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Research Article

A STUDY ON ANTIMICROBIAL SENSITIVITY AND COST ANALYSIS OF ANTIBIOTICS IN PEDIATRIC UNIT AT A TERTIARY CARE HOSPITAL

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ABSTRACT

Objectives: (1) To determine the antimicrobial susceptibility pattern in pediatrics, (2) to identify the pattern of empirical antibiotic usage, (3) to determine the cost analysis of generic antibiotic usage pattern, (4) to assess the different dosage forms of antibiotics.

Methods: A retrospective observational study was carried out. The study population included the medical records of children aged day 1–15 years with bacterial infection who got admitted in the pediatric department of the hospital. The average cost for each generic dosage form of antibiotic was calculated.

Result: Among the 176 cases taken for the study, sepsis (35.8%) was found to be the most common disease. Bacterial infection showed gender predominance in males (62.5%) and occurrence of sepsis was highly found in age groups of 0–1 years (55.68%). Among the 14 causative organisms, methicillin-resistant coagulase negative staphylococci (61.93%) was predominant in Gram-positive and *Escherichia coli* (38.06%) for Gram-negative. Highly prescribed drug for empirical therapy was considered to be amikacin (39.20%). Widely prescribed antibiotics were amikacin (21%), ceftriaxone (15.1%), ampicillin (12.34%) and meropenem (9.57%), among which meropenem was found to be of high cost.

Conclusion: It should be taken care that the drug should be given not only based on the sensitivity pattern but can also consider the economic affordability of the patient, with reference to existing brands from the formulary. This would help in reducing the burden of health-care cost for the patients.

Keywords: Antimicrobial agents, Blood stream infection, Neonatal intensive care unit, Medical records department, Hospital information system.

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INTRODUCTION

An antibiotic is a compound that is either derived from nature or chemically synthesized, which acts on bacteria through inhibiting normal biochemical functions such as cell wall synthesis, protein synthesis, DNA replication/transcription, or cellular respiration.

Mechanisms of bacterial resistance to antimicrobial agents are enzyme inactivation, altered receptors, and altered antibiotic transport.

The primary goal of antimicrobial susceptibility testing is to provide accurate *in vitro* testing of a bacterial pathogen to a cadre of available antibiotics to determine its “antibiogram” or susceptibility profile to predict the *in vivo* effectiveness of a particular antibiotic or antibiotic regimen being used to treat a patient. A second function of antibiotic susceptibility tests is to monitor the effectiveness of therapy is compromised by the potential development of tolerance or resistance to that component [1-5]. It is true for all agents used in the treatment of bacterial, fungal, parasitic, and viral infections. Unfortunately, greater use of antibiotic during the past 50 years has exerted selective pressure on susceptible bacteria and may have favored survival of resistant strains, some of which are resistant to more than one antibiotic. In the absence of the development of new generation of antibiotics, appropriate use of existing antibiotics is needed to ensure the long-term availability of effective treatment for bacterial infections.

Several studies have clearly shown that the rapid reporting of antibiotic susceptibility results may influence the patient outcome from infection, shorten hospital stays, and allow improved tailoring of antibiotic regimens, resulting in cost minimization and potentially decreased the development of antibiotic resistance due to inappropriate or subinhibitory drug exposure of the bacterium [6].

Bloodstream infection in children is the common cause of morbidity and mortality worldwide. It varies from a minor infection to life-threatening sepsis and causes a significant public health problem. The various systemic infections occurring in pediatrics include septicemia, meningitis, pneumonia, and urinary tract infection (UTI). In pediatrics, infections can cause prolonged hospital stay particularly those in born preterm and of very low birth weight. Infectious agent can be transmitted from the mother to the fetus or newborn infants by diverse modes.

The clinical manifestation of newborn infection varies and includes subclinical infection, mild-to-severe manifestation, or focal or systemic infection and rarely congenital syndromes, resulting *in utero* infection. The timing of exposure, inoculums size, immune status, and virulence of the etiological agents influences the exposure of disease. The prognosis depends on underlying health status, host defense, and early appropriate empirical antibiotic therapy.

The selection of antibiotics depends on the clinical condition of the child and the hospital policy regarding the use of antibiotics based on previous culture sensitivity reports. Indiscriminate and inadequately prolonged use of antimicrobials also leads to the emergence and proliferation of resistant strains, moreover antimicrobials are prescribed prophylactically and empirically without carrying out sensitivity studies. However, the use of broad-spectrum antimicrobial agents may be associated with induction of resistance among common pathogens. Appropriate antimicrobial stewardship that includes optimal selection, dose, and duration of treatment as well as of antibiotic use will prevent or slow the emergence of resistance among microorganism.

The proper use of the antibiotics and appropriate selection of antimicrobials can reduce the cost of treatment in hospital. Inappropriate use of antibiotics can increase the cost of care by increasing drug cost, increasing toxicity, increasing resistance, and increasing laboratory cost. Production of drugs by modern techniques and biotechnology has considerably increased the cost of drug therapy. Cost is one among the various factors to be taken account in antibiotic prescribing. Thus, it is highly recommended for the analysis of treatment cost and makes strategies to reduce treatment cost.

METHODS

Study design and site

- A retrospective study is done in Medical Records Department of PSG Institute of Medical Science and Research Centre, Coimbatore.

Study population

- Pediatrics patient files from Medical Records Department.

Study duration

- A 6 months study conducted from February 2016 to July 2016.

Study approval

- The study protocol was prepared for the retrospective study using patient medical records data from the past 2 years.
- The study protocol and approval letters from MRD and Microbiology Department were submitted to the Institutional Human Ethical Committee.
- IHEC approval was obtained (project no.16/095)

Inclusion/exclusion criteria

Inclusion criteria

- All the children admitted in pediatric unit from 1st January, 2014 to 31st January, 2016 with culture-positive bacteremia were included in the study.

Exclusion criteria

The following criteria were excluded from the study:

- Patients who did not receive antibiotic treatment.
- Patient's information about treatment and sensitivity is not available.
- Death cases.
- Patient discharged against medical advice.

