UDC 616.08; 616.6
DOI: 10.21668/health.risk/2024.2.12.eng

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Research article

MULTIDRUG RESISTANCE OF UROPATHOGENS AS A RISK FACTOR IN PROVIDING MEDICAL CARE TO PATIENTS FROM CENTRAL BULGARIA

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The emergence of resistance to multiple antimicrobial agents in uropathogenic bacteria has become a significant public health problem. These microorganisms are the cause of urinary tract infections, which are among the most frequently treated diseases in the outpatient medical care.

A cross-sectional study was conducted among 353 outpatients over 18 years of age with positive urine sample culture. It involved measuring the index of multiple antibiotic resistance of uropathogens causing infections among individuals. The research was conducted in the period January – June 2023 at a private clinical laboratory center located in Stara Zagora, Bulgaria.

One third of the isolates of E. coli and more than a half of those of Klebsiella pneumoniae had a measured MAR index greater than 0.2, with confirmatory high rates of resistance to aminopenicillins and cephalosporins. Alarmingly high MARI values were measured in all representatives of Enterococcus faecalis, Enterobacter species and Pseudomonas aeruginosa. These strains were also established to have high levels of resistance (varying from 58.3 to 100 %) to some of antimicrobial medicines most commonly prescribed in the outpatient healthcare.

Findings of this study emphasize the importance and seriousness of the existing problem with the increasing prevalence of uropathogenic microorganisms with multiple resistance to oral antibiotics. This creates elevated risks of failure to provide effective treatment for patients.

Keywords: *urinary tract infections, bacterial microorganisms, multiple antibiotic resistance index, uropathogens, antimicrobial medicines, risk factor.*

Primary and secondary healthcare are responsible for the majority of antibiotic prescriptions in human health [1]. Irresponsible and incompetent behavior of patients in self-medication with antibacterial agents is the other gross mistake with their mass application [2]. Urinary tract infections (UTIs) as the most common bacterial diseases affecting both men and women in outpatient medical settings are becoming increasingly difficult to treat and require more time to resolve due to acquired antibiotic resistance of isolated bacterial strains. Unfortunately, antimicrobial resistance is one of the biggest threats to public health leading to growing healthcare costs and more frequent treatment failure [3]. It is defined as an ability of a microorganism to resist the action of one or more antimicrobial agents, as a result of mutation in chromosomal genes or acquisition of exogenous resistance genes [4, 5]. By acquiring multiple resistance mechanisms, bacterial strains become resistant to several classes of antibiotics, which seriously limits available therapeutic opportunities to treat an infection [6].

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In the scientific databases, there is a relatively small number of research regarding the spread of microorganisms with multiple antibiotic resistance causing urinary tract infections and their diagnosis in primary and secondary health care across the globe. There are only a few publications regarding the indexing of multiple antibiotic resistance in bacterial strains causing infections in hospitalized patients. **The purpose of our study** was to determine the multiple antibiotic resistance index of uropathogens in outpatient settings and their rates of resistance to commercial and routinely prescribed antimicrobial chemotherapeutics.

Materials and methods. A cross-sectional study was conducted among 353 adults over 18 years of age suspected of urinary tract infections in the outpatient medical settings. Additional inclusion criteria were that all examined patients had a positive urine sample culture and applied antimicrobial susceptibility test. Individuals over 18 years of age suspected of infectious disease of urinary pathways, who were not referred by physicians working in system of primary or secondary healthcare and with a confirmed negative urine sample culture were excluded from the study.

The study was carried out in the Clinical laboratory center located in Stara Zagora, Bulgaria. The duration of the research was six months from January to June 2023.

The sample included 763 outpatients from Stara Zagora region and Haskovo region. Only individuals with a positive urine culture were selected, namely 353.

Standard microbiological techniques were applied to analyze all bacterial isolates – Gram staining, urine culture, biochemical testing and microscopy for verification.

Bacterial uropathogens used in this study were not duplicate isolates of microorganisms identified from urine sample culture of patients with suspected urinary tract infections seeking medical care in outpatient health settings.

A standard Kirby – Bauer disc diffusion technique was used to determine the susceptibility of microorganisms to antimicrobial chemotherapeutics. Antibiotics Susceptibility Testing was performed using Mueller-Hinton agar plates and in accordance with the guidelines of the Clinical Laboratory Standard Institute[1].

