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RESEARCH ARTICLE

Drug Use Evaluation in the Pediatrics Admitted with Severe Respiratory Tract Infections

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Abstract

The objective of the present study is to evaluate drug prescribing patterns in children admitted with respiratory tract infections into pediatric ward. This is a prospective cross-sectional study conducted for a period of one year at a tertiary hospital located in a city of Andhra Pradesh, South India. The study was done by using prescribing indicators from the World health organization (WHO) manual for the conduction of drug use evaluation studies. The prevalence of respiratory tract infections, particularly lower respiratory tract infection is high among children less than 5 years. 54.39% of drugs are prescribed with brand names, of which the majority of drugs are administered through parenteral route (58.26%). Antibiotics (34.7%) are highly prescribed in all the cases followed by other category drugs. A significant difference was found in the evaluation of prescribed daily dose and standard dose. The profile of drug use in the present study was similar to previous Indian studies. Most of the prescribing encounters are parental forms and band names that need exploration of the present treatment trends. The present baseline data can serve for the development of national Pediatric prescribing guidelines in the future.

Keywords: *Pediatrics, Respiratory tract infections, Drug use evaluation, Prescribing indicators.*

Introduction

Acute Respiratory tract infections may occur in any part of the respiratory tract from the middle ear to the nose and can invade the lungs. The Severe form of infection affecting the lungs is said as Pneumonia. International classification of diseases defined respiratory infections as any infection affecting the airways below the epiglottis [1]. Acute respiratory infections can be classified as:

- Upper respiratory tract infections (URTI) include common cold, laryngitis, pharyngitis/tonsillitis, acute rhinitis, acute rhinosinusitis, and acute otitis media.
- Lower respiratory tract infections (LRTI) include acute bronchitis, bronchiolitis, and pneumonia [2].

It is estimated that over 95 % of new pneumonia cases worldwide are being reported in children less than 5 years of age, particularly in developing countries. India accounts for 44 million new cases per year and stood in first place among 15 other underdeveloped and developing countries [1]. Pediatrics differs from normal adults physiologically and anatomically made them more vulnerable to infections. Indian population constitutes 40% of pediatrics, are at high -risk for spreading infections, particularly respiratory tract infections, which are the most common cause of hospital visit in the pediatric department [2].

A wide practice of irrational prescription of antibiotics for upper respiratory tract infections without justifying viral or bacterial cause contributed to AMR, drug-related adverse events, increased cost of the prescription.

The most common cause of respiratory tract infections is Gram +ve facultative anaerobic bacteria; *Streptococcus* or *Staphylococcus* pathogens and viral infections. However, the use of antibiotics for every infectious symptom (for common cold of viral origin) is a common practice across the

world has led to a situation called antimicrobial resistance (AMR), which means, antibiotics can no more kill the microorganisms. Currently, AMR among community-acquired respiratory tract infections has become a common clinical challenge to the physicians.

Currently, 90% of *Moraxella catarrhalis* and 25% of nontypeable *Haemophilus influenzae* produce b-lactamase, 3 requiring treatment with b-lactamase-stable cephalosporins or combination drugs that include b-lactamase inhibitors such as amoxicillin-clavulanate [3]. World health organization (WHO) estimates that in 2016, 600,000 children died from acute lower respiratory infections caused by polluted air.

One reason why children are particularly vulnerable to the effects of air pollution is that they breathe more rapidly than adults and so absorb more pollutants [4]. World health organization has developed certain indicators to assess the quality of prescribing, hospital facilities and patient's experiences; prescribing indicators, hospital facility indicators, patient care indicators, complementary indicators. Using these research tools one cannot only assess significant problems in overall drug use at hospital settings but also develop hospital guidelines in correlation with standard national guidelines. In this context, the objective of the present study is to evaluate drug prescribing patterns in children admitted with respiratory tract infections into pediatric ward.

Materials and Methodology

Site of the Study

The present study was conducted during the period of August-2018 to April-2019 in Andhra Hospital's, a tertiary care hospital located in Vijayawada city within Andhra Pradesh state, India.