Sampling

- After obtaining the approval from the Institutional Human Ethical Committee, the study was initiated from 1 February, 2016 in the Medical Records Department, PSG Hospitals, Coimbatore.

Sample size

- The sample size for this study as per Creative Survey software with a confidence level (95%), confidence interval (5), and study population (250) was estimated to be around 176.

Study tools

- Data collection form, case files, microbiology laboratory results, and hospital information system were used.

Statistical analysis

- This was a descriptive statistical analysis.

RESULTS

The age of subjects in the study ranged from age day 1 to 15 years. As per the results obtained, maximum patients (55.68%) were in the age group ranging from 0 to 1 year, followed by subjects in the age group of 2–5 years (24.43%), 11–15 years (11.36%), and 6–10 years (8.52%) (Table 1).

Of 176 subjects, 110 (62.5%) were males and 66 (37.5%) were females. As per the study results, male subjects were predominant as compared to female subjects (Table 2).

In this study, sepsis 63 (35.8%) was found to be the most common disease, followed by respiratory tract infections 35 (19.8%), gastroenteritis 9 (5.1%), typhoid and hepatitis 7 (3.9%), UTI 6 (3.4%), meningitis 5 (2.8%), cellulitis and infective endocarditis 4 (2.2%), measles and osteomyelitis 3 (1.7%), toxoplasmosis 2 (1.1%), and others 28 (15.9%) (Fig. 1).

From the total number of cases (176) in the study, 109 (61.93%) were found to be Gram-positive and 67 (38.6%) were Gram-negative. We have selected a total of 14 predominant organisms, of which 7 were Gram-positive and 7 were Gram-negative (Fig. 2).

Among the selected 7 Gram-positive organisms, the most frequently occurring organisms was found to be methicillin-resistant coagulase negative staphylococci (MRCONS) (29%) 34 cases, followed by *Staphylococcus epidermidis* (18%) 21 cases, *Staphylococcus aureus* (14%) 17 cases, CONS and *Streptococcus* species (8%) 10 cases each, *Enterococcus* (3%) 3 cases, finally methicillin-resistant *S. aureus* (MRSA) with (1%) 1 case, and others were 13 cases (19%) (Fig. 3).

Among the Gram-negative organisms, the most frequently occurring organisms were found to be *Escherichia coli* and *Klebsiella pneumoniae* (27%), i.e., 18 cases each followed by *Acinetobacter baumannii* (16%) 11 cases, *Pseudomonas aeruginosa* (13%) 9 cases, *Enterobacter* (7%) 5 cases, *Pseudomonas stutzeri* (4%) 3 cases, *Salmonella typhi* (3%) 2 cases, and others 1 case (3%) (Fig. 4).

In MRCONS species, the most sensitivity antibiotics were found to be levofloxacin, linezolid, ofloxacin, tetracycline, and vancomycin, and the resistant antibiotics were amoxicillin, ampicillin, aztreonam, and cefotaxime (Fig. 5).

In *S. epidermis*, the most sensitive antibiotics were amikacin, cefoxitin, and linezolid, and the resistant ones were ampicillin and penicillin (Fig. 6).

In *S. aureus*, the sensitive antibiotics were cefepime, cefotaxime, ceftazidime, ceftriaxone, cefuroxime, doxycycline, levofloxacin,

Table 1: Age-wise distribution of patients

Age group (years)	Number of patients (%)
0–1	98 (55.68)
2–5	43 (24.43)
6–10	15 (8.52)
11–15	20 (11.36)
Total	176 (100)

Table 2: Gender-wise distribution of patients

Gender	Number of patients (%)
Males	110 (62.5)
Females	66 (37.5)
Total	176 (100)

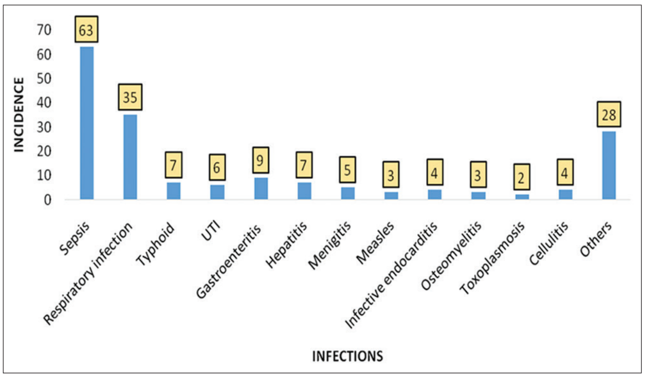

Fig. 1: Percentage of occurrence of infection in pediatrics

linezolid, nitrofurantoin, rifampin, and vancomycin, and resistance was observed only for amoxicillin (Fig. 7).

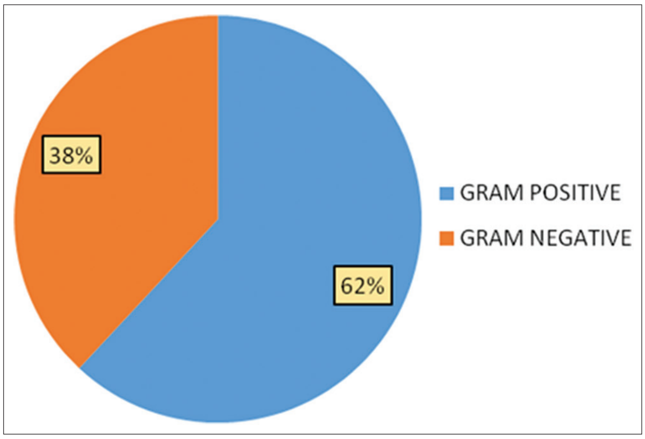

Fig. 2: Distribution of Gram-positive and Gram-negative organism

In *E. coli*, the sensitive antibiotics were found to be colistin, meropenem, netilmicin, nitrofurantoin, piperacillin, and tigecycline, and the resistant ones were found to be amoxiclav, aztreonam, cephalothin, cefotaxime, ceftazidime, ceftriaxone, cefuroxime, nalidixic acid, norfloxacin, and tetracycline (Fig. 8).

