Antibiotic Molecules Efficacy in Pediatric Bacterial Infections

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The antibiotic resistance of microorganisms involved in pediatric infections represents a significant cause of healthcare-associated infections (HAIs), and is also a matter of management, requiring specific intervention. The aim of the study was to evaluate the efficacy of some antibiotic molecules on pathogens isolated from patients admitted in a pediatric hospital. We carried out a descriptive study on a group of 411 patients admitted to the Sf. MariaClinical Emergency Hospital for Children Iasi, between January 1st and March 31st, 2016. Bacterial infections were most prevalent in the age group of 0-1 year (54.98% of the total isolates). Most affected by multidrug-resistant bacterial infections services were: general pediatrics (24.08% of the total isolates), then the intensive care unit (19.95%), surgical wards (14.84%), and acute therapy (11.43%). The germs were isolated from pathological samples: most often pus (23.85%), hypo-pharyngeal aspiration (21.65%), conjunctival secretion (12.42%), and ear secretion (9.48%). Penicillin G and oxacillin were inefficient in 30.26% of the Staphylococcus aureus strains, while erythromycin in 18.42%. Antibiotic resistance of Streptococcus pneumoniae was observed for penicillin G in 7.14% of the strains, while for erythromycin in 13.09%. Klebsiella pneumoniae strains were resistant to amoxicillin + clavulanic acid in 35.85% of the cases, and to cefuroxime, ceftazidime, ceftriaxone, cefepime in 33.96%. Our study highlighted that Staphylococcus aureus was resistant to penicillin G and oxacillin in more than one-third of the isolates, Streptococcus pneumoniae was resistant to penicillin G and erythromycin, and Klebsiella pneumoniae to amoxicillin + clavulanic acid and 1st, 2nd and 3rd generation cephalosporins. Continuing antibioresistance monitoring is crucial in order to promote appropriate guidelines in antibiotic prescription, which could result in decreasing HAIs' rates.

Keywords*: antibiotic molecules, multidrug resistant (MDR) bacteria, healthcare-associated infections (HAIs)*

The increasing prevalence of antibiotic-resistant pathogenic bacterial infections is one of the major issues for clinical practice in all medical and surgical fields nowadays. Healthcare-associated infections (HAIs) because of multi-resistant bacteria are important causes of morbidity and mortality, leading to an increased financial burden for healthcare institutions, with a major impact on the quality of life of patients, and also on health systems and society as a whole [1-7].

Over the past two decades, antibiotic resistance, especially for Gram negative bacteria, has grown at an alarming rate, requiring a continuing concern for solving and controlling this extremely important therapeutic aspect in any medical department, but especially in areas of intensive care units (ICU), neonatology, pediatrics, burn units, and in immunosuppressed patients. Specialists noted a particular concern for the resistance of *Enterobacteriaceae* to third generation cephalosporins and to aztreonam, with a resistance profile commonly associated with extended-spectrum β-lactamase (ESBL) expression. This enzyme family was identified in the 1980's and provides resistance to almost all â-lactam antibiotic molecules, except for carbapenems and cephamycins. Genes encoding ESBL are found on plasmids that also carry other antibiotic resistance genes, which cause ESBL-producing strains to be multidrug resistant (MDR). In addition to ESBLs, resistance to extended-spectrum â-lactamase-producing *Enterobacteriaceae* is increasingly provided by other chromosomally encoded plasmid enzymes such as carbapenemases and AmpC cephalosporinases. Such mobile genetic and molecular equipment of resistant bacteria has further complicated the detection of ESBL-producing species. Because of the limitations and variability of the tests and of the different reporting, resistance to third generation cephalosporins is used as a more reliable indicator for the real ESBL strain prevalence [1, 2, 8-11].

Recent reports of the Centers for Disease Control and Prevention (CDC) revealed that antimicrobial resistance is a serious problem requiring prompt and sustained action to ensure limitation and avoid extension of this issue. The National Health Safety Network (NHSN) reported that 4% of the pathogens identified from all HAIs were *Escherichia coli* or *Klebsiella spp* resistant to extended-spectrum cephalosporins, usually in multi-hospitalized patients with prolonged hospitalizations, resulting in higher hospitalization and higher mortality [11-16].