In addition, a method for determining minimum inhibitory concentrations was applied to establish antibiotic susceptibility of the most demanding bacteria with certain nutritional preferences. Antimicrobial susceptibility test covered up to 26 antibiotics including Ciprofloxacin, Ampicillin + Sulbactam, Amoxicillin, Amoxicillin + Clavulanic Acid, Cefadroxil, Cephalexin, Cefprozil, Ceftazidime, Cefixime, Trimethoprim / Sulfamethoxazole, Imipenem, Meropenem, Amikacin, Nitroxoline, Rifampicin, Piperacillin + Tazobactam, Vancomycin, Gentamicin, Cefuroxime, Doxycycline, Levofloxacin, Moxifloxacin, Fosfomycin, Colistin, Tigecycline, Ceftazidime + Avibactam.

Determination of Multiple Antibiotic Resistance Index. The bacterial isolates included in the research have public health importance because they often demonstrate cross- or co-resistance to multiple classes of antimicrobials, making them multiple drugs resistant. The Multiple Antibiotic Resistance Index (MARI) is a measure applied to determine levels of multiple antibiotic resistance nature of each resistant uropathogen that is isolated. For this purpose, it was calculated using the following mathematical formula:

$$MAR = R / E,$$

where R represents the number of antibiotics to which a tested bacterial isolate showed resistance, and E represents the total number of antibiotics for which a tested bacterial isolate was evaluated. Our study refers to the concepts of resistance patterns defined by A.-P. Magiorakos et al. [7], allowing identification of multidrug resistance (MDR) strains that are resistant to at least one drug in tree antimicrobial medication classes.

[1] CLSI – M100. Performance Standards for Antimicrobial Susceptibility Testing, 32nd ed. USA, Clinical and Laboratory Standards Institute, 2022, 362 p.

The indexing of multiple antibiotic resistance is an additional and effective method for tracking the source of bacteria [8]. MAR index values greater than 0.2 are indicative of a high-risk source of contamination where antibiotics are often applied [9].

Statistical analysis. The analysis of the data was conducted with the statistical package SPSS for Windows, version 26.0. Descriptive statistics were calculated to summarize the characteristics of the selected sample and key variables. Frequencies and proportions were used to describe categorical variables and measures of central tendency and dispersion (mean, median, standard deviation) was applied for continuous variables. Bivariate analysis was applied to explore the relationships between the independent variables and the outcome variables. Chi-square tests were performed to assess associations between categorical variables. *P*-values less than 0.05 were considered to be statistically significant.

Results and discussion. Out of a total of 763 samples processed for urine culture and sensitivity, 410 (53.70 %) showed no growth and 353 (46.30 %) revealed growth in the culture. Twenty-one point fifty-two percent (76) of positive urine culture were from males and 78.47 % (277) of them were from females. The mean age of the respondents was found to be 52.4 years (SD ± 18.54) with a relatively even representation of all age groups over 18 years. Sixty-nine point ninety-seven percent of individuals with symptomatic bacteriuria were referred by a general practitioner or specialists in secondary outpatient healthcare. The rest of the subjects (30.02 %) were appointed by the relevant doctor. Forty-six point seventy-four percent (165) of the individuals with significant bacteriuria and presence of complains from the urinary tract provided sterile urine for microbiological examination without a working diagnosis by a doctor. The most common diagnoses based on the international classification of diseases applied as a reason for carrying out the microbiological tests are cystitis and chronic tubulointerstitial nephritis – 22.94 % (81). The next most frequent conditions with reported positive urine sample culture were nephrolithiasis and monitoring on the course of pregnancy (3.96 %).

Antimicrobial-resistant rates were observed in six gram-negative bacteria and one gram-positive bacterium. *Escherichia coli* was the leading uropathogen identified in the sample (52.97 %). Based on the multidrug resistance analyses of the isolates of Escherichia coli, 55 (29.41 %) showed resistance to at least three antibiotics of three different classes. The MARI values of the isolates ranged from 0.07 to 1.0 with a mean value of 0.166. Sixty percent of urine isolates of this Gram negative rod with a MAR index above 0.2 were detected in women, which is visible in Figure.