Study Population and Sample Size

Children of either sex between 1 month and 12 years identified with respiratory tract infections and admitted as inpatients in different wards were recruited into the study over August-2018 to April-2019 period. Children in emergency unit and seriously ill are excluded in to the study.

$$Sample\ size = \frac{\frac{z^2 \times p\,(1-p)}{e^2}}{1 + \left(\frac{z^2 \times p\,(1-p)}{e^2\,N}\right)}$$

The estimation of sample size necessary for this study was done utilizing the sample size equation given below. Based on previous literature, a sample of 385 was obtained using the below expression, where '*p*' was assumed to be 50%, allowable error '*e*' was 5% and '*z*' being the standard normal deviate with a value of 1.96 [5]. In was suggested in WHO manual, that at least 100 cases or above per health facility or prescriber is recommended for the study of prescribing indicators [6].

However, in our present study, over a period of one year, 309 children were admitted to the pediatric ward with various clinical conditions, among them132 (42.7%) children were identified with respiratory tract infections and recruited in to our study. Willingness of parents to give consent was the key for sampling the subjects who have satisfied the inclusion criteria.

Study Design

This is a prospective cross-sectional study presenting the data on drug utilization in patients admitted with respiratory tract infections in the pediatric ward of Andhra hospitals. The standard methodology for drug utilization research was adopted from a manual published by, World Health Organization; "How to investigate drug use in health facilities: Selected drug use indicators" [6].

There are four types of indicators in the manual for complete drug utilization study in hospital settings. However due to certain limitations, only prescribing indicators are opted for our present research. Predesigned prescribing indicators form was developed and used for the patient data collection. The prescribing indicators used in the study are:

- The average number of drugs per encounter.
- Drugs prescribed by generic name
- Percentage of encounters with an injection prescribed
- The number of antibiotics prescribed per encounter

Additional parameter we have intended to study is prescribed daily doses (PDD) of drugs in pediatrics admitted with respiratory tract infections. The PDD is the average daily dose prescribed, which is obtained from a representative sample of prescriptions and the standard dose is calculated by Clark's Formula.

Clarks formula=Adult Dose in mg X (Child Weight in kg ÷ 70) = Childs Dose in mg.

Adult dose of each medication in the above formula was calculated by the ATC code and Defined Daily Dose given by the WHO Collaborating Center for Drug Statistics Methodology. The drugs and the doses are further cross checked with, WHO model formulary for children and Model List of Essential Medicines 2019 to ensure that particular given drug in prescribed dose is safe in children [7, 8].

During the study period, the medication charts were also monitored for drug-drug interactions and any possible adverse drug reactions. The collected data was analyzed by using Microsoft excel 2007 program. Quantitative data was processed and analysed using appropriate descriptive statistics such as, frequencies, averages/means, standard deviations, and percentages.

Further, by using Data analysis toolpak available in Microsoft excel add-ins, mean ± standard deviation for prescribed total daily dose and standard total daily dose of all the drugs were calculated and compared using independent Student's t-test.

The statistical significance level (α) was 0.05 with confidence interval of 95% [9]. Ethical clearance was obtained from the institutional ethical committee present at SIMS college of pharmacy, Acharya Nagarjuna University, with a reference number; IHEC/SIMS/2018/028, before initiation of the study.

This is a non-experimental surveillance study with minimal risk, however written informed consent was obtained from a parent or legal guardian of the child included in the study under ICH GCP Guidelines. This is a non-experimental surveillance study with minimal risk, however written informed consent was obtained from a parent or legal guardian of the child included in the study under ICH GCP Guidelines [10].

Results

During the study period, 309 children were admitted to the pediatric ward with various clinical conditions, among them 132 (42.7%) children were admitted with respiratory tract infections. From them, 54 (40.9%) were male and 78 (59%) were female, 73(55.3%) are neonates, 29 (21.9%) are 1-5 years and 30 (22.7 %) children are above 5 years. Among hospital admissions, the prevalence of lower respiratory tract infections accounts for higher incidence (81 %) than upper respiratory tract infections (18.9%) (Table 1).

A total of 853 drugs of various categories were prescribed for indications of the respiratory tract. Thus, the average number of drugs per prescription or mean was 2.3 (SD 0.91) with a range between 3 and 8. The total number of drugs prescribed by generic names was 389 (45.60%).

