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Bacterial Infections and Antibiotic Resistance in Romanian Children: Insights from a Hospital-Based Study

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ABSTRACT

Antibiotic resistance is a growing global concern, with Romania being one of the countries most affected. This study examined bacterial infections in children over one year at the "Saint John" Emergency Clinical Hospital for Children in Galati. A total of 9,910 pathological samples were examined. The most frequently identified bacteria were *Staphylococcus aureus, Escherichia coli,* and *Klebsiella pneumoniae*. Among these, 25.4% of S. aureus strains were methicillin-resistant (MRSA), and many showed strong resistance to beta-lactam and macrolide antibiotics. E. coli infections were less responsive to aminopenicillins and cephalosporins, although resistance to third-generation cephalosporins was lower than national reports. These strains also showed relatively low resistance to fluoroquinolones and aminoglycosides. On the other hand, *Klebsiella* species had higher rates of resistance to third-generation cephalosporins, fluoroquinolones, and aminoglycosides than those typically reported in Europe. While overall resistance levels were lower than in some national studies, they still exceeded European averages. Given that most patients were under nine years old, the high rates of resistance are particularly troubling. These findings highlight the need for urgent and ongoing efforts to monitor and manage antibiotic resistance in pediatric care.

Keywords: Antibiotics, Drug Resistance, Pediatric Infections, Bacterial Pathogens, Romania

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Introduction

Antibiotic resistance is a growing global concern that threatens the effectiveness of treatments, the quality of life, and even survival for many patients. Less than 70 years after the introduction of antibiotics, we are now facing the possibility that they may no longer be effective. The overuse and misuse of antibiotics, along with the slow development of new medications, have contributed to this issue. It is estimated that antimicrobial resistance causes at least 700,000 deaths annually worldwide, with predictions that this number could rise to around 10 million per year if no effective measures are taken [1-5].

In Saudi Arabia, a study found that half of the parents preferred antibiotics as the best option for treating infections in their children, despite 76% being aware of the negative side effects, especially on liver function [6, 7]. In Europe, antimicrobial resistance is increasingly recognized as a severe threat to public health. It has led to higher healthcare costs, treatment failures, and even deaths. In 2009, it was estimated that antimicrobial resistance caused 1.5 billion euros in economic losses and 25,000 deaths, and these numbers have only grown since then [8].

Romania is one of the most vulnerable countries in terms of antimicrobial resistance. Between 2015 and 2019, the incidence of infections caused by certain bacterial strains increased significantly. In addition, Romania had the highest antibiotic consumption rates in Europe, following Greece and Cyprus, and the use of surgical antibiotics was often not aligned with clinical guidelines [9].

According to data from the European Antimicrobial Resistance Surveillance Network (EARS-Net), the most common bacteria isolated in Europe were *Escherichia coli* (44.2%), *Staphylococcus aureus* (20.6%), and *Klebsiella pneumoniae* (11.3%). The increasing resistance to key antibiotics, such as carbapenems and fluoroquinolones, is primarily observed in *Klebsiella* species and *Escherichia coli* in Europe. In Romania, resistance levels for *Escherichia coli* and *Klebsiella pneumoniae* are higher than the European average, and *Staphylococcus aureus* shows concerning rates of methicillin resistance (MRSA) [9].

Pediatric infections, particularly respiratory ones, are common. In children, viral infections often cause conditions like pneumonia, but bacterial pathogens such as *Streptococcus pneumoniae* and *Staphylococcus aureus* are also frequent culprits, especially in severe cases or when viral infections lead to complications. However, many pediatric infections are viral, and antibiotics are either unnecessary or harmful. Despite this, antibiotics continue to be widely prescribed for pediatric infections, sometimes leading to resistance problems that could be prevented [10-16].