In *K. pneumoniae*, sensitive antibiotics were amoxicillin, clindamycin, penicillin, erythromycin, and tigecycline, and the resistant ones were cephalothin and piperacillin (Fig. 9).

A. baumannii species was sensitive to aztreonam, colistin, and ertapenem and was resistant to ampicillin, cefazolin, cefoxitin, and tetracycline (Fig. 10).

Vancomycin showed sensitivity to a maximum number of organisms [8], followed by doxycycline and ciprofloxacin [6] (Table 3).

Majority of the patients (78.9%) were empirically treated, whereas the others (21.02%) were not.

Table 3: Antibiotic sensitivity pattern in pediatrics

Name of the antibiotics	Name of the organism sensitive	Number of organism sensitive
Vancomycin	MRCONS, *Staphylococcus epidermidis, Staphylococcus aureus,* CONS, *Streptococcus, Enterococcus,* MRSA, *Pseudomonas aeruginosa*	8
Doxycycline	MRCONS, *Staphylococcus epidermidis*, CONS, *Streptococcus, Enterococcus, Pseudomonas stutzeri*	6
Ciprofloxacin	*Staphylococcus epidermidis, Staphylococcus aureus, Streptococcus, Enterococcus,* MRSA, Enterobacter	6
Linezolid	*Staphylococcus epidermidis, Staphylococcus aureus*, CONS, *Streptococcus, Enterococcus*	5
Rifampin	MRCONS, *Staphylococcus epidermidis, Staphylococcus aureus, CONS MRSA*	5
Amikacin	*Staphylococcus epidermidis, Escherichia coli, Klebsiella pneumonia, Pseudomonas aeruginosa*	4
Ceftriaxone	*Staphylococcus aureus*, CONS, *Pseudomonas stutzeri, Salmonella typhi*	4
Levofloxacin	MRCONS, *Staphylococcus aureus, Streptococcus, Enterobacter*	4
Colistin	*Escherichia coli, Acinetobacter baumannii, Pseudomonas aeruginosa, Enterobacter*	4
Cefalothin	*Staphylococcus epidermidis, Streptococcus, Pseudomonas aeruginosa*	3
Chloramphenicol	CONS, *Streptococcus, Klebsiella pneumonia*	3
Ampicillin	*Streptococcus, Enterococcus, Pseudomonas stutzeri*	3
Clindamycin	*Streptococcus,* MRSA, *Klebsiella pneumonia*	3
Netilmycin	*Escherichia coli, Pseudomonas aeruginosa, Pseudomonas stutzeri*	3
Tigecycline	*Escherichia coli, Klebsiella pneumonia, Acinetobacter baumannii*	3
Cefoxitin	MRCONS, *Staphylococcus epidermidis*	2
Cefotaxime	*Staphylococcus aureus*, CONS	2
Cefuroxime	*Staphylococcus aureus*, CONS	2
Nitrofurantoin	*Staphylococcus aureus, Escherichia coli*	2
Co-trimoxazole	*Streptococcus, Enterococcus*	2
Gentamycin	*Streptococcus, Klebsiella pneumonia*	2
Piperacillin	*Escherichia coli, Pseudomonas aeruginosa*	2
Amoxicillin	*Klebsiella pneumonia, Pseudomonas stutzeri*	2
Aztreonam	*Acinetobacter baumannii, Pseudomonas aeruginosa*	2
Tetracycline	MRCONS, *Salmonella typhi*	2
Cefepime, Ceftazidime	*Staphylococcus aureus*	1
Cloxacillin	CONS	1
Ampicillin+sulbactam, Polymycin-B	*Enterococcus*	1
Erythromycin		1
Meropenem		1
Ertapenem, Cefoperazone+Sulbactam		1
Tobramycin	*Pseudomonas stutzeri*	1
Azithromycin	*Streptococcus*	1
Ofloxacin	*Escherichia coli*	1
	Acinetobacter baumannii	

MRSA: Methicillin-resistant *S. aureus,* MRCONS: Methicillin-resistant coagulase negative staphylococci

Table 4: Number of patients not on empirical antibiotic therapy

Empirical therapy	Patients on empirical therapy (%)	Organism resistant
Amikacin	69 (39.20)	*Acinetobacter baumannii* (84%), *Enterobacter* (67%)
Ceftriaxone	50 (28.40)	*Escherichia coli* (100%), *Klebsiella pneumonia* (88%), MRCONS (71%)
Ampicillin	20 (11.36)	MRCONS (100%), *Staphylococcus epidermis* (100%), MRSA (100%), *Enterobacter* (100%), *Escherichia coli* (87%)

Table 5: Pattern of antibiotic usage in pediatrics

Antibiotics	Number of patients (n=397)	Percentage
Amikacin	84	21
Amoxicillin+clavulanic acid	27	6.8
Ampicillin+sulbactam	1	0.2
Ampicillin	49	12.34
Azithromycin	8	2.01
Cephalexin	1	0.2
Ceftazidime	15	3.77
Cefoperazone+sulbactam	2	0.50
Cefotaxime	34	8.56
Ceftriaxone	60	15.11
Ciprofloxacin	5	1.25
Colistin	2	0.50
Dicloxacillin	3	0.75
Erythromycin	5	1.25
Gentamycin	10	2.51
Levofloxacin	2	0.50
Linezolid	3	0.75
Meropenem	38	9.57
Ofloxacin	2	0.50
Piperacillin+tazobactam	3	0.75
Rifampicin	2	0.50
Sulfamethoxazole+trimethoprim	2	0.50
Tobramycin	8	2.01
Vancomycin	31	7.80