Different types of dosage forms are used in the treatment process, 81 (9.49%) are oral solid dosage forms, 162 (18.99%) oral liquid dosage form, 113 (13.65%) inhalational dosage forms and 497(58.26%) parenteral forms (Table-2). One or more antibiotics were prescribed in almost every encounter which accounts for 297 (34.70%) followed by proton pump inhibitors and bronchodilators 78 (9.14%) (Table 3) (Fig. 1).

The most commonly prescribed antibiotics were Amoxicillin 77 (27.8%), Amikacin 26 (9.4%), Meropenem 24 (7.2%), Cefuroxime 20 (7.2%), Clarythromicin 19 (6.8%), Vancomycin 17 (6.1 %), Ceftriaxone 16 (5.7

%), Doxycycline 14 (5 %), Ceftazidime 12 (4.3 %) and Azithromycin 10 (3.6 %) (Table-4) (Fig-2).It was observed that in all 132 prescriptions the dose calculation was done based on age and body weight of the child by a clinical pharmacist. However, PDD and standard total daily dose of each drug was re-calculated by the researchers to test the accuracy and standards, and a statistically significant difference among antibiotics was observed in clarithromycin (p=0.02), and other antibiotics with p >0.05 are found with no statistical significance. Similarly, sodium bicarbonate among gastro intestinal drugs, ondensetron among antiemetic group and Ipratropium bromide among bronchodilators are observed to have a statistical significance between PDD and standard total daily (Table-5). When the researchers monitored for drug interactions and adverse drug reactions, there was no evidence of such significant event during the study period in the study subjects.

Table 1: Age, gender and diagnosis wise distribution

Parameter	Total number of patients (n=132)	Percentage
Age: 0-1 years	73	55.3%
1-5 years	29	21.9%
> 5 years	30	22.7%
Gender: Male	54	40.9%
Female	78	59%
Diagnosis: Upper respiratory tract infections	25	18.9%
Lower respiratory tract infection	107	81%
Bronchopneumonia +Fever	36	27.2%
Asthma	12	9%
Bronchiolitis	13	9.8%
Pleural sepsis	6	4.5%
Fever with pleural effusion	3	2.2%
Meconium aspiration syndrome	21	15.9%
Others	16	12.12%

Table 2: Pattern of drugs prescribed for various respiratory indications

Parameter	Number of drugs	Percentage of drugs prescribed
Brand name	463	54.39%
Generic name	389	45.60%
Oral solid	81	9.49%
Oral liquid	162	18.99%
Inhalational	113	13.24%
Parenteral	497	58.26%
Total drugs prescribed	853	100%

Table 3: Total drugs prescribed form various pharmacological classes

Drugs class	Total drugs	Percentage of drugs prescribed
Antimicrobials	297	34.70%
PPI	78	9.14%
H2 Blockers/Antacids	22	2.57%
Diuretics	22	2.57%
Antiemetic's	32	3.63%
Bronchodilators	78	9.14%
Antihistamines	17	1.99%
Corticosteroids	30	3.51%
Multivitamins& Multi minerals	87	10.19%
Electrolytes	24	2.69%
NSAIDs	47	5.50%
Others	119	13.95%
Total	853	100%

Table 4: Antimicrobials prescribed

Antimicrobial Class	No. encounters (n=297)	Percentage
Pencillin + ß Lactamase Inhibitors	98	32.9 %
Cephalosporines	45	15.1 %
Carbapenems	**24**	**8 %**
Fluroquinolones	14	4.7 %
Macrolide Antibiotics	29	9.7 %
Aminoglycosides	30	10.1 %
Glycopeptide	17	5.7 %
Tetracyclines	14	4.7 %
Nitroimidazoles	8	2.6 %
others	4	1.3 %
Anti-viral drugs	14	4.7 %