Urinary tract infections (UTIs) are the leading bacterial infections in children under two years of age. Like adults, a confirmed diagnosis of UTI in children requires a positive culture from an appropriate urine sample. *Escherichia coli* is the predominant pathogen found in UTIs, with other bacteria like *Klebsiella* and *Proteus* species, along with gram-positive cocci, being less commonly observed [17, 18].

Meningitis can be difficult to diagnose in children due to its variable presentation and nonspecific symptoms. Viral causes are more frequent, but the pathogen depends on the child's age. Neonatal bacterial meningitis often stems from pathogens passed during birth, such as *Streptococcus agalactiae*, *Escherichia coli*, and *Klebsiella* species. In older infants and children, the infection is usually caused by pathogens such as *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae*, *Listeria monocytogenes*, and *Escherichia coli* [19].

Sepsis diagnosis in children presents challenges, as common febrile illnesses can mimic the condition, and clinical signs lack specificity. The infection can stem from bacteremia, respiratory, genitourinary, or central nervous system infections. While *Staphylococcus aureus* and *Escherichia coli* are the most common pathogens, in many cases, no pathogen is identified [20, 21].

Children with acute osteoarticular and skin infections are also often treated with antibiotics. These conditions are relatively common and can contribute to the rise of antibiotic resistance.

When prescribing antibiotics, it's crucial to base treatment on local pathogen patterns and resistance data, as well as consider the child's health status and any pre-existing conditions. The growing issue of antibiotic resistance in pediatric infectious diseases affects multiple medical disciplines and calls for attention to prevent long-term complications.

This study examined bacterial infections in children over one year at the "Saint John" Emergency Clinical Hospital for Children in Galati.

Materials and Methods

This retrospective analysis was conducted at the Emergency Clinical Hospital for Children "Saint John" in Galati, Romania, covering the period from January to December 2019. The study examined 9,910 clinical samples from pediatric patients aged 0-18 years, which included feces, urine, blood, pus, vaginal discharge, nasal secretions, laryngeal-tracheal secretions, otic secretions, and urethral secretions. The data were retrieved from the hospital's electronic medical records, laboratory reports, and archived data. The study was performed in compliance with the Declaration of Helsinki, and approval was granted by the hospital's Ethics Committee (Approval No. 68/2020).

All samples were collected before the administration of any antibiotics, following strict aseptic protocols. The samples were then processed in the microbiology laboratory using appropriate media for each specimen type. Bacteriological identification was conducted based on colony morphology, Gram staining, and biochemical testing. For bacterial identification, *Escherichia coli*, *Klebsiella*, and *Pseudomonas* spp. were cultured on AABTL lactose agar, blood agar, and MacConkey agar. *Staphylococcus aureus* was isolated using blood agar and Chapman media, while *Enterococcus* species were cultured on both blood agar and ABE media. For gram-negative bacilli, identification was based on cultural and biochemical tests using various multitest media (MIU, TSI, Simmons, MILF). Antibiotic susceptibility was determined using the Kirby-Bauer disk diffusion method, and results were evaluated by measuring the zones of inhibition for each antibiotic, following CLSI 2020 guidelines [22].

Results and Discussion

Out of the total 9,910 samples analyzed, 1,606 samples (16.20%) tested positive for bacterial growth. The patient population showed a near-equal distribution of male (48%) and female (52%) patients, with the slight difference attributed to the inclusion of female-specific samples, such as vaginal discharge. In terms of age distribution, infections were most commonly observed in children aged 0-4 years (**Table 1**).

Table 1. Distribution of samples according to the age group of patients

Age category	0-4 years	5-9 years	10-14 years	15-18 years
Number of samples (%)	821 (51%)	354 (22%)	191 (12%)	240 (15%)

Among the positive samples, the largest proportion came from nasal exudates (46.45%), followed by fecal samples (14.88%), urine cultures (12.51%), and laryngeal-tracheal secretions (11.2%). Smaller portions were from pus (4.91%), vaginal secretions (4.48%), ear secretions (4.23%), and urethral samples (1.3%).

