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AETIOLOGY OF BACTERIAL INFECTIONS AND ANTIBIOTIC RESISTANCE IN PEDIATRIC PATIENTS FROM A ROMANIAN HOSPITAL

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ABSTRACT

The development of microorganism resistance to antibiotics is a topic of global interest and Romania is among the most vulnerable countries in terms of antimicrobial resistance. Our retrospective study was carried out for a year at the Emergency Clinical Hospital for Children "Saint John" in Galati, on a number of 9910 pathological samples. The main isolated strains were *Staphylococcus aureus*, *Escherichia coli*, and *Klebsiella pneumoniae*. A percent of 25.4 was methicillin-resistant *Staphylococcus aureus* infections and strains displayed high rates of resistance to beta-lactams and macrolides. Less effective for the treatment of infections with *Escherichia coli* were aminopenicillins and cephalosporins although resistance to third-generation cephalosporins had a relatively small value than the national one. Isolated *Escherichia coli* strains showed low resistance to fluoroquinolones and aminoglycosides also. *Klebsiella* sp strains showed increased resistance to third-generation cephalosporins, fluoroquinolones, and aminoglycosides higher than the values recorded at the European level. Results obtained in terms of antibiotic resistance are lower than those recorded in some studies at a national level but higher than the European average. The situation remains worrying if we consider the fact that the selected group is a pediatric one, with most children under nine years. More than ever, we must take active measures in perspective about the seriousness of the problem and the long-term consequences.

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Introduction

The development of microorganism resistance to antibiotics is a problem of global interest, which endangers the effectiveness of antibiotic treatments, quality of life, or survival of some patients. Only 70 years after the introduction of antibiotics, we are facing the possibility that soon they will no longer have an effect. For this reason, bacterial infections can again become a threat due to excessive and inappropriate use of antibiotics, as well as the relatively slow pace of development of new drugs [1-5]. It is estimated that globally at least 700,000 deaths a year have been associated with antimicrobial resistance, with the prospect of alarming growth to around 10 million per year in the coming years, if effective strategies are not implemented to curb the current trend [6]. In a study conducted in Saudi Arabia it was shown that 50% of the participants preferred antibiotics as their best option for the management of the infections among their children notwithstanding the fact that 76 % of them know that the use of antibiotics is linked with negative effects on the body systems, particularly hepatotoxicity [7].

In Europe, antimicrobial resistance has become a severe threat to public health and patient safety, leading to high healthcare costs, treatment failures, and even worse, many deaths. In 2009, the economic losses due to this were estimated at 1.5 billion Euro and the estimated deaths at 25 000. Currently, with the increase in antimicrobial resistance, these estimates are far exceeded [8].

Romania is among the most vulnerable countries in terms of antimicrobial resistance. There were significant increases in the incidence of infections with two bacterial strains between 2015-2019 and it was in the most unfavorable positions for two

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other strains among the reporting countries of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Also in 2019, Romania was in a critical position regarding the total consumption of antibiotics - the most unfavorable situation after Greece and Cyprus, out of a total of the same 30 countries [9]. the use of surgical antibiotic prophylaxis at the hospital was not based on the recommendations of clinical practice guidelines [10].

According to the same EARS-Net data, the main strains isolated in Europe were *Escherichia coli* (44.2%), followed by *Staphylococcus aureus* (20.6%), *Klebsiella pneumoniae* (11.3%), *Enterococcus faecalis* (6.8%), *Pseudomonas aeruginosa* (5.6%), *Streptococcus pneumoniae* (5.3%), *Enterococcus faecium* (4.5%) and *Acinetobacter* species (1.7%). The trend of increasing resistance was mainly shown by *Klebsiella* sp to carbapenems and fluoroquinolones, *Escherichia coli* to the third generation of cephalosporins, and less frequently to carbapenems and *Enterococcus faecium* to vancomycin. *Pseudomonas aeruginosa* and *Acinetobacter* species showed stationary carbapenem resistance. MRSA *Staphylococcus aureus* showed mild reductions in incidence, but combined resistance is common, raising serious therapeutic issues. Decreases during the same period were also noted for non-wild type penicillin and macrolide resistance in *Streptococcus pneumoniae* [9].

The same strains raise therapeutic problems in Romania, even if the reported data are not rigorous. *Escherichia coli* have high rates of resistance to fluoroquinolones, *Klebsiella pneumoniae* to the third generation of cephalosporins and carbapenems, and a percentage of invasive isolates resistant to methicillin (MRSA) and vancomycin-resistant *Enterococcus faecium* above European average [9].