Antibiotics represent the most prescribed drugs in pediatric hospitals, children receiving antibiotics more frequently than any other type of pharmacological treatment. Excessive or inappropriate antibiotic prescription has increased the risk of bacterial strains that are resistant even to the third generation cephalosporins. The lack of specific pediatric clinical trials on the use of antibiotics has led to a lack of knowledge in the field worldwide. In a study on pediatric units, Nicolini G. *et al.* showed [17] that

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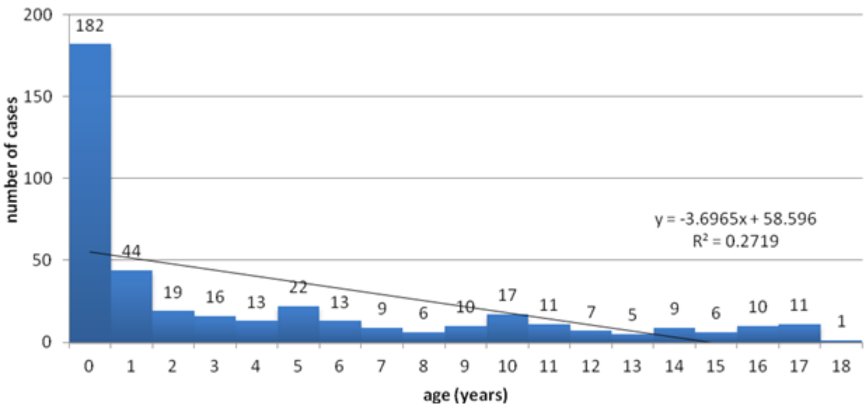

Fig. 1. Age histogram of the study group

the problem of increasing antibiotic resistance should be disclosed to all health professionals and even to general population. More frequent reviews of literature, as well as hospital guidelines, presenting the sensitivity and resistance of circulating microbial strains at least annually are also required. An antibiotic programme as a current practice in hospitals should also be considered. The use of existing antibiotics with updated specific guidelines could represent a key measure to avoid abusive use of antibiotics. Some Italian authors suggested the idea of using online educational tools for the general population as useful strategies for disseminating knowledge about antibiotic prescription and timing, aiming to limit self-medication, as well as preventing the emergence of resistant strains [11, 18].

Antibiotic prescription is increasing especially in pediatric patients, US statistics and reports showing that over 50 million antibiotic prescriptions are annually performed and more than one out of five pediatric ambulatory visits require prescription of antibiotics. Inappropriate antibiotic prescription, especially for upper respiratory tract infections in children, is common in outpatients, over 10 million prescriptions being annually reported in the USA. Prescription of broad-spectrum antibiotics increased recently, and was also found to be performed even when no antimicrobial therapy was required or when narrow-spectrum antibiotics could be prescribed. Such overuse of antibiotics leads to more side effects, contributes to the emergence and increase of antibiotic resistance and also to the multiplication of medical costs. Currently, new, but not numerous antibiotic molecules used to treat antibiotic-resistant infections are under development; therefore, the burden of antibiotic prescribing have to be limited, and, instead, appropriate antibiotherapy have to be promoted in practice in order to prioritize patient safety and improve healthcare management related to antimicrobial costs [19-21].

The aim of the study was to evaluate descriptively the antibiotic resistance of pathogens isolated from patients admitted in a pediatric hospital.

Experimental part

Study group and methods

The descriptive study was carried out on a group of 411 patients admitted to the Sf. Maria Clinical Emergency Hospital for Children Iasi, between January 1st and March 31st, 2016. The age groups were established according to the new internationally published regulations [22]. The exclusion criteria were the repetition of the same microbial agent in the same patient collected from various sites (in order not to overload the data), as well as the age over 18, because in the microbiology laboratory of the hospital there were also performed analyzes for adults as patients attendants and employees of the hospital. The data collection was performed using the hospital's statistic reports, hospital recordings and microbiological and epidemiological reports. The study was approved by the local Ethic Committee and was carried out in accordance to the mandatory principles of medical ethics [23-26]. Statistical processing was carried out using MS Excel 2010 and SPSS 20.0 software.