Table 5: Comparison of prescribed/standard daily dose of drugs

Drugs Prescribed	No of encounters	Prescribed Dose(mean±std deviation)	Standard Dose (mean±std deviation)	P-Value (independent t-test)
Antibiotics				
Amoxicillin+ clavulanic acid	77	1276.6±1163.41	1273.4±1130.07	0.493
Piperacillin+ tazobactam	9	1079.8±1215.839	961.8±976.716	0.406
Ceftriaxone	23	1464±871.49	1732.3±1307.41	0.257
Cefoperazone+ sulbactam	2	925±813.172	842±794.788	0.4636
Ceftazidime	12	85.291±106.38	80.37±81.31	0.45
Cefuroxime	20	727.55±434.801	905.55±411.66	0.09
Meropenem	24	543.25±708.77	411.5±499.18	0.230
Vancomycin	17	533.94±579.36	495.23±513.46	0.419
Doxycycline	14	127.57±147.299	82.178±42.689	0.14
Azithromycin	10	139±111.674	116.3±98.55	0.317
Clarithromycin	19	260.78±212.75	396.15±188.35	**0.02**
Levofloxacin	4	495±285.83	540±223.308	0.4062
Ofloxacin	3	71±60.77	85±73.654	0.406

Ciprofloxacin	7	44.14±22.003	50.57±17.11	0.277
Metronidazole	8	113.75±109.06	149.3±150.485	0.29
Amikacin	26	53.82±47.83	56.70±50.38	0.416
Gentamicin	4	13.628±4.230	13.8±4.354	0.47
Linezolid	2	300±212.13	295±219.20	0.49
Colistin	2	15.35±4.73	4.68±6.109	0.216
Antivirals				
Oseltamivir	10	54.5±20.20	57.86±35.044	0.3983
Acyclovir	4	390±106.77	324±101.85	0.202
Proton pump inhibitor/H2 blockers **Pantoprazole**	78	18.45±15.06	26.81±20.96	0.13
Ranitidine	16	27.81±48.94	16.21±17.95	0.178
Sodium bicarbonate	6	6.5±2.38	2.75±0.42	**0.02**
Diuretics				
Furosemide	13	8.97±11.12	8.07±7.83	0.41
Mannitol	9	78.5±75.9	122..2±131.55	0.21
Antiemetic's				
Domperidone	18	4.80±3.899	4.03±3.71	0.29
Ondansetron	14	4.69±2.86	2.79±1.11	**0.02**
Bronchodilators				
Ipratropium bromide	36	117.14±479.88	1292.85±334.783	**0.04**
Salbutamol	42	10.20±3.82	5.36±2.42	0.09
Antihistamines				
Fexofenadine	17	9.5±2.34	7.5±2.73	0.10
Corticosteroid's				
Prednisolone	5	25.66±14.011	22.33±11.67	0.38
Dexamethasone	16	6.655±8.500	6.52±6.23	0.448
Hydrocortisone	9	76.6±59.73	47.2±36.84	0.19
NSAIDs				
Paracetamol	47	399.39±410.76	366.54±260.98	0.324
Opioid analgesics				
Morphine	3	5.1±6.929	4.6±4.808	0.470
Fentanyl	2	308±412.95	81±89.09	0.293
Sympathomimetics Adrenaline	11	11.427±8.91	10.525±7.51	0.40
Noradrenaline	3	0.533±0.057	0.533±0.057	0.05
Others				
Acetylcysteine	2	8±0	12±4.24	0.20
Caffeine	4	11.375±6.75	12.875±5.54	0.3715
Midazolam	8	0.96±0.48	0.95±0.45	0.482
Phenytoin	6	188.16±301.21	102.58±92.06	0.265
Levetiracetam	8	148.75±92.80	106.61±57.58	0.14
Sildenafil	5	6.36±8.40	2.65±1.03	0.193
Urseodeoxycholic acid	3	308..6±287.19	252±233.6	0.402
Ketamine	2	308±412.95	81±89.09	0.293
Artesunate	10	117.3±76.74	115.06±67.36	0.47