The primary pathogens responsible for infections in children were *Staphylococcus aureus*, which was most commonly found in nasal exudates and also in ear secretions. *Escherichia coli* was the main cause of genitourinary infections. *Klebsiella* species were largely isolated from laryngeal-tracheal secretions and fecal samples. In cases of skin infections, both *Staphylococcus aureus* and *Escherichia coli* were identified as the main pathogens (**Table 2**).

Table 2. Distribution of bacterial strains according to the type of sample

Sample type	*E. coli* 239 (15%)	*Klebsiella* spp. 363 (23%)	*Pseudomonas* spp. 59 (4%)	*S. aureus* 875(54%)	*Enterococcus* sp. *70 (4%)*	Total
Ear secretion	4	1	26	33	4	68
Tracheal laryngeal secretion	31	80	9	56	4	180
Urethral secretion	3	5	-	3	10	21
Vaginal secretion	33	9	2	1	27	72
Nasal exudate	-	-	-	746	-	746
Feces	-	225	14	-	-	239
Urine	139	38	4	3	17	201
Pus	29	5	4	33	8	79

Staphylococcus aureus was the most frequently identified pathogen in the samples. Infections caused by staphylococci can become severe due to factors such as the increased aggressiveness of the bacteria, a patient's impaired immune defenses, or challenges in treating infections caused by antibiotic-resistant strains. Since beta-lactams are among the most commonly used antibiotics, studies have primarily focused on staphylococcal resistance mechanisms, such as the production of beta-lactamases, which render penicillin and ampicillin ineffective, or alterations in the bacterial target site, which allow methicillin-resistant *Staphylococcus aureus* (MRSA) to survive exposure to all beta-lactam antibiotics, including those designed specifically for staphylococci. Staphylococci are categorized into MSSA (methicillin-sensitive *Staphylococcus aureus*) and MRSA, depending on their resistance to beta-lactams. In our study, 25.4% of the isolated strains were MRSA, which is above the European average of 15%. Resistance rates varied, with quinolones and linezolid showing minimal resistance (2%), while penicillin resistance was observed in 95% of the cases (**Table 3**).

Table 3. Rates of antibiotic resistance of *Staphylococcus aureus* and *Enterococcus* spp. strains

Antibiotic	Resistant rate for	
	S. aureus	*Enterococcus* spp.
Levofloxacin	2 %	-
Moxifloxacin	2 %	-
Linezolid	2 %	5 %

Ciprofloxacin	3 %	-
Norfloxacin	3 %	-
Ofloxacin	3 %	-
Gentamicin	4 %	23 %
Cefoxitin	25.30 %	-
Oxacillin	25.40 %	-
Clindamycin	34 %	-
Erytromycin	37 %	-
Clarithromycin	38 %	-
Azithromycin	38 %	-
Penicillin	94.80 %	25 %
Vancomycin	0	2 %
Teicoplanin	-	10 %
Ampicillin	-	24 %

In our evaluation of *Staphylococcus aureus* resistance, we found that the strains exhibited significant resistance to beta-lactams and macrolides. However, when tested against fluoroquinolones, the majority of strains remained sensitive, with resistance rates below 4% across all fluoroquinolone antibiotics. Similar results were observed for aminoglycosides and linezolid, with linezolid resistance particularly low at just 2%. This minimal resistance to linezolid may be due to its selective use, as it is reserved for treating multi-drug resistant infections or nosocomial cases [23, 24].

The past thirty years have seen a steady rise in infections caused by *Enterococcus* species. These organisms naturally resist certain antibiotics, such as cephalosporins and aminoglycosides, and can acquire additional resistance mechanisms, including against penicillin, glycopeptides, and aminoglycosides. Penicillin resistance typically arises from modifications in target proteins, rather than beta-lactamase production, meaning that combinations of penicillin with beta-lactamase inhibitors (like ampicillin-sulbactam or amoxicillin-clavulanate) are not particularly effective compared to other aminopenicillins. In our study, resistance to penicillins remained relatively low, with sensitivity rates of 76% for ampicillin and 75% for penicillin (**Table 3**).