Results and discussions

The distribution of the cases by age groups showed that newborns and infants (0-1 year age group) prevailed (n = 182 cases, representing 44.29% of total isolates) (fig. 1). In the 0-1 year age group bacterial infections were most prevalent - more than half of the total number of samples (n = 226 isolates, representing 54.98%) (table 1).

In the order of the frequency of isolates, another age group often involved in MDR pathogens was that of pre-school children (2-5 years old), followed by the 6-11 years group, and 12-18 years group (table 1).

Table 1
DISTRIBUTION OF BACTERIAL STRAINS ISOLATES IN EACH STANDARD PEDIATRIC AGE GROUP

Age groups (years)	Bacterial strains	
	Number	%
0-1	226	54.98
2-5	70	17.03
6-11	66	16.06
12-18	49	11.93
Total	411	100.00%

Gender distribution revealed a predominance of boys (n = 230 isolates, representing 55.96% of the total), compared to girls (n = 181, representing 44.04%), with no significant statistical difference.

One of the major issues concerning the management level of HAIs was the distribution by the hospital wards from where the samples were collected. General pediatrics was most often involved with 99 samples (24.08%), while in the burn unit only 6 samples (1.45%) were collected (table 2).

The isolates with MDR microorganisms were collected from various pathological products, the most numerous, almost 1/4 of the total isolates, as expected, from pus (98 samples, representing 23.85%) of which 49 were taken from the wounds (11.92%), 42 from abscesses (10.22%), 5 from fistulas (1.21%) and 2 from sinuses (0.48%), as shown in table 3.

The MDR microorganisms identified in cultures isolates from various pathological samples collected from the pediatric patients enrolled in our study group are expressed in figure 2 and table 4. As expected, *Staphylococcus aureus*

Table 2
DISTRIBUTION OF BACTERIAL ISOLATES BY HOSPITAL WARDS

Ward	Isolates	
	Number	%
General Pediatrics	99	24.08
Intensive Care Unit	82	19.95
Surgery (general, orthopedics, neurosurgery)	61	14.84
Acute Therapy	47	11.43
Pneumology	33	8.03
Allergology	8	1.94
Cardiology	7	1.70
Burns	6	1.45
Toxicology	4	0.97
Pediatric rehabilitation	4	0.97
Nephrology	3	0.72
Hematology-oncology	1	0.24
Diabetes	1	0.24
Pediatric urology	1	0.24
Day-care hospitalization and ambulatory	32	7.85
Patients admission room	22	5.35
Total	411	100%

was the most frequent microorganism present in the collected pathological samples (isolated from 152 samples, representing 27.73%), followed by *Streptococcus pneumoniae, Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, *Haemophilus spp*, *Escherichia coli*.

The MDR microorganisms identified in cultures isolates from various pathological samples collected from the pediatric patients enrolled in our study group are expressed in figure 2 and table 4. As expected, *Staphylococcus aureus* was the most frequent microorganism present in the collected pathological samples (isolated from 152 samples, representing 27.73%), followed by *Streptococcus pneumoniae, Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, *Haemophilus spp*, *Escherichia coli*.

Antibiotic resistance is responsible for HAIs in over than 50% of the cases [27, 28]. Unfortunately, during the last decades, the development of new antibiotic molecules has not progressed in parallel with the increasing rates of common bacterial microorganisms' resistance, leaving fewer treatment options for MDR bacterial infections [28-31].

Concerning our study, we assessed the efficacy of some antibiotic molecules on the main bacterial strains collected from the patients of the study group (figs. 3-7).