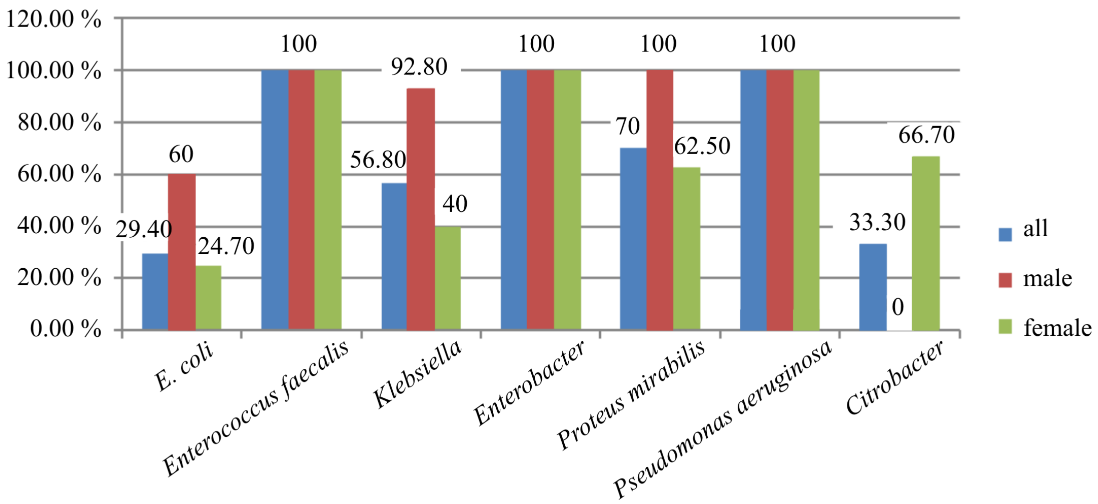

Figure. Distribution of bacterial isolates with MARI > 0.2 among outpatients

The second most common microorganism isolated in outpatients with significant bacteriuria was Enterococcus faecalis, 16.99 % (60). All examined isolates of the indicated Gram positive bacteria, as well as those of Enterobacter and Pseudomonas aeruginosa had MAR index values greater than 0.2. The third most frequent bacterial agent found in the sample was Klebsiella pneumoniae 12.46 % (44). The mean MARI value of Klebsiella pneumoniae isolates was 0.336 and more than half of the bacterial strains (56.81 %) had a calculated MAR index above 0.2. Despite the small number of Proteus mirabilis (10) isolates in the sample, overall multidrug resistance was reported in 7 of them.

MDR isolates of E. coli showed pronounced resistance to fluoroquinolones, aminopenicillins and cephalosporins, as well as high rates of susceptibility to carbopenems, fosfomycin and nitroxoline, as illustrated in Table 1.

Resistance rates of 100 % to aminopenicillins combined with beta-lactamase inhibitors and 92 % respectively to second-generation cephalosporins were measured in MDR isolates of Klebsiella pneumoniae, as shown in Table 2.

Meropenem and Amikacin are antibiotics to which Klebsiella and two other representatives of the Enterobacteriaceae family, Enterobacter and Pseudomonas aeruginosa, showed sensitivity of 80 % or 100 %. Resistance values of 100 % to the second generation cephalosporins were established in Enterococcus faecalis, Enterobacter and Pseudomonas

Table 1

Antimicrobial susceptibility pattern of E. coli

Antibiotic	Total number of isolates *n* = 187		MDR isolates *n* = 55	
	Sensitive	Resistant	Sensitive	Resistant
Ciprofloxacin	144 (77 %)	43 (23 %)	15 (27,3 %)	40 (72.7 %)
Levofloxacin	144 (77 %)	43 (23 %)	15 (27,3 %)	40 (72,7 %)
Amikacin	168 (89.8 %)	19 (10.2 %)	37 (67.3 %)	18 (32.7 %)
Cefuroxime	156 (83.4 %)	31 (16.6 %)	24 (43.6 %)	31 (56.4 %)
Ceftazidime	162 (86.6 %)	25 (12.8 %)	30 (54.5 %)	25 (45.5 %)
Ampicillin / Sulbactam	149 (79.7 %)	38 (20.3 %)	18 (32.7 %)	37 (67.3 %)
Amoxicillin / Clavulanic acid	149 (79.7 %)	38 (20.3 %)	18 (32.7 %)	37 (67.3 %)
Nitroxoline	169 (90.4 %)	18 (9.1 %)	45 (81.8 %)	10 (18.2 %)
Meropenem	181 (96.8 %)	6 (3.2 %)	48 (87.3 %)	7 (12.7 %)
Fosfomycin	179 (95.7 %)	8 (4.3 %)	47 (85.5 %)	8 (14.5 %)
Trimethoprim / Sulfamethoxazole	120 (64. 1 %)	67(35.8 %)	18 (32.7 %)	37 (67.2 %)