After genetic diseases, pediatric infectious pathology is common, the prescription of antibiotics is much more common, and the approach to these infections is similar to that of adults [11, 12]. Viral etiology is often found in children and in some types of pathologies, which is why the administration of antibiotics is useless and contraindicated. The recommended therapeutic measures are hydro-electrolytic rebalancing, O2 administration, and symptomatic.

Respiratory infections are common in children regardless of age. Community-acquired pneumonia is a common cause of hospitalization, and its etiology in the first two years of life is in over 90% of viral cases, involving respiratory syncytial virus, influenza virus types A and B, and other viruses. The bacterial etiology of pneumonia is represented by *Streptococcus pneumoniae* also found in adults, *Streptococcus pyogenes* and *Staphylococcus aureus* commonly isolated in patients who require hospitalization or complications of viral pneumonia, *Haemophilus influenzae*, and *Moraxella catarrhalis*. It is worth mentioning the rapid, unfavorable evolution with pleural collections that pneumonia with *Staphylococcus aureus* and *Streptococcus pyogenes* may present [13, 14]. Atypical pathogens are less involved in children younger than school age, but *Mycoplasma pneumoniae* is a major player in children of school age or older [15, 16]. Unfortunately, only a small percentage of samples reveal the causative pathogen [17].

UTIs are the most common bacterial infection in children less than two years of age. As in adults, a definite diagnosis of UTI in children requires a positive urine culture from an appropriate urine sample. The etiology of urinary tract infection is similar when comparing adults with children, *Escherichia coli* has been reported in several studies [18]. *Klebsiella* or *Proteus* species and gram-positive cocci are rarely isolated from patients with UTIs.

Symptoms of meningitis may be nonspecific, especially in children, and clinical presentation is variable. Viruses account for more cases of meningitis and the most common viral pathogen isolated is an enterovirus, but the etiology depends on the age of the patient. Early-onset neonatal bacterial type of meningitis is usually caused by the transfer of pathogens in utero or during vaginal delivery such as *Streptococcus agalactiae, Escherichia coli, and Klebsiella* species while late-onset neonatal one and meningitis in all other pediatric age groups are more likely to be caused by community-acquired pathogens such as *Streptococcus pneumoniae, Neisseria meningitides, Haemophilus influenzae, Listeria monocytogenes, Escherichia coli* [19].

The diagnosis of sepsis in children can be a challenge, taking into account the high prevalence of common febrile conditions, and poor specificity of clinical signs. The most common sites of infection in pediatric sepsis are bacteremia (primary), respiratory, genitourinary, and central nervous system and isolated pathogens are *Staphylococcus aureus, Escherichia coli*, but in a large proportion of cases, no pathogen was identified [20, 21].

Antimicrobial therapy is also prescribed for acute osteoarticular and skin infections in children. Acute osteoarticular and skin infections are not uncommon infections in children and could be responsible for the development of resistance.

The choice of empirical therapy should be based on the most likely pathogens and knowledge of local susceptibility, as well as host-specific factors such as immune status, associated conditions, or previous illnesses. Considering all these, we considered of interest the study on antibiotic resistance in pediatric infectious pathology, considering the effects caused by this problem on all medical specialties and the complications that the medical act generates.

Materials and Methods

Our study is a retrospective one and took place between January and December 2019 at the Emergency Clinical Hospital for Children "Saint John" in Galati, Romania on some 9910 pathological samples: feces, urine culture, blood, pus, vaginal discharge, secretion nasal, laryngeal-tracheal secretion, otic secretion and urethral secretion collected from hospitalized patients aged 0-18 years. Data were provided by the hospital's computer system, the medical reports from a laboratory, and the hospital archive. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the Emergency Clinical Hospital for Children "Saint John" from Galati (no 68/2020).

The collection of the samples was performed before the beginning of the antibiotic treatment, with the condition of the asepsis measures and by specific methods for each product. The samples were transported to the microbiology laboratory where they were seeded on a culture medium. The bacteriological diagnosis was based on cultural characteristics, microscopic examination - GRAM staining, and biochemical tests. Isolation in pure culture of bacteria of the genus *Escherichia coli*, *Klebsiella,* and *Pseudomonas* spp was made on AABTL lactose agar medium (Blue Bromine Thymol Lactose Agar), on blood agar, on MacConkey medium. Blood agar and Chapman mediums were used to isolate bacteria of the genus *Staphylococcus aureus* and for the genus *Enterococcus* - blood agar and ABE medium. The identification of the studied Gram-negative bacilli was performed based on cultural and biochemical characters on a multitest culture medium (MIU, TSI, Simmons, MILF). The Kirby-Bauer method was used to determine antibiotic sensitivity, and the results were read by measuring the diameters of the growth inhibition zones caused by different antibiotics using a standard inoculum of 0.5 McFarland. The interpretation of the results as well as the quality control were performed according to CLSI 2020 [22].