Table 3
PATHOLOGICAL PRODUCTS CONTAINING MDR BACTERIA ISOLATES IN THE STUDY GROUP

Pathological product	Frequency	
	Number	%
Pus – total	98	23.85
wounds	49	11.92
abscesses	42	10.22
fistulas	5	1.21
sinuses	2	0.48
Hypo-pharyngeal aspirates	89	21.65
Conjunctival secretions	51	12.42
Ear secretions	39	9.48
Skin – cultures (MBC*)	29	7.06
Tracheal aspirates	29	7.06
Gastric aspirates	19	4.62
Sputum – microscopic ex.	14	3.42
Sputum – culture	13	3.16
Blood cultures	9	2.19
Peritoneal liquids	7	1.70
Catheter – tip	6	1.46
Stool culture	4	0.97
Tympanocentesis	2	0.48
Urine cultures	1	0.24
Others	1	0.24
Total	411	100.00%

**MBC = minimum bactericidal concentration*

Penicillin G and oxacillin were inefficient in 46 *Staphylococcus aureus* strains samples (30.26% of 152 isolates), erythromycin in 28 isolates (18.42%), and clindamycin in 19 isolates (12.50%) (fig. 3).

On *Streptococcus aureus* strains penicillin G proved inefficient in 6 isolates (7.14% of a total of 84 isolates), erythromycin in 11 isolates (13.09%), clindamycin and tetracycline in 9 isolates (10.71%) (fig. 4).

A major problem was the antibiotic resistance of *Klebsiella pneumoniae* strains, which were resistant to ampicillin in 20 cases (37.73% of the 53 isolates), to amoxicillin + clavulanic acid in 19 cases (35.85%). *Klebsiella pneumoniae* proved resistant to cephalosporins such as cefuroxime, ceftazidime, ceftriaxone, cefepime in 18 isolates (33.96%), in concordance to data published

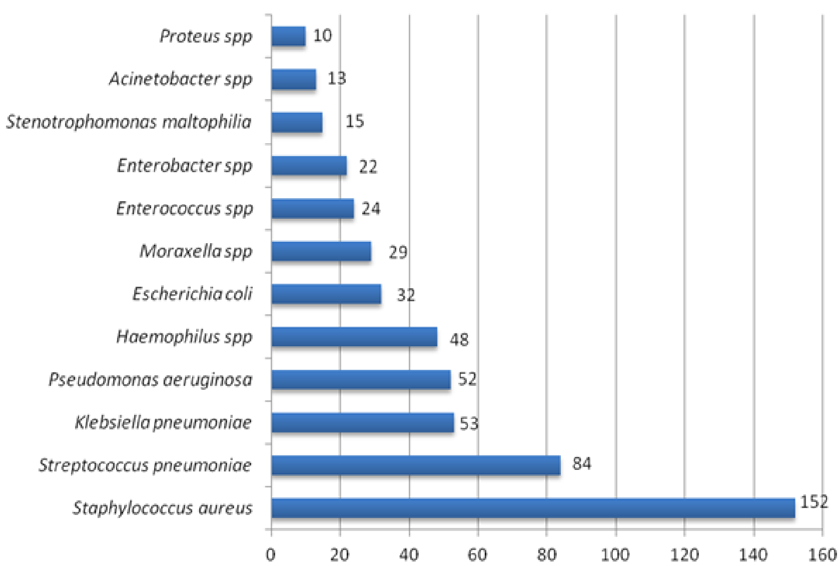

Fig. 2. Most frequent MDR microorganism identified in the pathological samples collected from the study group