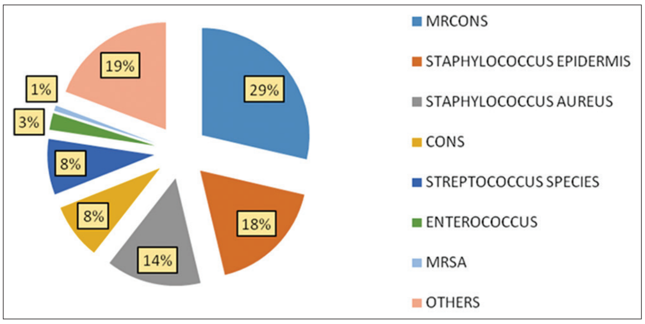

Fig. 3: Gram-positive organisms

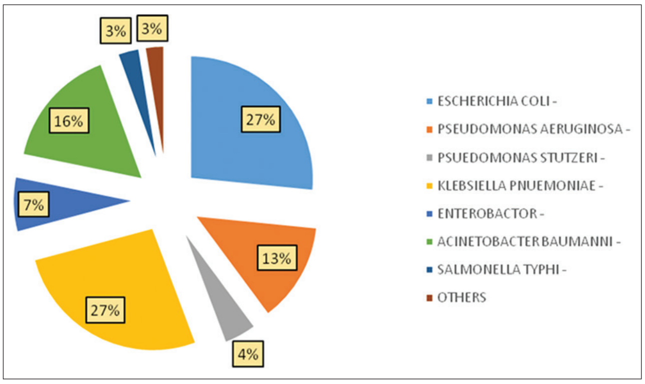

Fig. 4: Gram-negative organisms

Among the empirically treated patients, amikacin 69 patients (39.20%), ceftriaxone 50 patients (28.40%), and ampicillin 20 patients (11.36%) are the drugs of choice for empirical therapy in our hospital (Table 4).

Of 176 cases, antibiotic treatment cost was analyzed according to the number of unit consumed along with a total number of days prescribed. Based on brands available in the formulary, averages for each generic drug were calculated for each dosage form (Table 5).

Most commonly used dosage form was injection (85%) followed by syrups (4%) (Fig. 11).

DISCUSSION

This present study provides us to identify the overall pattern of AMA use in pediatrics which may help to promote rational drug use. In the current study, a total of 250 cases were taken, and after screening based on inclusion and exclusion criteria, 176 cases were selected.

Age predominance

The study involved pediatric patients under the age group of day 1–15 years. Among these, infections were highly noticed in the age group of day 1–1 year (55.68%). Blood culture positivity showed reduced isolation rates with an increase in age [7]. The probable reason for this predominance is because, new-borns most probably acquire these Gram –negative rods from the vaginal and faecal flora of the mother and the environment where the delivery occurs [10].

Gender distribution

Gender-wise distribution showed high occurrence in males (62.5%) when compared to females (37.5%) presenting with infection [8]. This is because in humans, females reportedly mount stronger humoral and cellular immune response to infection than males. The underlying mechanism for these sexual dimorphism is multifactorial, including the endocrine and genetic effects on the immune system [13].

Gram-positive and Gram-negative organism occurrence

From the total number of cases in the study, most of the organisms were found to be Gram-positive isolates (61.93%) and the rest being Gram-negative (38.6%) [9,12]. Among the Gram-positive organisms, the most frequently occurring organisms were found to be MRCONS (29%) followed by *S. epidermis* (18%). In Gram-negative organisms, the most frequently occurring organisms were *E. coli* (27%) and *K. pneumoniae* (27%) [11]. The probable reason for increased MRCONS isolates is because it colonizes the skin of health-care worker and hospitalized patients.

Antimicrobial sensitivity pattern

High sensitivity to most of the organisms found in this study was vancomycin [8], followed by doxycycline [16] and ciprofloxacin [6], linezolid, and rifampin [5].

Antibiotic drugs such as cefepime, ceftazidime, cloxacillin, ampicillin + sulbactam, polymyxin B, erythromycin, meropenem, ertapenem, cefoperazone + sulbactam, tobramycin, and azithromycin showed sensitivity to less number of organisms; however, it does not mean that it was resistant because the sample size available was less.

Empirical antibiotic therapy

In the present study, highly prescribed drugs for empirical therapy were found to be amikacin 69 patients (39.20%), ceftriaxone

