk source.

The susceptibility analysis of the detected *Enterococcus* isolates to antibacterial agents revealed that the pathogen was highly sensitive to ampicillin, vancomycin, nitrofurantoin, linezolid, and tigecycline (Table 4).

The susceptibility test of *Enterococcus* bacteria to imipenem demonstrated that the microorganism did not show complete sensitivity to this antibiotic. Moderate susceptibility to imipenem was shown by

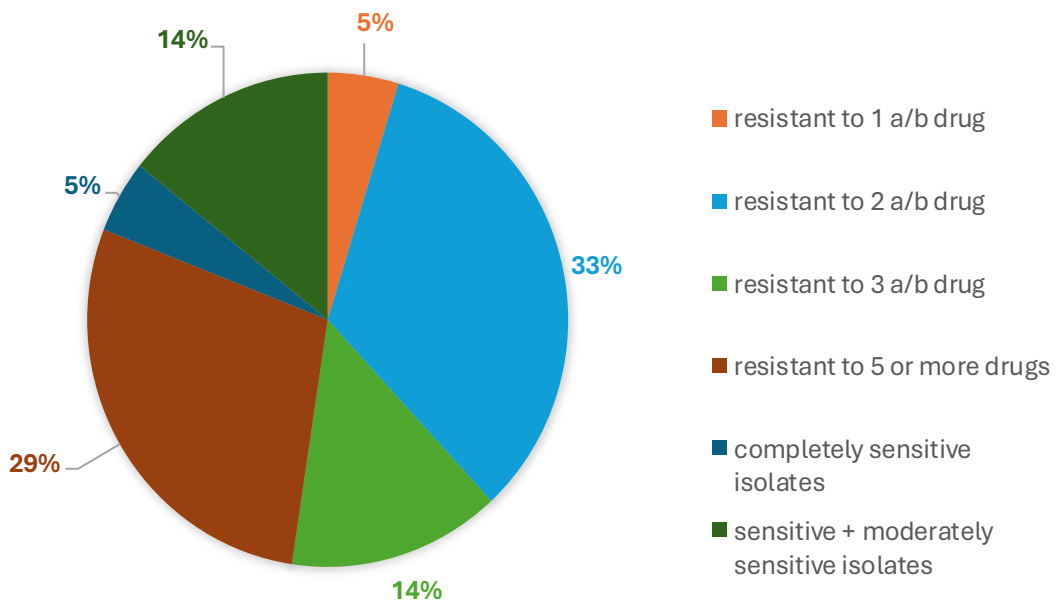
82.1% of *Enterococcus* strains, and 17.9% of the microorganism strains were imipenem-resistant. The frequency of detection of antibiotic-resistant strains of this pathogen was 17.9%, among which only 1 (1.8%)

case was resistant to 2 antibiotics, the remaining 9 (16.1%) isolates were insensitive to 1 tested drug. The average MAR values for *Enterococcus* bacteria were  $0.03 \pm 0.006$  units.

**Table 4.**

**Antibiotic susceptibility of *Enterococcus* bacteria isolated from children with acute urinary tract infections (%)**

Antibiotic	Sensitive strains	Moderately sensitive strains	Resistant strains
Imipenem	0	82,1	17,9
Ampicillin	98,2	0	1,8
Linozolid	98,2	0	1,8
Tigecycline	100	0	0
Vancomycin	100	0	0
Nitrofurantoin	100	0	0



**Figure 4 – Antibiotic resistance profiles of *Klebsiella pneumoniae* isolated from children with acute urinary tract infections**

#### ОБГОВОРЕННЯ

The results of this study demonstrated that the spectrum of pathogens of acute inflammatory processes of the urinary system continued to change compared to previous years [4], while maintaining the dominance of *Escherichia coli*, which was the most common bacterial species (37.4%). The second most common uropathogen was *Enterococcus faecalis* (28.7%). *Klebsiella pneumoniae* took the third place (10.8%). Our findings are consistent with the results of other researchers, who indicate that the vast majority of UTIs in children are caused by Gram-negative microorganisms from the

*Enterobacteriales* family, with *Escherichia coli* being the most common pathogen, followed by other *Enterobacteriales* such as *Klebsiella spp.*, *Enterobacter spp.* and *Proteus spp.* Potential gram-positive uropathogens in children include *Enterococcus spp.* and *Staphylococcus saprophyticus* [12, 13].