Pathogen	Total of isolates		Girls		Boys		p
	No.	%	No.	%	No.	%	
Staphylococcus aureus	152	27.73	90	59.21	62	40.79	< 0.05*
Streptococcus pneumoniae	84	15.33	41	48.81	43	51.19	> 0.05
Klebsiella pneumoniae	53	9.68	26	49.06	27	50.94	> 0.05
Pseudomonas aeruginosa	52	9.48	20	38.46	32	61.54	< 0.05*
Haemophilus spp	48	8.78	25	52.09	23	47.91	> 0.05
Escherichia coli	32	5.84	16	50.00	16	50.00	> 0.05
Moraxella spp	29	5.29	15	51.72	14	48.28	> 0.05
Enterococcus spp	24	4.38	19	71.16	6	28.84	< 0.05*
Enterobacter spp	22	4.02	18	81.81	4	18.19	< 0.05*
Stenotrophomonas maltophilia	15	2.74	7	46.67	8	53.33	> 0.05
Acinetobacter spp	13	2.37	6	46.15	7	53.85	> 0.05*
Proteus spp	10	1.82	2	20.00	8	80.00	< 0.05*
Serratia spp	5	0.91	0	0.00	5	100.00	< 0.05*
Salmonella spp	4	0.73	4	100.00	0	0.00	< 0.05*
Candida spp	3	0.54	0	0.00	3	100.00	< 0.05*
Alcaligenes faecalis	1	0.18	1	100.00	0	0.00	< 0.05*
Ewingella americana	1	0.18	0	0.00	1	100.00	< 0.05*
Total	548	100	290	52.92	258	47.08	> 0.05

Table 4
THE PREVALENCE OF ISOLATED PATHOGENS AND GENDER COMPARISON

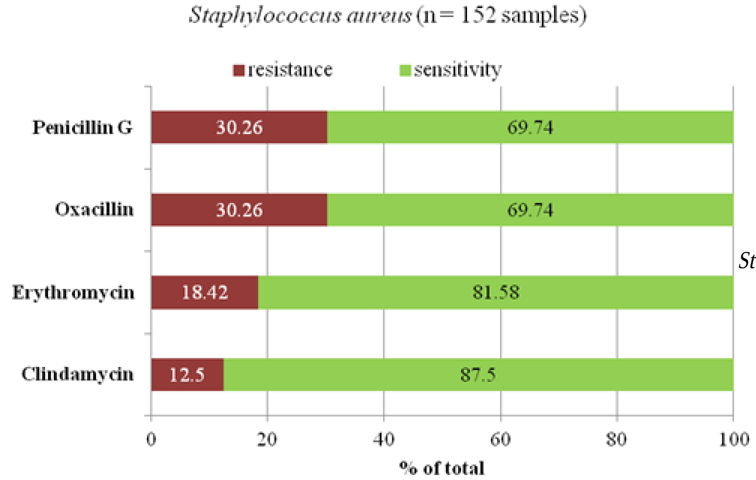

Fig. 3. Efficacy of commonly used antibiotic molecules on *Staphylococcus aureus* strains collected from the patients from the study group

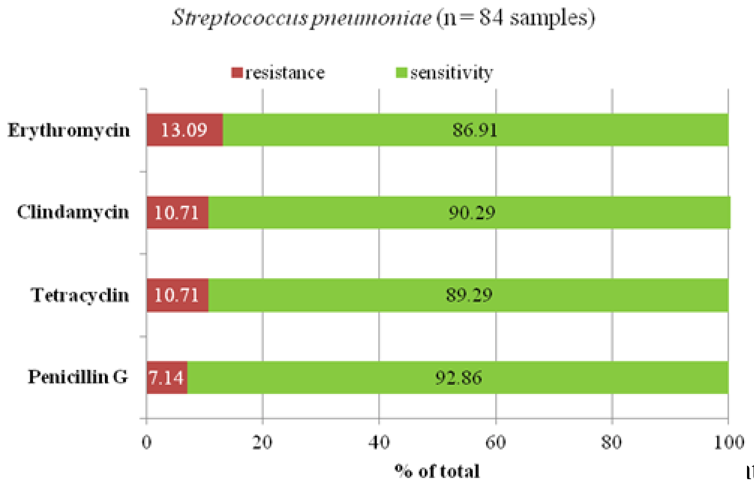

Fig. 4. Efficacy of commonly prescribed antibiotic molecules on *Streptococcus pneumoniae* strains collected from the patients from the study group

in previous studies performed in Romania and worldwide [10, 12, 17] (fig. 5).

On *Haemophilus spp* strains ampicillin was inefficient in 14 of 48 samples (29.17%) the combination of amoxicillin and clavulanic acid molecules proved inefficient in 2 samples (4.17%), while cefaclor in 8 strains (16. 67%) (fig. 6).