Table 2

Antimicrobial susceptibility pattern of *Klebsiella pneumoniae*

Antibiotic	Total number of isolates *n* = 44		MDR isolates *n* = 25	
	Sensitive	Resistant	Sensitive	Resistant
Ciprofloxacin	30 (68.2 %)	14 (31.8 %)	12 (48 %)	13 (52 %)
Levofloxacin	31 (70.5 %)	13 (29.5 %)	12 (48 %)	13 (52 %)
Amikacin	40 (90.9 %)	4 (9.1 %)	21 (84 %)	4 (16 %)
Cefuroxime	21 (47.7 %)	23 (52.3 %)	2 (8 %)	23 (92 %)
Ceftazidime	29 (65.9 %)	15 (34.1 %)	10 (40 %)	15 (60 %)
Ampicillin / Sulbactam	19 (43.2 %)	25 (56.8 %)	0 (0 %)	25 (100 %)
Amoxicillin / Clavulanic acid	19 (43.2 %)	25 (56.8 %)	0 (0 %)	25 (100 %)
Nitroxoline	37 (84.1 %)	7 (15.9 %)	18 (72 %)	7 (38 %)
Meropenem	39 (88.6 %)	5 (11.4 %)	20 (80 %)	5 (20 %)
Fosfomycin	22 (50 %)	22 (50 %)	10 (40 %)	15 (60 %)
Trimethoprim / Sulfamethoxazole	24 (54.5 %)	20 (45.5 %)	10 (40 %)	15 (60 %)

aeruginosa. These three bacterial species are leaders with reported 100 % or high levels of resistance to Trimethoprim sulfamethoxazole, another widely used antimicrobial agent in primary and secondary healthcare. While absolute resistance to aminopenicillins was measured in MDR isolates of Enterobacter spp. and Pseudomonas aeroginosa (100 %), those of Enterococcus faecalis showed significant levels of susceptibility to them (98.3 %).

The number of other isolates belonging to the family Enterobactericea was insignificant and unrepresentative to further comment on their calculated MAR index and rates of resistance.

Bacterial diseases of urinary pathways account for 80 % of community-acquired infections [10]. This determines the high frequency of application of antibiotics for their treatment in the outpatient healthcare. Overuse of antimicrobial chemotherapeutics, their hasty and inappropriate prescribing, along with existing regulatory obstacles have created the conditions for some bacteria to develop the ability to thrive in an antibacterial medicine environment, leading to 'antibiotic resistance'. The problem continues to grow and take on more threatening proportions due to deficit of new, alternative classes of antimicrobial agents which are in the process of development and clinical trials of their efficacy. Data from scientific research and epidemiological surveillance conducted in different healthcare facilities, countries and regions confirm the identification of multidrug-resistant microorganisms causing urinary tract infections that are difficult to respond to antibiotic therapy. In some cases, an employed therapeutic antimicrobial regimen is inadequate and ineffective and is associated with poor patient outcomes, precisely because of detection of an uropathogen remaining susceptible only to potentially more toxic antibacterial drugs and resistant to all others for which it has been examined. Urinary tract infections and pyelonephritis are the forth global burdens attributable to and associated with antimicrobial resistance (AMR) in 2019 [11]. Multi-drug resistant organisms are reasons for recurrent infections despite adequate treatment, for pathological process becoming chronic and for complications. All urinary tract infections in immunocompromised patients, males, pregnant women, and those associated with fevers, nephrolithiasis and urolithiasis, urinary obstructions, urinary catheters, or involving the kidneys are considered complicated infections. Complicated urinary tract infections tend to be caused by a much wider range of organisms, which is associated with increasing multidrug resistance [12]. A vicious cycle of recurrent urinary tract infections and antibiotic resistance can lead to urosepsis, which can be fatal for a patient [13]. *E. coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* are some of pathogens responsible for significant number of deaths associated with AMR reported by Lancet. Additionally, for deaths attributable to AMR, *E coli* was responsible for the most deaths in 2019 [11]. According to the report of the WHO, resistance to fluoroquinolones and β-lactam antibiotics- carbapenems, cephalosporins, and penicillins, which are often accepted as the first line for empirical therapy of severe infections, accounted for more than 70 % of deaths attributable to AMR across pathogens [14].