Results and Discussion

Of the total of 9910 pathological samples collected corresponding to our pediatric patients, some 1606 samples were positive which corresponds to a positivity rate of 16.20%. The distribution of the group studied by sex shows approximately equal percentages, with a slight share of females (52%) compared to males (48%). One cause of the difference is the presence in the study group of the female-specific sample - vaginal discharge. A higher incidence of infections was 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 year	5-9 year	10-14 year	15-18 year
Number of samples (%)	821 (51%)	354 (22%)	191 (12%)	240 (15%)

Of the total positive samples, the majority were nasal exudates (46.45%), followed by feces cultures (14.88%), urine cultures (12.51%), and tracheal laryngeal secretions (11.2%). Lower percentages were recorded for pus (4.91%), vaginal (4.48%), ear (4.23%), and urethral (1.3%) secretion.

The etiology of infections in children was mainly given by *Staphylococcus aureus*, isolated mainly from nasal exudate samples, in which this bacterium is most frequently isolated, but also from ear secretions. Genitourinary tract infections had *Escherichia coli* as the main etiological agent. *Klebsiella* sp was isolated mainly from laryngotracheal secretions as well as from feces. Pus from skin infections had *Staphylococcus aureus* and *Escherichia coli* as etiological agents **(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 common pathogen isolated from samples. Staphylococcal infections can progress unfavorably due to increased aggression of the bacterial strain, compromised patient's ability to defend against infection, or difficulty in treating an infected patient with an antibiotic-resistant strain. Because beta-lactams are the most commonly used antibiotics in medical practice, most studies have investigated the ability of staphylococci to resist the action of these antibiotics: the synthesis of beta-lactamases (they inactivate penicillin and ampicillin) and the change in target structure (methicillin-staphylococcus aureus resistant - able to withstand the action of any beta-lactam, including "ant staphylococcal" penicillins). Depending on the staphylococcal response to beta-lactamides, it is divided into MSSA (penicillin and oxacillin-sensitive or penicillin-resistant and oxacillin-sensitive - if it is a beta-lactamase-producing MSSA) and MRSA (penicillin and oxacillin-resistant) resistant to all beta-lactams. In our study, 25.4% of the isolated strains were MRSA (higher than the European average of 15%) with resistance rates ranging from 2% for quinolones and linezolid to 95% for penicillin **(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%

Evaluation of *Staphylococcus aureus* strains' resistance by classes showed high rates of resistance to beta-lactams and macrolides. In contrast, in the case of fluoroquinolones, it was observed that most strains were sensitive to them, the resistance registering values below 4% for all antibiotics in this class, as well as in the case of aminoglycosides, as well as in the case of linezolid (2%. Such a low resistance of linezolid can be explained by the less frequent prescription, as it is an antibiotic considered a reserve and used only in infections with multi-drug resistant bacteria and in nosocomial infections [23, 24].

In the last three decades, there has been a steady increase in the incidence of infections with *Enterococcus* species. having an intrinsic resistance to various categories of antibiotics, such as cephalosporins and aminoglycosides at clinically used doses. In addition, they can acquire relatively easily, including by transferring gene fragments from other species, mechanisms of resistance to penicillin, glycopeptides, and aminoglycosides. Penicillin resistance is most often caused by changes in target proteins and extremely rarely by the production of beta-lactamases, which translates clinically into a lack of a benefit of the combinations of penicillin with beta-lactamase inhibitors (ampicillin-sulbactam, amoxicillin-clavulanate) compared to aminopenicillins. In our study, sensitivity to penicillins is still good, with 76% for ampicillin and 75% for penicillin **(Table 3)**.

Escherichia coli strains were identified as the main etiological agent of urinary tract infections in children in our study. The less effective were aminopenicillins (ampicillin, augmentin) and cephalosporins **(Table 4)**. There is a worrying global trend of increasing the number of enterobacterial strains –ESBL and carbapenem resistance including in pediatric patients because the risk factors are the same: antibiotic use, chronic and recurrent diseases, healthcare infections plus 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 values of resistance of *Escherichia coli* strains to cephalosporins recorded different percentages, depending on the generation of which the antibiotic is part, from 8.57% for the second generation to 25.2% for the first generation of cephalosporins. In our study, we calculated, on average, a resistance of 12.13% for third-generation cephalosporins -a relatively small value than the national one (20.3%) [9].