Gram-negative bacteria of the *Enterobacteriales* family, *Escherichia coli* and *Klebsiella pneumoniae*, have acquired resistance to various classes of antibiotics, and the treatment of infections caused by these bacteria has become a problem in both developed and developing countries, which greatly complicates

therapy and, unfortunately, is a manifestation of the global trend of increasing antibiotic resistance [14]. Our study demonstrated a high percentage of multidrug-resistant strains of *Escherichia coli* (39.7%) and *Klebsiella pneumoniae* (80.9%). Based on our data, the majority of *Escherichia coli* and *Klebsiella pneumoniae* strains were resistant to  $\beta$ -lactam antibiotics, which is likely due to the frequent use of these antibiotics as starter therapy. Similar results were obtained in previous studies in different countries [15–17]. Moreover, a systematic review that examined the prevalence of antibiotic resistance in urinary tract infections caused by *Escherichia coli* in children revealed that children receiving antibiotics in primary care clinics were more likely to have antibiotic-resistant bacteria in their urinary tract that remained resistant for up to 6 months [18]. Taking into account the fact that children are overexposed to these classes of antibiotics in primary care clinics, constant regulation and caution in prescribing these antibacterial drugs is necessary [5].

An important mechanism of resistance of enterobacteria to  $\beta$ -lactam antibiotics is associated with the production of extended-spectrum  $\beta$ -lactamases of class A and class C, or AmpC, by these microorganisms, which led to the development of their partial resistance to third- and fourth-generation cephalosporins [19]. Resistance of enterobacteria to antibiotics of this group can be caused by mutation or the presence of mobile DNA elements, such as plasmids, transposons, and integrons, in the bacterial cell [20]. It is the AmpCs encoded by  $\beta$ -lactamase plasmids are easily transferred between bacterial species, are associated with multidrug resistance, and can lead to carbapenem resistance [21]. Despite the fact that carbapenem antibiotics are recommended as a last-line therapy for multidrug-resistant strains of *Escherichia coli* and *Klebsiella pneumoniae* [16, 22], reports from around the world indicate a steadily increasing resistance of enterobacteriaceae to carbapenems over the past few years [23, 24]. The results of our study also indicate an increase in carbapenem-resistant *Klebsiella pneumoniae* strains, which amounted to 14.3%, which may indicate the emergence of carbapenemase-producing strains and significantly complicated the treatment of UTIs in children.

Despite the fact that the use of fluoroquinolones is limited in pediatric practice, in our work we found low sensitivity of *Escherichia coli* and *Klebsiella pneumoniae* strains to ciprofloxacin (43.8% and 33.3%, respectively). Recent studies in adults have demonstrated an increase in fluoroquinolone resistance, as fluoroquinolones are among the most commonly prescribed antimicrobials [25]. The gene for

fluoroquinolone resistance can be derived from the maternal microbiota, and even patients who have not previously received antibiotics of this group but live in a community with a high level of fluoroquinolone resistance may demonstrate low sensitivity to them [26]. In addition, a link between fluoroquinolone resistance and the production of extended-spectrum  $\beta$ -lactamases (ESBLs) has been proven. According to the analysis, the percentage of resistance to ciprofloxacin in ESBL-producing *Enterobacteriales* was higher than among strains that do not produce ESB [27].

For today, phosphomycin is considered as an alternative treatment for resistant antibiotic-resistant *Enterobacteriales* sludge, which has a unique mechanism of action, high susceptibility and high penetration, so it is widely used to treat multidrug-resistant *Enterobacteriaceae* strains in both Europe and Asia [28]. However, in the last few years, an increase in the level of resistance of carbapenem-resistant *Klebsiella pneumoniae* isolates to phosphomycin has been reported [29, 30]. Our study also indicates a high rate of resistance of *Klebsiella pneumoniae* strains to phosphomycin (28.6%), which limits the use of this antibiotic as an empirical therapy for patients with acute urinary tract infection. Several mechanisms of resistance of *Enterobacteriales* to phosphomycin have been described, including modification of the antibiotic target, non-functional transporters, and regulation of phosphomycin resistance genes [28].

Currently, there is also a renewed interest among physicians concerning the use of trimethoprim-sulfamethoxazole as the drug of choice for *Klebsiella pneumoniae* infections, especially carbapenem-resistant strains [31]. Recent retrospective single-center series of studies have shown that the use of trimethoprim-sulfamethoxazole for the treatment of carbapenemase-producing *Klebsiella pneumoniae* infections susceptible to trimethoprim-sulfamethoxazole was promising [32]. In our study, the level of resistance of *Klebsiella pneumoniae* to trimethoprim-sulfamethoxazole was 19.0%, which coincides with the study by J. Li et al. (2020), whose results demonstrated fluctuations in the resistance of this pathogen to the abovementioned antibiotic in the range of 16.9%–26.7% [31]. And although the level of resistance to trimethoprim-sulfamethoxazole of another uropathogen from the genus *Enterobacteriales* – *Escherichia coli* was below 10%, it was noteworthy that in children with acute UTIs, trimethoprim-sulfamethoxazole-resistant isolates of *Klebsiella pneumoniae* and *Escherichia coli* revealed combined resistance to other commonly used antibiotics, such as protected penicillins and cephalosporins, as well as to fluoroquinolones and, in rare cases, carbapenems, which also limits the use of

trimethoprim-sulfamethoxazole in the treatment of UTIs in children caused by *Enterobacterales* bacteria.