In pediatric patients, *Escherichia coli* was identified as the primary cause of urinary tract infections in our research. The antibiotics that proved least effective in treating these infections were aminopenicillins (ampicillin, augmentin) and cephalosporins (**Table 4**). On a global scale, there is growing concern over the rise in resistance among enterobacterial strains, particularly those resistant to extended-spectrum beta-lactamase (ESBL) and carbapenems, which is also increasingly observed in children. Common risk factors for such resistance include frequent antibiotic use, chronic conditions, healthcare-associated infections, and neurological diseases in children [25].

Table 4. Resistant rate for the major Enterobacterales isolated

	Resistant rate for	
	***Klebsiella* sp.**	***E. coli***
Imipenem	5 %	1 %
Meropenem	6 %	1 %
Amikacin	10 %	-
Ertapenem	14.40 %	2 %
Levofloxacin	14.50 %	4.20 %
Norfloxacin	20 %	6.50 %
Ciprofloxacin	22.70 %	6 %
Cefoxitin	28 %	1.85 %
Tobramycin	31.50 %	12.80 %
Gentamicin	40 %	9.30 %
Cefepime	46.20 %	13.80 %
Ceftriaxone	46.30 %	27 %
Cefotaxime	49.30 %	11.90 %
Ceftazidime	51 %	12.10 %
Cefuroxime	55.40 %	15 %
Cefazolin	70 %	25.20 %
Augmentin	94 %	75 %

Ampicillin	-	83 %

The resistance rates of *Escherichia coli* strains to cephalosporins varied across different generations, with the first generation showing the highest resistance at 25.2%, and the second generation at 8.57%. In our study, the resistance to third-generation cephalosporins averaged 12.13%, which is lower than the national average of 20.3% [9].

EARS-Net data indicate a concerning trend in Europe regarding *Escherichia coli* resistance to aminopenicillins, third-generation cephalosporins, fluoroquinolones, and aminoglycosides. For 2019, Europe reported a resistance rate of 15.1% to third-generation cephalosporins, which is lower than the rate observed in our study [9].

The resistance of *Escherichia coli* to fluoroquinolones in Europe averages around 23.8%, while Romania reports a higher rate of 28.3% [9]. In contrast, the strains we studied exhibited fluoroquinolone resistance levels between 4.2% and 6.5%, which are notably lower (**Figure 1**). The resistance of *E. coli* to aminoglycosides ranged from 9.3% to 12.8%, with an average of 11.05%, which is comparable to the national average of 11.6%. Carbapenem resistance was less than 2% in our study, which is higher than the national (0.6%) and European (0.3%) averages [9].

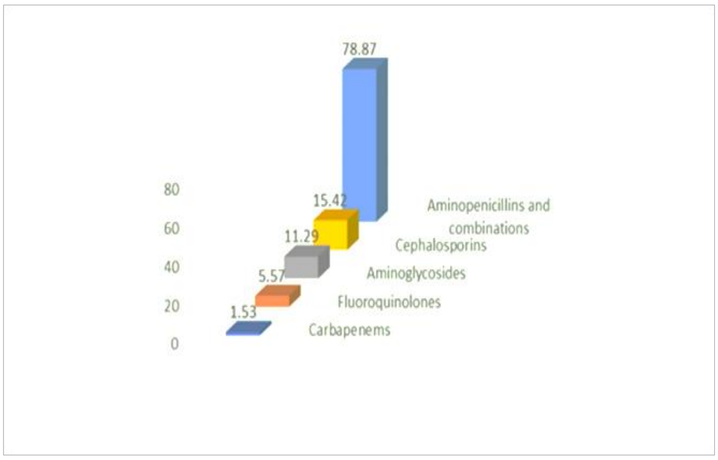

Figure 1. The classes of antibiotic resistance rates of *Escherichia coli* strains

Klebsiella pneumoniae is a significant public health issue due to its role in the development of carbapenem resistance, a phenomenon that has spread through *Enterobacteriaceae*. The emergence of carbapenem-resistant *Klebsiella* strains presents a serious challenge for infection treatment, as therapeutic options are extremely limited. In our study, resistance patterns in *Klebsiella* species were similar to those observed in *E. coli*, particularly concerning aminopenicillins and related combinations (**Table 4**).