According to EARS-Net data, the resistance of *Escherichia coli* to aminopenicillins, generation III cephalosporins, fluoroquinolones, and aminoglycosides is worrying in Europe. For 2019, Europe had a resistance percentage to third-generation cephalosporins of 15.1%, lower compared with our study [9].

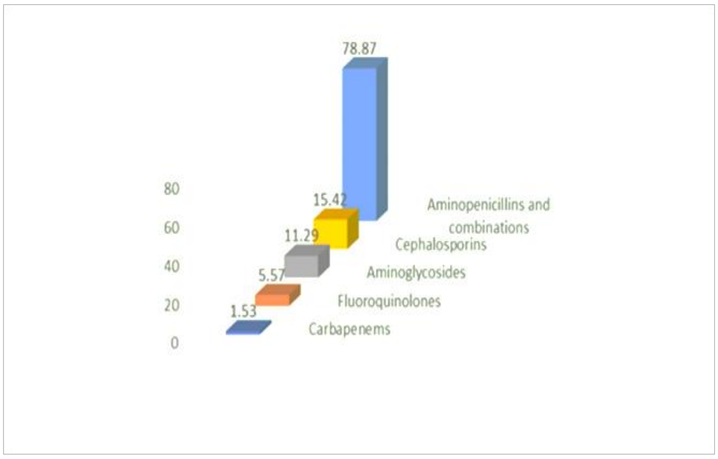

Figure 1. Classes of antibiotic resistance rates of *Escherichia coli* strains

Quinolone resistance at the European level shows that the percentage of fluoroquinolone-resistant *Escherichia coli* isolates is around 23.8% and Romania has an average of 28.3% [9]. The strains isolated from the patients in our group showed resistance to fluoroquinolones between 4.2% and 6.5%, i.e. lower values **(Figure 1)**. The resistance to aminoglycosides of *Escherichia coli* strains varied between 9.3% and 12.8% with an average of 11.05%, and the national resistance was 11.6%. Resistance to carbapenems was below 2%, but higher than those recorded at the national level (0.6%) or European level (0.3%) [9].

Klebsiella pneumoniae is a major public health problem related to bacterial resistance to antibiotics, as it is a "laboratory" for the production of new carbapenemases, subsequently transmitting to other Enterobacteriaceae the genetic material that encoded it. By expanding the circulation of carbapenem-resistant strains, a major problem has arisen related to the treatment of infections, which they cause because the therapeutic alternatives are extremely limited. Strains of *Klebsiella pneumoniae* sp showed resistance rates similar to those of *E. coli* for aminopenicillins and combinations **(Table 4)**.

Analyzing the results of antibiograms performed for *Klebsiella* sp, an increased global resistance was found for almost all generations of cephalosporins (49.4%). Resistance values ranged from 41.7% for the second to 70% for the first generation of cephalosporins. *Klebsiella* sp strains showed third-generation cephalosporins (cefotaxime, ceftazidime, ceftriaxone) also represented an increased resistance, on average 48.8%. The value obtained was higher than the results recorded at the European level where the resistance of *Klebsiella* sp strains to cephalosporins is 31.3%, but lower than the national level (64.1%) [9].

The study of the resistance of *Klebsiella* sp strains to fluoroquinolones in our group reveals an overall resistance rate of 19%. Resistance to ciprofloxacin was 22.7%, to levofloxacin 14.5% and norfloxacin 20%. Evaluation of the resistance of *Klebsiella pneumoniae* strains to aminoglycosides showed a resistance rate of 40% to gentamicin, 31.5% to tobramycin, and 10% to amikacin. The discordant results (amikacin sensitivity and gentamicin resistance) are because amikacin is slightly superior in vitro to gentamicin.

In 2019, the highest EU/ EEA population-weighted mean resistance percentage was reported for third-generation cephalosporins (31.3%), followed by fluoroquinolones (31.2%), aminoglycosides (22.3%) and carbapenems (7.9%) [9]. In our study, antibiotic resistance was higher for all of these classes of antibiotics except aminoglycosides.

Pseudomonas aeruginosa has been identified as one of the major causes of nosocomial pneumonia, nosocomial urinary tract infections, or systemic infections. *Pseudomonas aeruginosa* has intrinsic resistance to most classes of antibiotics (due to the difficult-to-cross outer membrane). Antibiotics with activity against the pyocyanin bacillus are fluoroquinolones, aminoglycosides, and beta-lactams. Being few, any newly acquired resistance mechanism drastically limits the existing therapeutic options. Its in-hospital presence was associated with repeated exposure to antibiotics, which led to the selection of resistant strains, including reserve antibiotics (carbapenems). Resistance of *Pseudomonas aeruginosa* to beta-lactams in our study has slightly increased values, from 5.5% for piperacillin-tazobactam, to 16% for ceftazidime and 22.8% for cefepime **(Figure 2)**.