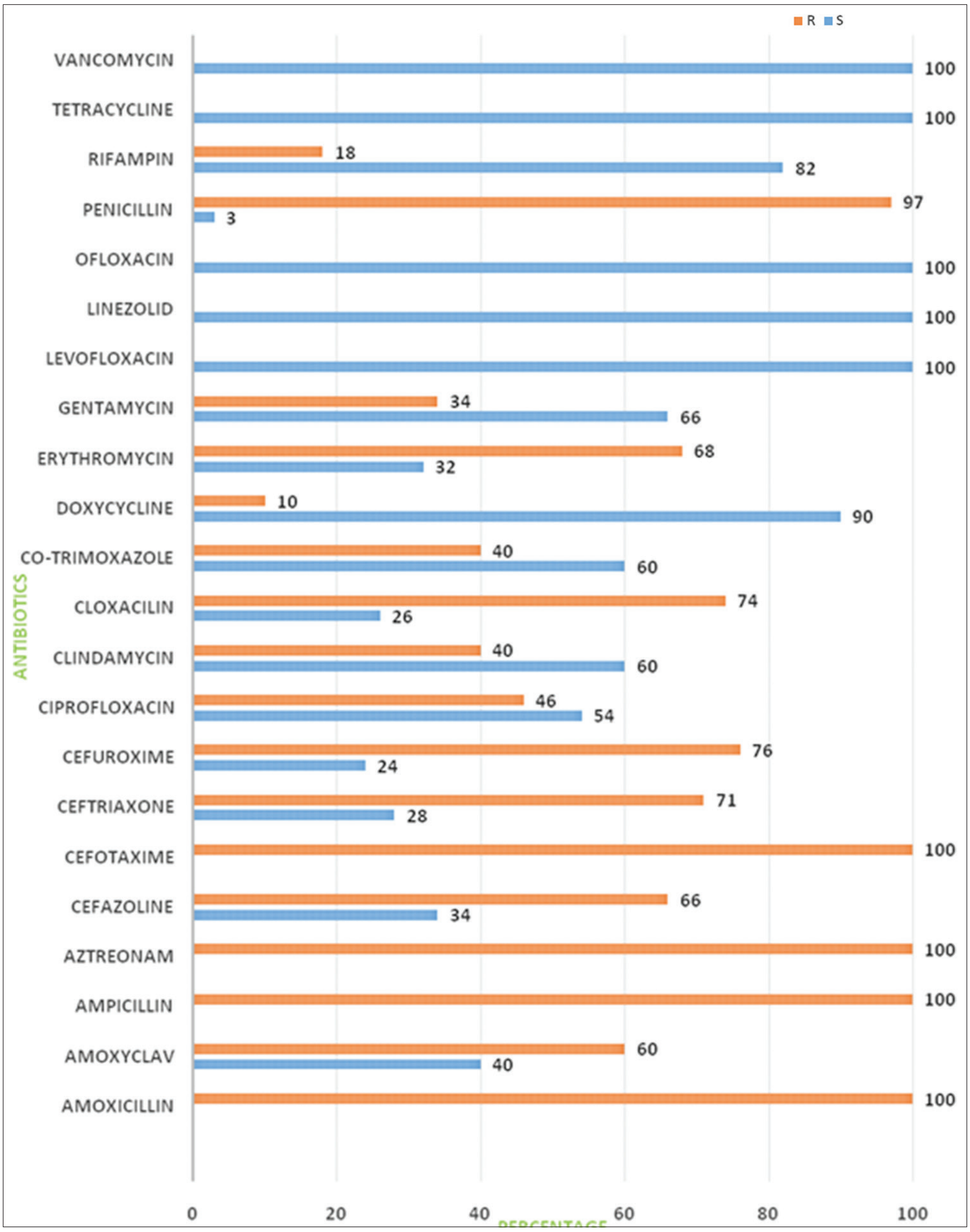

Fig. 5: Sensitivity and resistance pattern of methicillin-resistant coagulase negative staphylococci

50 patients (28.40%), and ampicillin 20 patients (11.36%). Among them, ceftriaxone showed high resistance to *E. coli* (100%), MRCONS (71%), and *K. pneumoniae* (88%) and ampicillin showed high resistance to MRCONS (100%), *S. epidermis* (100%), and *E. coli* (87%). Unfortunately, the occurrence of microorganisms such as MRCONS (29%), *E. coli* (27%), *K. pneumonia* (27%), and *S. epidermis* (18%) was found to be significantly high. Amikacin also showed resistance to *A. baumannii* (84%) and *Enterobacter* (67%). Since the occurrence of these organisms was rare in the collected data, it was considered to be of less significance. Hence, the use of amikacin as an empirical therapy in pediatrics was rational.

Route of administration of antibiotics

From the collected data, it was observed that the most preferred route of antibiotic administration was intravenous (85%), followed by oral (7%), drops (3%), ointments (2%), and miscellaneous IV dose (3%) dosage form [14]. The absolute requirement for IV antibiotics is present when patients cannot swallow or absorb oral antibiotics (i.e. during critical illness) or when intolerance or microbial susceptibility requires an agent that is effective when given intravenously. The more rapidly achieved peak antibiotic levels after IV dosing may be important when treating rapidly progressing infection such as severe sepsis and respiratory infections [15].

Cost analysis of antibiotics

In tablet dosage form, mostly prescribed tablets were ciprofloxacin 250 mg and azithromycin 500 mg. Among the tablets prescribed, azithromycin 500 mg was found to be of high cost (rs.110.5) and rifampicin 250 mg was of low cost (rs.14). In syrup dosage form, the most prescribed antibiotic was amoxiclav. Among the syrups prescribed, amoxiclav was found to be of high cost (rs.133.356) and sulfamethoxazole + trimethoprim was of low cost (rs.12.9).

In ointments, T-bact was mostly prescribed and was also the one with high cost (rs.83.9) and ciprofloxacin ointment was of low cost (rs.5.7), but was least prescribed.