Resistance to cephalosporins in *Klebsiella* strains was high, with an average of 49.4%. Resistance rates ranged from 41.7% for second-generation cephalosporins to 70% for first-generation cephalosporins. Third-generation cephalosporins, including cefotaxime, ceftazidime, and ceftriaxone, showed an average resistance rate of 48.8%, which is higher than the European rate of 31.3%, but lower than the national resistance rate of 64.1% [9].

The resistance to fluoroquinolones in *Klebsiella* strains was 19%, with ciprofloxacin resistance at 22.7%, levofloxacin at 14.5%, and norfloxacin at 20%. The resistance of *Klebsiella pneumoniae* to aminoglycosides was 40% for gentamicin, 31.5% for tobramycin, and 10% for amikacin. This variation in resistance is explained by the slightly superior in vitro efficacy of amikacin over gentamicin.

In 2019, the highest resistance rates across Europe were recorded for third-generation cephalosporins (31.3%), followed by fluoroquinolones (31.2%), aminoglycosides (22.3%), and carbapenems (7.9%) [9]. Our findings indicated higher resistance across all these antibiotic classes, except for aminoglycosides.

Pseudomonas aeruginosa is a major contributor to nosocomial infections, such as pneumonia and urinary tract infections, and is known for its intrinsic resistance to many antibiotics. This bacterium's resistance to fluoroquinolones, aminoglycosides, and beta-lactams has significant implications for treatment, as few antibiotics are effective. In our study, the resistance of *Pseudomonas aeruginosa* to beta-lactams ranged from 5.5% for piperacillin-tazobactam, 16% for ceftazidime, to 22.8% for cefepime (**Figure 2**).

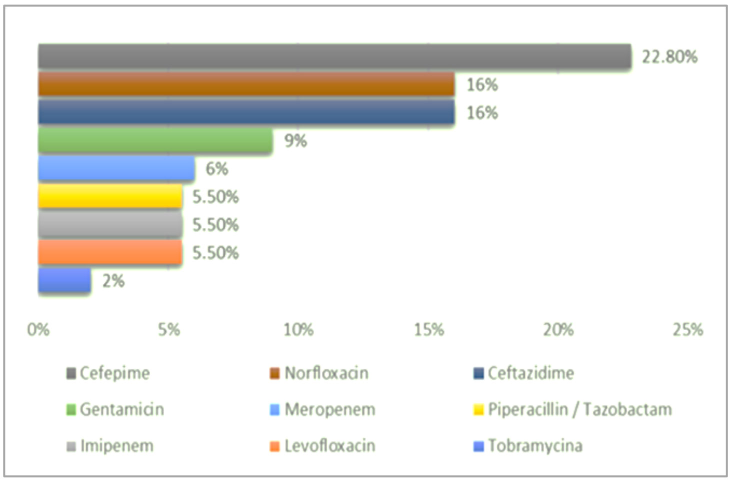

Figure 2. Rates of antibiotic resistance of *Pseudomonas aeruginosa* strains

Antibiotic resistance in *Pseudomonas aeruginosa* strains, particularly to fluoroquinolones, was observed to differ based on the specific antibiotic tested. While ciprofloxacin exhibited full sensitivity (100%), norfloxacin resistance was detected at a rate of 16%.