*$p<0.05$ considered as significant

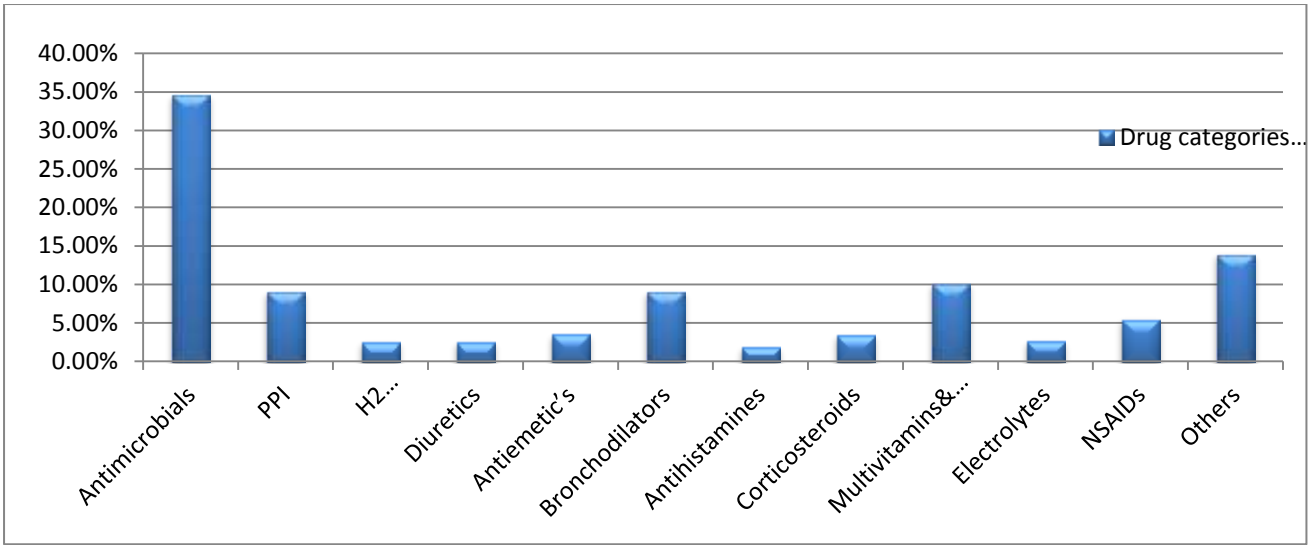

Fig 1: Categories of drugs prepared for the treatment of respiratory infections in children

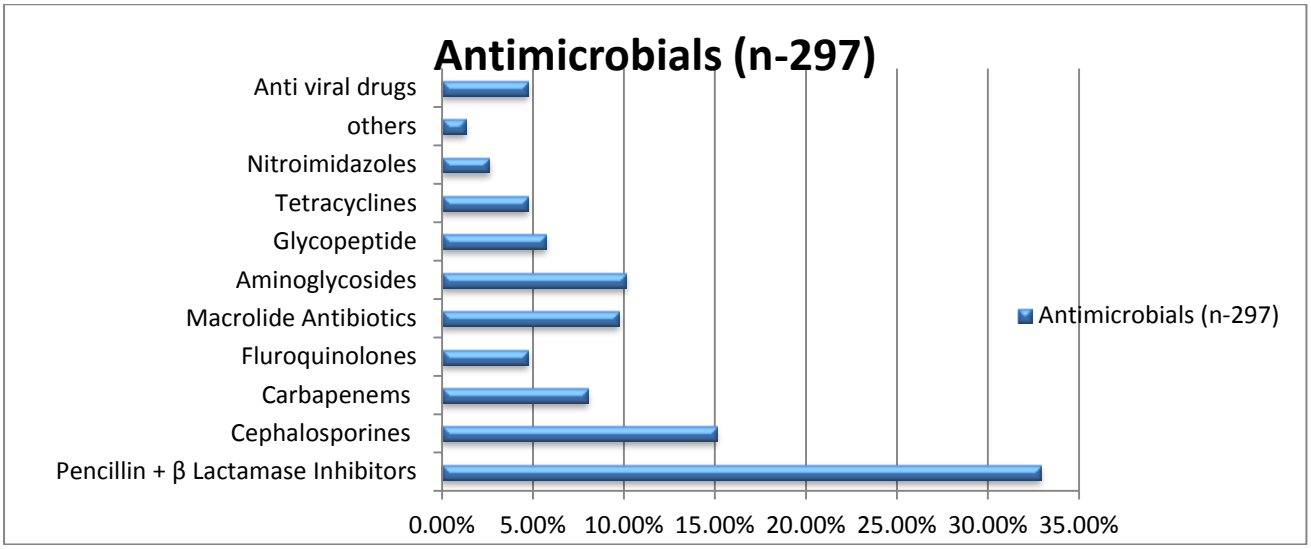

Fig 2: Different types of antimicrobials prescribed during treatment of children admitted with respiratory tract infections

Discussion

Rational drug use as per WHO requires that patients receive appropriate medication for their clinical condition in required doses for an adequate period of time, in the lowest possible cost. Several studies have been documented across the world on drug use patterns which have aided in the development of prescribing guidelines in many countries.