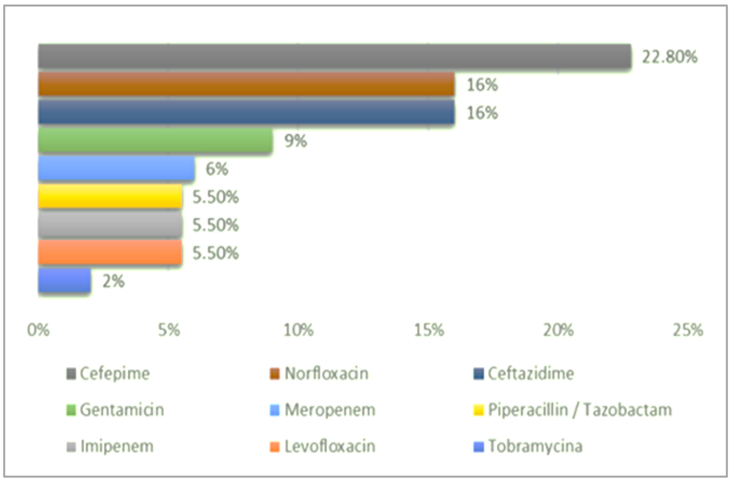

Figure 2. Rates of antibiotic resistance of *Pseudomonas aeruginosa* strains

The fluoroquinolone resistance of *Pseudomonas aeruginosa* strains recorded different values depending on the antibiotic tested in this class; in the case of ciprofloxacin, the sensitivity was 100%, less sensitive were the strains of *Pseudomonas aeruginosa* to norfloxacin with a resistance rate of 16%.

In Europe, for the same *Pseudomonas aeruginosa*, between 2015 and 2019 trends decreased significantly for all antimicrobial groups under surveillance. High resistance percentages and combined resistance persisted in many countries, especially in the eastern and southeastern parts of Europe. In 2019 the highest percentage of resistance was reported for fluoroquinolones (18.9%), followed by piperacillin + tazobactam (16.9%), carbapenems (16.5%), ceftazidime (14.3%) and aminoglycosides (11.5%) [9]. The values obtained in our study were below the European average: fluoroquinolones (10.7%), piperacillin + tazobactam (5.5%), carbapenems (5.7%), ceftazidime (16%), and aminoglycosides (5.5%).

Resistance to glycopeptides has been described for more than three decades, but its frequency in isolates in Europe has been extremely low until recent years. One of the few positive things in the field of bacterial resistance to antibiotics in Romania so far has been maintaining the efficiency of glycopeptides on enterococci at a level close to 100%. Unfortunately, resistant strains have emerged and have grown in number in recent years. In our study, glycopeptide resistance was 2% for vancomycin and 10% for teicoplanin and gentamicin (23%). Prolonged exposure to linezolid may cause resistance. Although the in vitro activity of ampicillin is still very good (90% of susceptible strains), clinicians are reluctant to prescribe this useful, inexpensive, and weak bacterial resistance-inducing antibiotic, still preferring glycopeptides or linezolid, which continues to exacerbate the problem of bacterial resistance to these reserve antibiotics. In our study, of the total strains tested, 5% had resistance to linezolid. The results of a study suggested that to maintain the potential of resistance of the strains not to develop, usage of BLBLIs has been recommended to minimize clinical practices [26].

Conclusion

Resistant multidrug bacteria (MDR) are recognized as one of the most important current public health problems even among children. In our study, most isolated strains were from children aged 0-4 years. Resistance values ranged depending on bacterial strain and antibiotic from 0% resistance of *Pseudomonas aeruginosa* strains to ciprofloxacin to a significant 49.4% resistance of *Klebsiella* sp to cephalosporins. In general, the results obtained in terms of antibiotic resistance are lower than those recorded in some studies at a national level but higher than the European average. This is a worrying thing if we consider the fact that the selected group is a pediatric one, with a majority of children under 9 years old and the exposure of a child of few months/years to the factors that determine the appearance of resistance is debatable. The main route of transmission of resistant bacteria is represented by infections associated with medical care, i.e. exposure to prolonged, inappropriate antibiotic therapy, minimally invasive and surgical maneuvers, or infection with a resistant strain. This situation is worrying if we think in perspective about the seriousness of the problem and the long-term consequences. More than ever, concrete steps must be taken to properly diagnose and treat infections, implement new policies to manage the crisis, and renew research efforts.

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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.