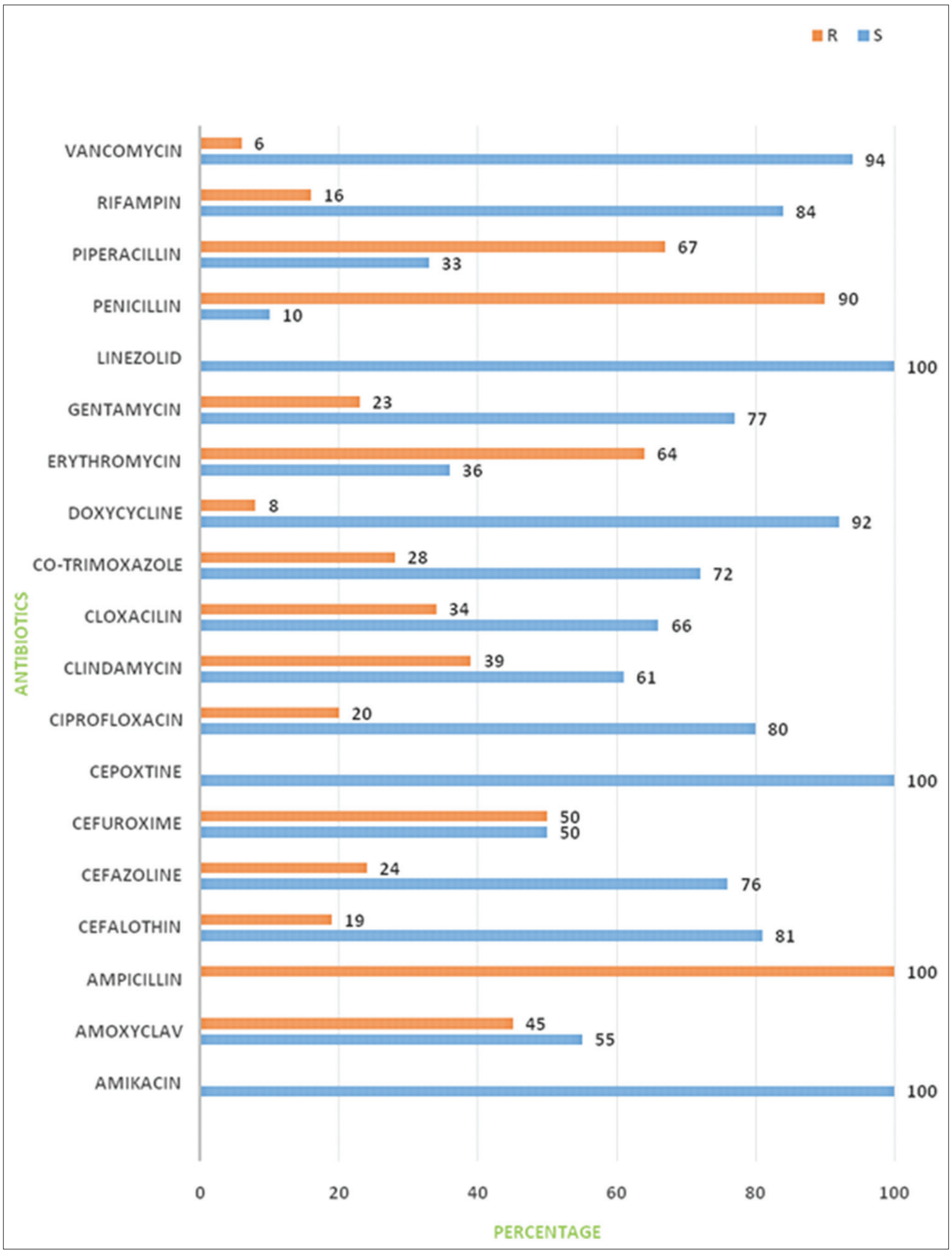

Fig. 6: Sensitivity and resistance of *Staphylococcus epidermis*

Tobramycin drops were mostly prescribed among the various available drops, and it was found to be of high cost (rs.55.42). Ciprofloxacin drops were found to be of low cost (rs.7.74) but were least prescribed.

In parenteral dosage form, ampicillin 250 mg and ceftriaxone 500 mg and 1 g were highly prescribed. Meropenem which was the drug of high cost among the parenteral dosage form was least prescribed.

Finally, all antibiotics prescribed in pediatrics were categorized from low to high cost (10–100), moderate (101–1000), and high cost (>1000). Among the drugs with low cost were observed to be sulfamethoxazole + trimethoprim (rs.12.90), rifampicin (rs.20.09), erythromycin (rs.44.19), gentamycin (rs.50.16), cephalexin (rs.50.80), azithromycin (rs.52.53), and ampicillin + sulbactum (rs.98.22), whereas the ones with moderate cost included drugs such as dicloxacillin (rs.136.05), amikacin (rs.155.94), cefotaxime (rs.221.55), tobramycin (rs.225.2), ampicillin (rs.227.07), levofloxacin (rs.345.94), ciprofloxacin (rs.594), and piptaz (rs.981.76) and the high cost antibiotics were ceftriaxone (rs.1101.63), ceftazidine (rs.1128.4), amoxicillin + clavulanic acid (rs.1248.837), cefaperazone + sulbactam (rs.1987.5), ofloxacin (rs.2432.98), vancomycin (rs.4654.51), colistin (rs.6077.5), linezolid (rs.6093), and meropenem (rs.14074.94).

Low-cost category drugs were prescribed only for less number of pediatric patients, i.e., 8%. Moderate- and high-cost antibiotics were prescribed almost equally in pediatrics, i.e., 47% and 45%, respectively.

CONCLUSION

Pediatric patients are more vulnerable to various infections. This study highlights the information regarding the various pathogens causing infection along with their sensitivity and resistance pattern which showed vancomycin was sensitive to more number of organisms.

The study revealed commonly occurring organisms being highly resistant to commonly used empirical antibiotics such as ceftriaxone