However, in highly populated countries like India, where there is a high irrational use of drugs, very few studies are being reported on the drug use evaluation. Particularly, the pediatric drug use is a major concern as the country lack adequate literature and pediatric prescribing guidelines. In the present study, we attempted to study drug use patterns in children affected with respiratory tract infections using WHO prescribing indicators.

The present study comprised slightly more girls than boys. Although many such studies are done across India, very few reports from South India and especially from the state of Andhra Pradesh there was no study done on drug utilization in pediatrics affected with respiratory tract infections. Our study result coincides with the results of Kokani VR, Pandit PR et. al., regarding age and gender-wise distribution [11].

The prevalence rate of ARTI in our study is less when compared to north Indian states like, Delhi, Gujarat), Assam, but higher than a study conducted in South India at Tamil Nadu, and coincides with results from Puducherry [12-16].

The indication in which large numbers of drugs were prescribed is bronchopneumonia (27.2%), which is similar in the study done by K Shamshy et al., in a province of south India [16].

The most commonly prescribed antibiotics in our study are Penicillin and cephalosporin's which are similar to prescribing patterns observed in the state of Tamilnadu [17]. Most of the drugs are prescribed with the brand name which may increase the cost of treatment and make it unaffordable for all economic groups of the population. In recent years, the Indian Prime Minister was considering legal steps for physicians to prescribe medicines with generic names and most of them are administered through parental rout which may also increase the cost of the prescription [18].

In our study generic prescription is quite appreciated with 45.6 % which is quite higher than 19.16 % in a study by Thiruthopu NS., et al., in a south Indian region [19]. The appreciable figure obtained in our study is the effort of a clinical pharmacist monitoring the prescriptions across the tertiary teaching hospital in which the present study was conducted. WHO recommends range of 20-26 percentage of antibiotics in a prescription, but it was higher 34.7% than the recommended.

Similar results was reported by 33.29 % in a study by Thiruthopu NS., et al., while the parenteral preparations are used in a remarkable rage out of recommended by WHO as 13.4-24% [19]. Markets for children's medicines tend to be small and the range of doses used may be wide for any drug formulation because many drugs prescribed widely for infants and children are not available in suitable dosage forms, leading to a lack of attention to pediatric medicines. Due to ethical issues and difficulties in carrying out clinical studies in the pediatric population, drugs are not being prior tested, hence many drugs are therefore have not been approved by the Food and Drug Administration for children [20]. However, pediatric dose calculation aids and referring pediatric essential drug list will help the health care provider to attain maximum therapeutic effects with less adverse events. It was a good sign observed in the present study hospital that, well qualified pediatricians along with clinical pharmacists are following the principle of pediatric dose adjustment based on weight and age. In India achieving optimal health care for all is being influenced by many factors. Such factors can be identified by investigations and drug utilization analysis. Attaining rational drug use and formulary management is one of the major challenges in the country.

In this plethora, Doctor of pharmacy course was introduced in India to recognize various prescribing patterns and to attain better Improving medication use and identifying areas in which there is a need for education and further information for healthcare professionals can be done by drug utilization studies [21-22].

Conclusion

We have found certain areas that need attention in our country to stand in global standards. There is a high rate of antibiotic prescribing that may result in the development of resistant strains, and many drugs are prescribed with brand names is not a good prescribing practice. However, the doses are calculated appropriately in the majority of encounters by the clinical pharmacist and physician is an appreciable scenario. We suggest further studies to be done in this area and hope the country develops personalized Pediatric prescribing guidelines in the coming future which can further improve the standards of treatment.

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