In the current study, significant part of the outpatients included in the representative sample had a positive urine culture (353 or 46.26 %). This confirms high prevalence of community-acquired urinary tract infections in outpatient medical facilities, especially in countries with low economic standards. Almost half of individuals with symptoms of urinary tract infections were referred by the physician without a working diagnosis (46.74 %). The most frequent working diagnoses according to the international classification of diseases with a confirmed positive culture from a microbiological test were acute and non-specific cystitis (N 30.0 and N30.9) and chronic tubulointerstitial nephritis (N11.9 and N11.8). Significant bacteriuria during pregnancy or during a nephrolithiasis crisis was reported in 14 persons (3.96 %). Female respondents, due to anatomical features and other additional predisposing factors, are a target contingent for occurrence of bacterial diseases of the urinary pathways [15]. Seventy-eight point forty-seven is the percentage of examined women with significant bacteriuria in the sample. The three most prevalent bacterial strains identified in urinary isolates were Escherichia coli, *Enterococcus faecalis* and *Klebsiella pneumonia*. The method of MAR indexing, which was applied in the research, is effective, rapid, easy to implement and it does not require specialized training and expensive equipment [9].

The number of MDR isolates of *E. coli* having a dominant position in the sample was 55 (29.41 %). Comparative analysis of the data from the antimicrobial susceptibility test of the total number of *E. coli* isolates with those having a MAP index greater than 0.2 in our research confirmed the high levels of susceptibility of the Gram negative rod to carbopenems, fosfomycin and nitroxoline. The increasing resistance of *E. coli* to fluoroquinolones and aminopenicillins combined with a beta-lactamase inhibitor, which are recommended and broadly prescribed in the clinical practice, becomes even more visible in strains with MAR index above 0.2. In 2021, *E. coli* resistance to fluoroquinolones generally was the highest in southern and eastern parts of European Region with reported resistance levels for Bulgaria at 33.5 % according to the last report of European Centre for Disease Prevention and Control and World Health Organization[2]. According to A. Kebbeh and co-authors, this class of antibiotics should be reserved and used only after confirmation of sensitivity in a specific uropathogen [16].

It should be noted that the distinct number of *E. coli* and *Klebsiella pneumoniae* isolates showed a marked tendency of resistance to cephalosporins of the second and third generations. Our study confirms the observed increasing levels of *Klebsiella pneumoniae* resistance to the third-generation cephalosporins in the European population. This suggests that it is not appropriate to give preference to the discussed antibacterial medicine in empirical treatment of urinary tract infections in the outpatient healthcare. Resistance rates of 100 % to aminopenicillins with a beta-lactamase inhibitor were observed in MDR isolates of *Klebsiella pneumoniae*. I.L. Miftode and co-authors mention that prolonged and often inappropriate exposure of *Klebsiella* strains to various β-lactam antibiotics has created a background for dynamic gene mutations and enhanced synthesis of β-lactamases [17]. This leads to appearance of extended-spectrum beta lactamase (ESBL)-producing gram-negative bacteria with multiple resistance to other commercially available antimicrobials, and especially to cephalosporins [18].

The results of multidrug resistance analysis of isolates of *Enterococcus faecalis*, *Enterobacter* species and *Pseudomonas aeruginosa* are also alarming. All representatives of the indicated bacterial species had MARI values greater than 0.2 with significantly high or 100 % levels of resistance to some of the antimicrobial medicines most commonly prescribed in the outpatient healthcare. For example, MDR isolates of *Pseudomonas aeruginosa* showed unexpectedly high resistance reaching almost 100 % to 6 antimicrobial groups / agents – fluoroquinolones, aminopenicillins, the second and third generation cephalosporins, Notroxoline, Fosfomycin, and Trimethoprim sulfamethoxazole. Despite the small number of MDR isolates of *Enterobacter* and *Proteus*, their established resistance to aminopenicillins, the second generation cephalosporins and Trimethoprim sulfamethoxazole varying from 50 to 100 % is disconcerting. The conducted research showed that representatives of the family *Enterobacteriaceae* – *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Enterobacter* spp. have the highest levels of susceptibility only to two classes of antibacterial agents, carbopenems and aminoglucosides. This observed multiple antibiotic resistance of the examined uropathogens