Between 2015 and 2019, a downward trend in *Pseudomonas aeruginosa* resistance was recorded across all antibiotic classes in Europe, with particularly high resistance and combined resistance levels seen in Eastern and Southeastern Europe. In 2019, resistance was highest for fluoroquinolones (18.9%), followed by piperacillin + tazobactam (16.9%), carbapenems (16.5%), ceftazidime (14.3%), and aminoglycosides (11.5%) [9]. However, in our study, resistance was found to be lower than the European average: fluoroquinolones (10.7%), piperacillin + tazobactam (5.5%), carbapenems (5.7%), ceftazidime (16%), and aminoglycosides (5.5%).

Glycopeptide resistance, though historically low in Europe, has started to rise in recent years. Romania has been one of the few countries where glycopeptides remained largely effective against enterococci. However, resistant strains have become more prevalent. In our research, glycopeptide resistance was observed at 2% for vancomycin, 10% for teicoplanin, and 23% for gentamicin. Prolonged use of linezolid has been linked to resistance development. Despite ampicillin showing strong in vitro effectiveness (90% susceptibility), clinicians often avoid prescribing it, preferring glycopeptides or linezolid, which worsens the resistance problem. In our study, 5% of strains exhibited resistance to linezolid. A study has suggested that the use of beta-lactam/beta-lactamase inhibitors (BLBLIs) could reduce resistance development [26].

Conclusion

The issue of multidrug-resistant (MDR) bacteria remains a pressing public health challenge, including in children. In our study, the majority of isolated strains were from children aged 0-4 years. Resistance rates varied from 0% for *Pseudomonas aeruginosa* to ciprofloxacin to 49.4% for *Klebsiella* sp. against cephalosporins. While the resistance rates were lower than those recorded in some national studies, they were still higher than the European average. This is especially concerning given the pediatric focus of our study, where many children under 9 years old were affected. The main route for the spread of resistant bacteria remains healthcare-associated infections, often due to overuse of antibiotics, surgical procedures, and exposure to resistant strains. Immediate steps must be taken to enhance diagnosis, treatment, and research in this critical area.