Regarding the antibiotic resistance of *Escherichia coli* strains, ampicillin was inefficient in 12 isolates (37.50%), amoxicillin + clavulanic acid in 7 isolates (21.87%), cephalosporins cefuroxime, ceftazidime, ceftriaxone in 4 ites (12.50%), and cefepime in 2 isolates (6.25%) (fig. 7).

In a study conducted in Romania, Cucu A. *et colab.* [31] reported the following antimicrobial resistance of the bacterial strains isolated from patients admitted to ICUs: 76.3% of *Staphylococcus aureus* isolates were resistant to erythromycin and 1.7% to chloramphenicol. Of the total number of strains of *Staphylococcus aureus*, 69.5% were methicillin-resistant and 35.1% were MRSA (resistant to all penicillins and 1st, 2nd, and 3rd generation cephalosporins). For *Escherichia coli* isolates, 56.7% were resistant to ciprofloxacin, and 54.4% to imipenem sensitive ESBL

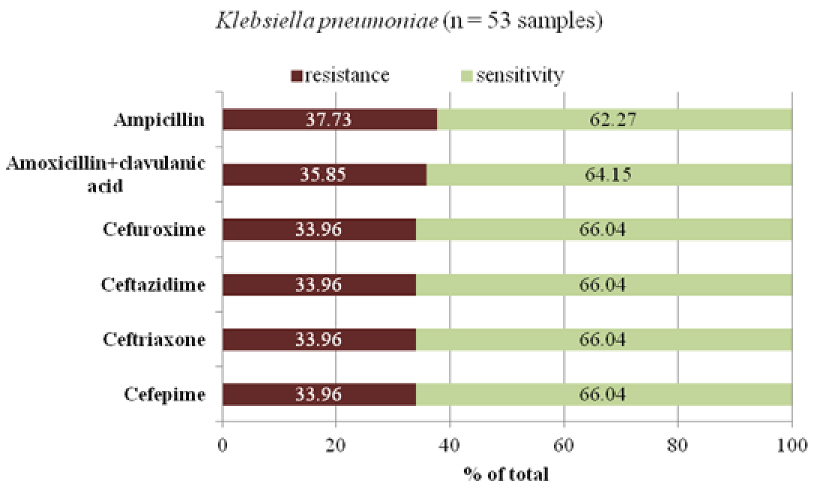

Fig. 5. Efficacy of commonly prescribed antibiotic molecules on *Klebsiella pneumoniae* strains collected from the patients from the study group

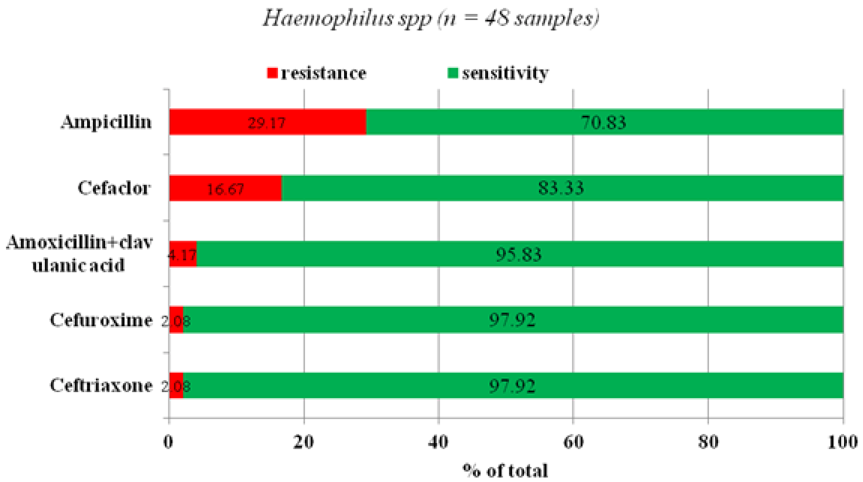

Fig. 6. Efficacy of commonly prescribed antibiotic molecules on *Haemophilus spp* strains collected from the patients fromthe study group