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[2] Antimicrobial resistance surveillance in Europe 2023–2021 data: Technical document. Stockholm, European Centre for Disease Prevention and Control and World Health Organization, 2023, 154 p.

to oral antibiotics reduces available options for outpatient treatment and sheds additional light on the choice of antimicrobial medicine in the initial therapy.

Growing prevalence of multidrug-resistant *Enterococcus faecalis* creates even greater challenges in the fight against urinary tract infections. MDR isolates of *Enterococcus faecalis* were resistant to five classes of antibiotics, namely, tetracyclines, the second and third generation of cephalosporin's, Trimethoprim sulfamethoxazole, Nitroxoline, and aminoglycosides, the levels of which varied from 98 to 100 %. The ability of Enterococci species to easily spread in the clinical environment and acquire additional resistance through the transfer of plasmids and transposons has placed them in the category of pathogens that represent a major threat to healthcare systems [19].

This growing incidence and expanding variety of antibiotic-resistant uropathogenic strains is becoming a serious concern for outpatient facilities. By calculating the MARI of the isolated bacteria, it is possible to determine the risk of ineffective treatment of urinary tract infections. With rates of MARI growing over 0.2, likelihood of developing a chronic form of a disease as a result of incorrect and inappropriate applied therapy increases significantly. These microorganisms with a high MAR index often do not respond to the standard antimicrobial therapeutic regimen, causing prolonged illness and complications, as proven by the results of our study. As the frequency of isolates of uropathogens with MARI values above 0.2 raises, the number of cases with UTIs in medical practice with unwanted and negative results after treatment also elevates. A number of circumstances and human factors have contributed to the increase in MDR isolates, starting from high consumption and selective prescription of antibiotics influenced by pharmaceutical marketing to lack of current information on the susceptibility of pathogens to antimicrobial agents in different geographic regions and areas and a deliberate behavior of a patient to self-medicate [20]. Therefore, the notion of antibiotic stewardship remains a core strategy in most national and international AMR management plans. Main interventions addressing the challenge of bacterial AMR, that WHO relies on, are based on the principles of infection prevention and control as well as minimizing use of antibiotics when they are not necessary to improve human health and building infrastructure that allows clinicians to diagnose infection accurately and rapidly, which is crucial for antimicrobial application [14].

Conclusions. Bacterial uropathogenic isolates from patients with significant bacteriuria revealed the presence of extremely high levels of multiple antimicrobial resistance to drugs commonly prescribed in the outpatient settings. By calculating the index of multiple antibiotic resistance, our study highlighted the seriousness of the existing problem. Infections of urinary tract caused by resistant strains are difficult to treat, creating additional challenges and costs for both a patient and healthcare. Monitoring antimicrobial resistance in microorganisms from urine samples, and in particular the frequency of those with a high MAR index, is essential to control their spread and introduce policies promoting the reasonable and evidence-based application of antimicrobial chemotherapeutics in the clinical practice.

Study limitations. The limitations of the research that should be mentioned are mainly related to the sample size and the number of representatives of some bacterial species causing urinary tract infections. This determines the need to study a sample that includes a larger, representative number of isolates of rarer strains of uropathogens for which the index of multiple antibiotic resistance will be verified. However, the tendency of growing prevalence of Gram negative and Gram positive bacteria with high MAR index is evident and the study findings confirm the need to implement mechanisms for adequate and reasonable use of antibiotics in the outpatient facilities.

Ethical consideration. Ethical issues (including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors. The patients were treated according to the Helsinki Declaration of biomedical ethics. Any information related with the patients and clinical laboratory tests was kept confidential. The study was approved by the Public Health Department Council staff.

Funding. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interests. The authors declare that there is no conflict of interests to the research, authorship, and / or publication of this article.

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Received: 23.04.2024
Approved: 31.05.2024
Accepted for publication: 20.06.2024