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References

1. Golkar Z, Bagasra O, Pace DG. Bacteriophage therapy: a potential solution for the antibiotic resistance crisis. J Infect Dev Ctries. 2014;8(2):129-36.
2. Gould IM, Bal AM. New antibiotic agents in the pipeline and how they can help overcome microbial resistance. Virulence. 2013;4(2):185-91.
3. Wright GD. Something old, something new: revisiting natural products in antibiotic drug discovery. Can J Microbiol. 2014;60(3):147-54.
4. Sengupta S, Chattopadhyay MK, Grossart HP. The multifaceted roles of antibiotics and antibiotic resistance in nature. Front Microbiol. 2013;4:47.
5. Centers for Disease Control and Prevention, Office of Infectious Disease Antibiotic resistance threats in the United States, 2019.
6. WHO. New report calls for urgent action to avert antimicrobial resistance crisis. Available from: https://www.who.int/news/item/29-04-2019-new-report-calls-for-urgent-action-to-avert-antimicrobial-resistance-crisis.
7. Alzaid A, Alosaimi M, Alkahtani KF, Alshehri BA, Asiri AE, Asiri AM, et al. Saudi Parents' Knowledge, Attitudes, and Practices Regarding Antibiotic use for Upper Respiratory Tract Infections in Children. Int J Pharm Res Allied Sci. 2020;9(1):115-20.
8. Antimicrobial Resistance and causes of (non-prudent) use of Antibiotics in human medicine in the EU ARNA, April 2016. Available from: http://www.srm.ro/pdf/1.CDM-Romania_Ann_26%20April%202016+PPS.PDF
9. Antimicrobial resistance in the EU/EEA (EARS-Net) - Annual Epidemiological Report for 2019. Available from: https://www.ecdc.europa.eu/en/publications-data/surveillance-antimicrobial-resistance-europe-2019) Surveillance report, 2020.
10. Huynh CT, Nguyen TT, Vo TQ, Le TT, Nguyen TD, Nguyen SH, et al. Trends in the Use of Surgical Antibiotic Prophylaxis at a Provincial Hospital in Vietnam. Arch Pharm Pract. 2020;11(1):32-9.
11. Dorobanțu FR, Hodoșan V, Tîrb AM, Zaha DC, Galușca D, Pop NO, et al. Pattern of Newborn Antibiotic Use in a Tertiary Level Maternity for Five Years. Pharmacophore. 2022;13(3):57-63. doi:10.51847/pq4Px0rkxG
12. Hodoșan V, Daina CM, Zaha DC, Cotrău P, Vladu A, Pantiș C, et al. Pattern of Antibiotic Use in the Perinatal Period in a Public University Hospital in Romania. Medicina (Kaunas). 2022;58(6):772. doi:10.3390/medicina58060772
13. Ralston SL, Lieberthal AS, Meissner HC, Alverson BK, Baley JE, Gadomski AM, et al. American Academy of Pediatrics. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. Pediatrics. 2014;134(5):e1474-502.
14. Messinger AI, Kupfer O, Hurst A, Parker S. Management of pediatric community-acquired bacterial pneumonia. Pediatr Rev. 2017;38(9):394-409.
15. Jain S, Williams DJ, Arnold SR, Ampofo K, Bramley AM, Reed C, et al. CDC EPIC Study Team. Community acquired pneumonia requiring hospitalization among U.S. children. N Engl J Med. 2015;372(9):835-45.
16. Bradley JS, Byington CL, Shah SS, Alverson B, Carter ER, Harrison C, et al. Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. Clin Infect Dis. 2011;53(7):e25-76.
17. Neuman MI, Hall M, Lipsett SC, Hersh AL, Williams DJ, Gerber JS, et al. Utility of Blood Culture Among Children Hospitalized With Community-Acquired Pneumonia. Pediatrics. 2017;140(3):e20171013.
18. Stein R, Dogan HS, Hoebeke P, Kočvara R, Nijman RJ, Radmayr C, et al. Urinary tract infections in children: EAU/ESPU guidelines. Eur Urol. 2015;67(3):546-58.
19. Alamarat Z, Hasbun R. Management of Acute Bacterial Meningitis in Children. Infect Drug Resist. 2020;13:4077-89. doi:10.2147/IDR.S240162
20. Cruz AT, Lane RD, Balamuth F, Aronson PL, Ashby DW, Neuman MI, et al. Updates on pediatric sepsis. J Am Coll Emerg Physicians Open. 2020;1(5):981-93. doi:10.1002/emp2.12173
21. Zaha DC, Zdrinca MM, Vesa CM, Daina LG, Daina MC. A six-year evaluation of sepsis in neonates. Rom Biotechnol Lett. 2020;25(5):1892-8. doi:10.25083/rbl/25.5/1892.1898
22. Performance Standards for Antimicrobial Susceptibility Testing. 30th ed. Clinical and Laboratory Standards Institute. 2020.

23. Dortet L, Poirel L, Nordmann P. Worldwide dissemination of the NDM-type carbapenemases in Gram-negative bacteria. Biomed Res Int. 2014;2014:249856.
24. Zerr DM, Weissman SJ, Zhou C, Kronman MP, Adler AL, Berry JE, et al. The Molecular and Clinical Epidemiology of Extended-Spectrum Cephalosporin- and Carbapenem-Resistant Enterobacteriaceae at 4 US Pediatric Hospitals. J Pediatric Infect Dis Soc. 2017;6(4):366-75.
25. Popescu GA, Șerban R, Pistol A. Consumul de antibiotice, Rezistența microbiană și Infecții Nosocomiale în România. București. 2014.
26. Mansy W, Rathod S. Temporal association between antibiotic use and resistance in Gram-negative bacteria. Arch Pharma Pract. 2020;11(2):13-8.