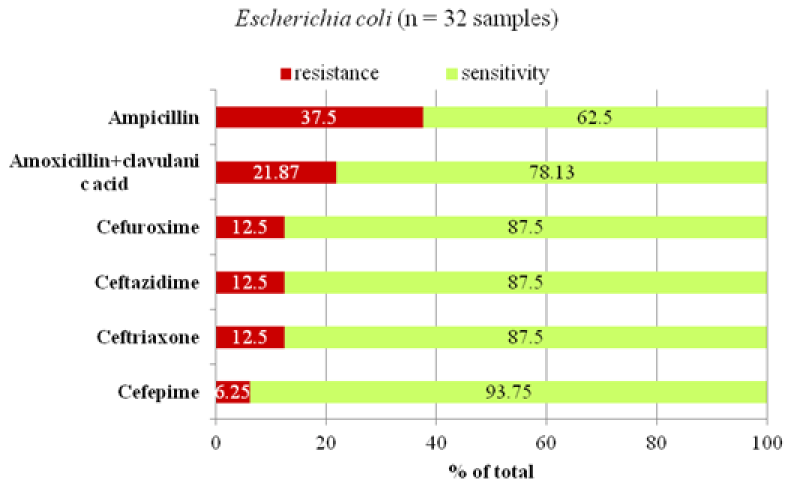

Fig. 7. Efficacy of commonly prescribed antibiotic molecules on *Escherichia coli* strains collected from the patients from the study group

strains. Over 66% of the *Pseudomonas aeruginosa* strains were resistant to all tested antibiotics except for colistin (sensitivity in 41.5% of the strains). *Klebsiella pneumoniae* isolates were ESBL-producing strains (resistance to all penicillin and 1st, 2nd, and 3rd generation cephalosporins) in 85.5% of the cases, and 77.0% were resistant to ciprofloxacin. The same study reported different antibioresistance prevalence values for the same microorganisms in other hospital wards: 45.4% of *Staphylococcus aureus* strains were resistant to erythromycin, 19.5% of *Pseudomonas aeruginosa* isolates were resistant to piperacillin-tazobactam and 28.0% to ciprofloxacin, and the colistin susceptibility was only 37.5%. The limitation of antibiotic as a self-medication, the use of narrow-spectrum antibiotics, restrictive strategies and guidelines at national level should be considered by healthcare providers in order to decrease the prevalence of antibiotic resistance [32-37].

The antimicrobial resistance of bacteria such as *Escherichia coli*, *Klebsiella spp.* has increased in recent years, reported data showing significant differences from year to year for common prescribed antibiotic molecules, like gentamicin. However, no increase in ciprofloxacin resistance of Gram-negative bacteria was noticed in 2016, as it was stated in a study conducted in Romania by Voicu M. *et colab.* [3]. In the same study, the authors reported that cephalosporins, aminoglycosides and carbapenemes were less used in 2016 compared to previous years, and a decrease of the number of hospitalization days was also noticed. For the same period of 2016 (the first trimester, as in our study), the authors observed an increased consumption of quinolones due to the use of ciprofloxacin as antimicrobial therapy in Gram-negative bacterial infections [3].

Conclusions

Our study revealed that penicillin G and oxacillin were inefficient in more than a third of *Staphylococcus aureus* strains collected from pathological samples in a pediatric hospital. *Streptococcus pneumoniae* was resistant to penicillin G and erythromycin; amoxicillin + clavulanic acid and 1st, 2nd and 3rd generation cephalosporins failed to combat *Klebsiella pneumoniae* infections; cefaclor was not efficient in *Haemophilus spp* isolates; *Escherichia coli* proved low sensitivity to ampicillin and 1st, 2nd and 3rd generation cephalosporins.

Continuous evaluation of antibiotic resistance of MDR bacterial strains, together with promotion of updated protocols and guidelines for appropriate antibiotic prescription, and development of new antibiotic molecules represent important objectives in reducing HAIs, expecting lower mortality rates, shorter hospitalization durations, and lower health care costs.

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