The major mechanisms of *Enterobacterales* resistance to trimethoprim-sulfamethoxazole are high rates of tolerance of resistance determinants (*sul* genes or *dfr* genes), which are closely related to class 1 integrin, which is located in plasmids and/or bacterial chromosome and has the ability to spread antimicrobial resistance genes into different strains [6, 31, 33]. The prevalence of integron 1 in trimethoprim-sulfamethoxazole-resistant *Klebsiella pneumoniae* according to J. Li et al. (2020) is 63.4%. There is a close correlation between integron carriage and antibiotic resistance, especially combinations of  $\beta$ -lactam/ $\beta$ -lactamase inhibitors, cephalosporins, quinolones, ertapenem, amikacin, and tobramycin. [31].

The analysis of the structure of pathogens of acute urinary tract infections in children of Zaporizhzhia Region demonstrated that, along with bacteria of the genus *Enterobacterales*, a significant proportion of the etiological factors of UTIs belonged to enterococci (29.2%), most of which were identified as *Enterococcus faecalis* (56 out of 57 isolates). This distribution of species is similar to that reported in other studies such as Boccella, M. et al. (2021), which found that of the 3236 *Enterococcus spp* strains identified, *Enterococcus faecalis* was the most isolated species (82.2%) compared to *Enterococcus faecium* (17.8%) [34]. These data emphasize the prevalence of *Enterococcus faecalis* in urinary tract infections. Despite their low virulence,

these microorganisms, like *Klebsiella pneumoniae*, belong to the group of ESKAPE, which are important as pathogens of hospital infections, are often extremely resistant to many antimicrobial agents and pose a serious problem for modern medicine [35, 36]. Our study has found high sensitivity of *Enterococcus* bacteria to most of the tested antibiotics. However, it was alarming that these uropathogens were resistant or moderately sensitive to imipenem, and in no case was an isolate found that was sensitive to this antibiotic, which limits its use in the treatment of acute UTIs in children. Taking into account the fact that *Enterococcus spp* bacteria possess intrinsic resistance to a number of antimicrobial agents, including cephalosporins and sulfonamides, and demonstrate moderate sensitivity to  $\beta$ -lactams and aminoglycosides [37], the formation of resistance to penicillins and nitrofurantoin, which are Access drugs according to the WHO AWARE classification [38], can lead to difficulties in choosing of antibacterial therapy.

Thus, the monitoring of pathogens and the analysis of their sensitivity to antibiotics indicate a significant percentage of antibiotic resistance of gram-negative pathogens of acute UTIs in children. The greatest concern is caused by 80.9% of *Klebsiella pneumoniae* isolates that had a MAR index above 0.2, which requires careful observation and mandatory monitoring of antibiotic resistance for selection of effective empirical therapy.

## CONCLUSIONS / ВИСНОВКИ

1. At the moment, the spectrum of urinary tract infections in children continues to change. However, the dominance of gram-negative microflora remains, and *Escherichia coli* continues to be the leading verified pathogen (37.4%).

2. Each nosological form of urinary tract infections in children has its own spectrum of

pathogens, which should be accounted when planning antibiotic therapy.

3. A certain leading role of *Enterococcus faecalis* (29.2%) as an etiologic factor of urinary tract infections in children was noted. This fact should be accounted during empirical antibiotic therapy, especially in the absence of its effect after the first two days of its start.

## PROSPECTS FOR FUTURE RESEARCH / ПЕРСПЕКТИВИ ПОДАЛЬШИХ ДОСЛІДЖЕНЬ

Taking into account the data on dynamic changes in the spectrum of pathogens, the study cannot be sustainable and requires further monitoring of changes in the spectrum of pathogens and their sensitivity to antibacterial agents in order to improve the effectiveness of the etiologic therapy and prevent the development and progression of antibacterial resistance.

## AUTHOR CONTRIBUTIONS / ВКЛАД АВТОРІВ

All authors substantively contributed to the drafting of the initial and revised versions of this paper. They take full responsibility for the integrity of all aspects of the work.

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