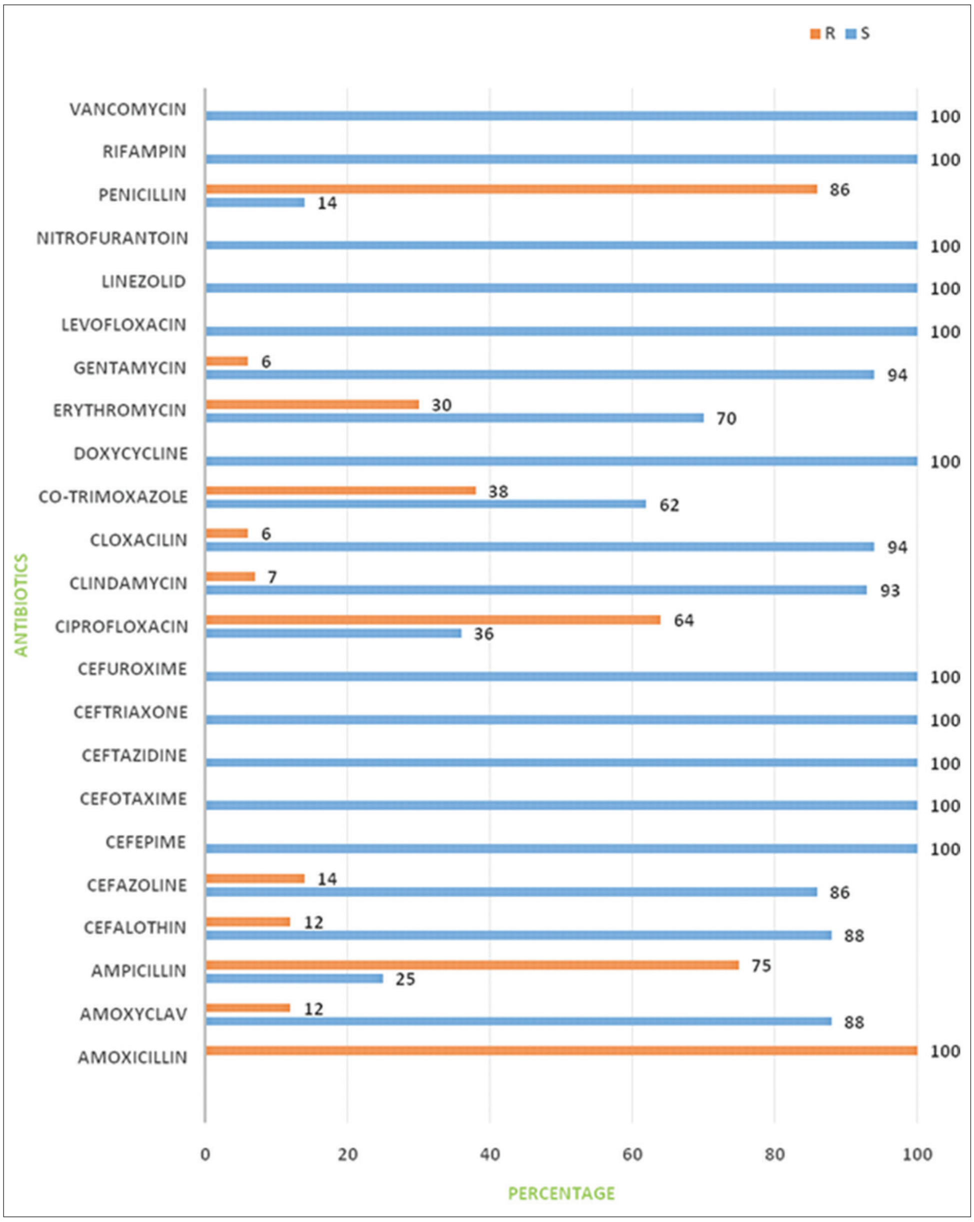

Fig. 7: Sensitivity and resistance pattern of *Staphylococcus aureus*

and ampicillin which is a cause of concern. The frequency of MRCONS isolates is high. Hence, they may emerge as a substantial challenge for health-care systems if ignored.

From the present study, it was observed that IV dosage forms were prescribed mostly, which was found to be essential in pediatric patients; however, safety and cost of therapy should be of concern.

Meropenem was found to be the drug of high cost which was moderately prescribed and showed more sensitivity to *E. coli.*

Monitoring should be done at regular intervals to describe various pathogens causing infection as well their changing antibiotic susceptibility pattern. Each and every hospital must have its own local antibiogram mentioning empirical therapy options.

Clinical pharmacist should be prudent enough to provide details regarding the various antibiotics available in the hospital formulary and details regarding their clinical pharmacology and dosing requirements for the selection of appropriate antibiotics.

The clinical pharmacist has a role in providing information to prescribers on antibiotic prescribing. Consideration about the cost of treatment is important to provide rational drug therapy and complete patient care. Clinical pharmacists play an important role in promoting optimal antibiotic prescribing practice among pediatrics by participation in their routine visit to wards.

LIMITATIONS

1. The sensitivity and resistance data from this study cannot be generalized for each antibiotic owing to the small sample size.
2. The cost analysis data provided in this study were done based only on the drugs available in the hospital formulary.
3. Cost-effectiveness analysis was not performed.

ACKNOWLEDGMENT

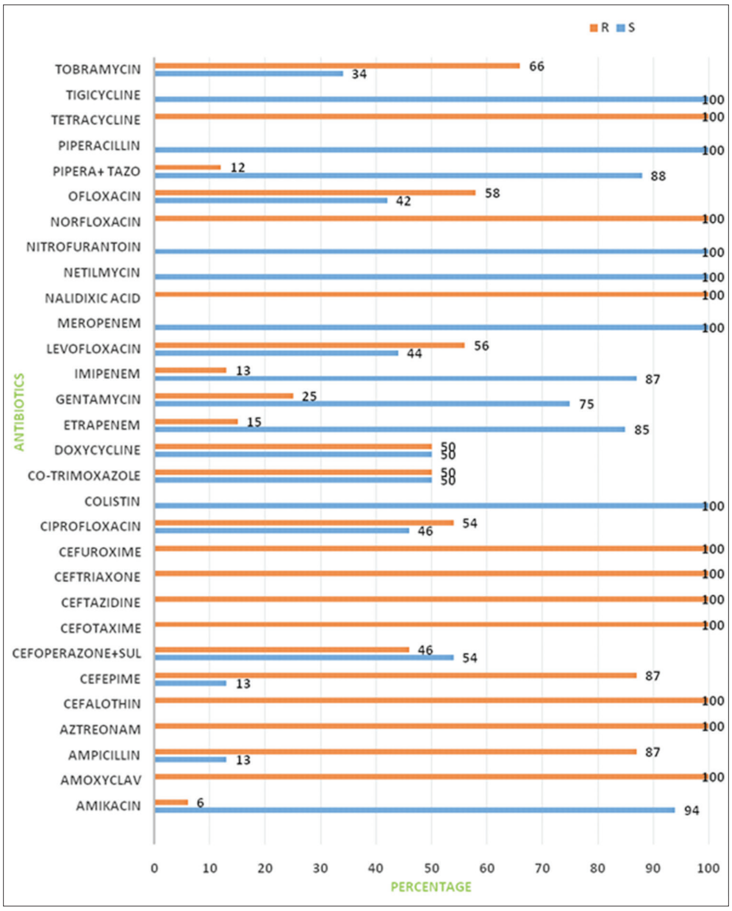

Fig. 8: Sensitivity and resistance pattern of *Escherichia coli*

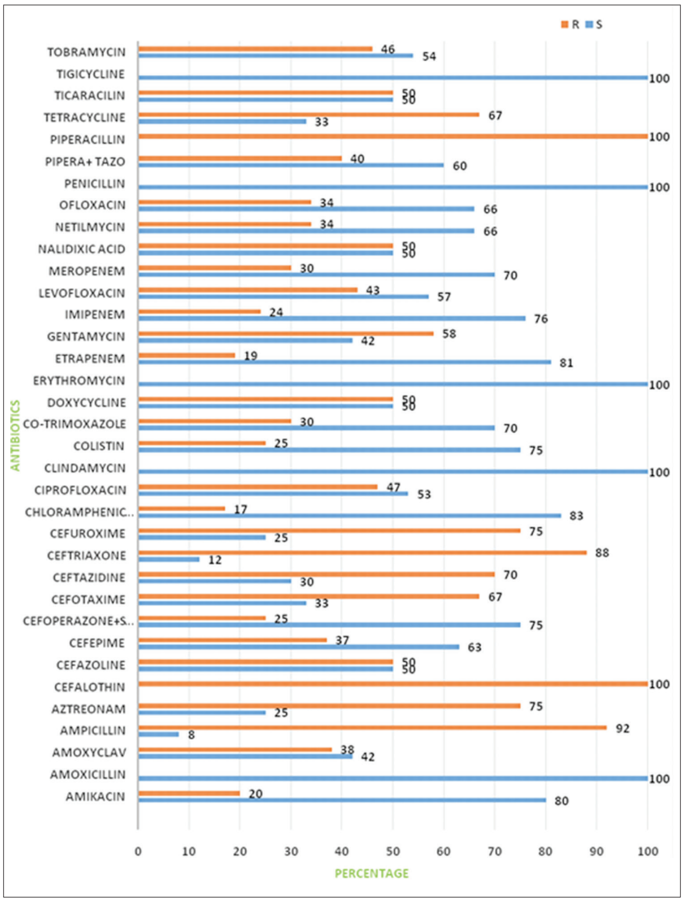

Fig. 9: Sensitivity and resistance pattern of *Klebsiella pneumoniae*

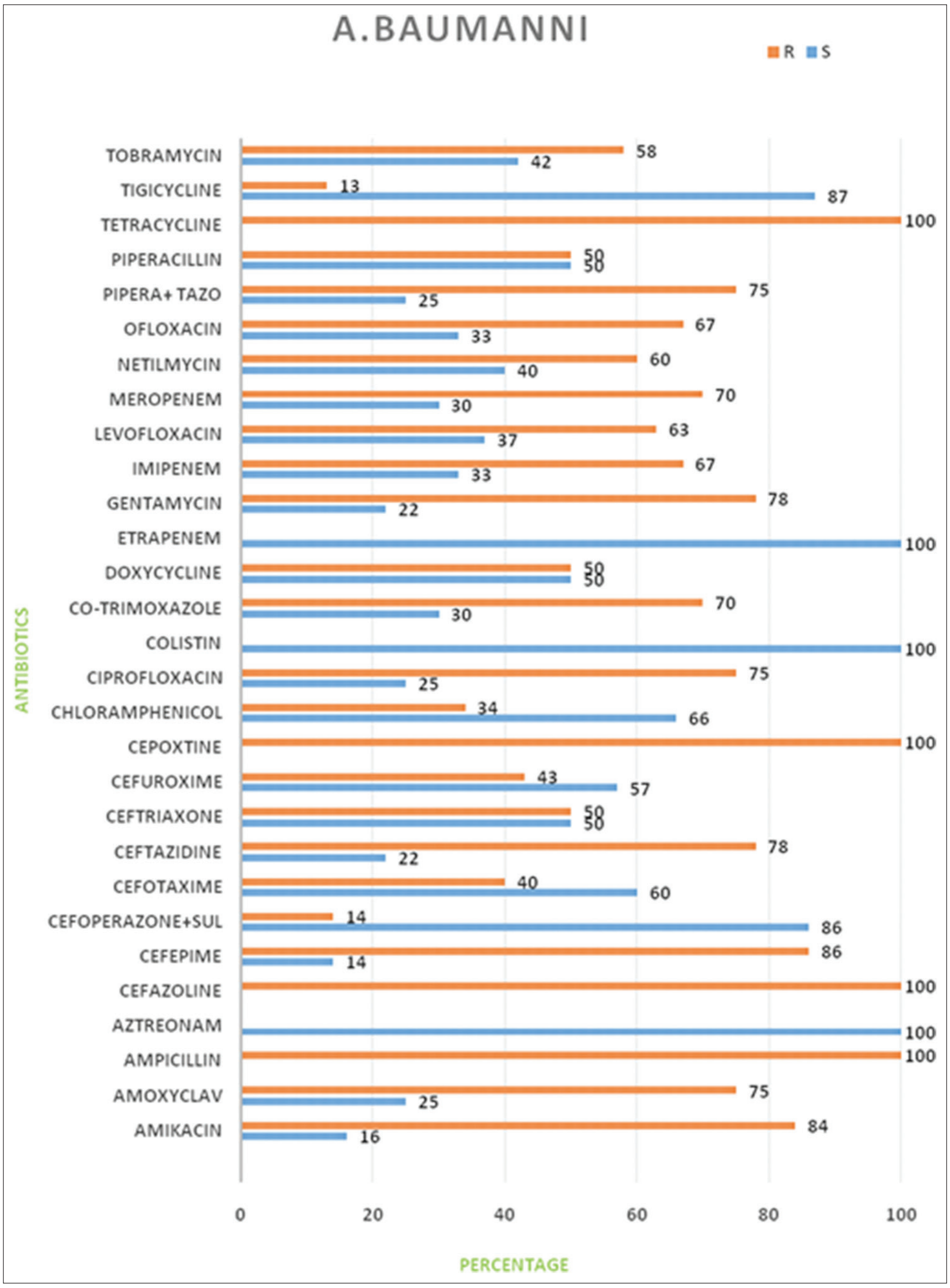

Fig. 10: Sensitivity and resistance pattern of *Acinetobacter baumannii*

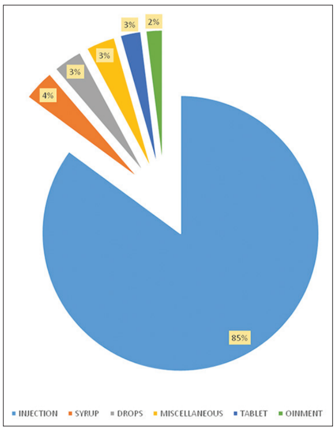

Fig. 11: Different dosage form of antibiotics used in pediatrics

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AUTHORS CONTRIBUTION

Conceptualisation of work and its realisation –AK & JD. Compiled the literature sources, interpreted data- SRB & AK. Data collection-AK, JD,SRB & AV. Result analysis-JD & RP. Final approval of the version to be published- VV ,RP.

CONFLICTS OF INTEREST

None to disclose.

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