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An Observational Study of Drug Utilization Pattern and Pharmacovigilance of Infective Wheeze Associated Disorders in Children

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Abstract
Background: *Wheeze associated lower respiratory tract infections occurring world-wide are prevalent most commonly in childhood. Observational drug utilization studies help to evaluate, interpret and improve drug use as well as monitor the efficacy and safety of drugs prescribed. There was no previous documentation on drug utilization pattern of wheeze associated lower respiratory tract infections in the pediatric age group. Therefore, this study analyses the prescription pattern and adverse effects observed in such disorders in children attending the Pediatric outpatient department in a tertiary care hospital in Chidambaram.*
Materials and Methods: *100 prescriptions from the Pediatric department of Raja muthiah Medical College and hospital were analyzed. Data collected from parents or care givers relating to wheeze associated respiratory disorders was evaluated for prescription pattern, drug efficacy, adverse effect and compliance observed in polytherapy.*
Results: *Majority of the children irrespective of severity received inhalation of β2 agonist levosalbutamol as a bronchodilator and sodium chloride (Nacl) nebulization compared to oral formulations in children. Antibiotics were used in almost all the prescriptions since most of them were of infective etiology. Adverse effects were minimal for drugs administered by nebulization.*
Conclusion: *Polytherapy was the main stay of treatment than monotherapy in infective wheeze associated disorders in children. Formulations such as hypertonic saline nebulization and levo salbutamol nebulization was found to be most commonly used in children. Among the bronchodilators. FDC of salbutamol with ipratropium bromide was more frequently used.*
Keywords: *Wheeze associated disorders, nebulization, inhalational β2 agonists, drug utilization study*.

Introduction

Wheeze is a continuous, coarse, high pitched whistling sound most prominent on expiration occurring as a result of obstruction in the thoracic air passages due to inflammation and narrowing of the airway[1]. Common causes of wheezing include asthma, allergies, infections- upper and lower respiratory tract infections, gastroesophageal reflex diseases, obstructive sleep apnea. Wheezing in children is encountered by family physicians

with 40% of children having an episode of wheezing by three years of age. Almost 50% of children will suffer an episode of wheeze by six years of age, with the prevalence being highest in infancy.[2] Children and infants are affected because of the small bronchi and less elastic tissue recoiling and one third of lower respiratory infections due to bronchiolitis requires hospitalization[1]. Management of wheeze associated disorders in children due to infective causes includes humidified oxygen therapy, bronchodilators, mucolytics, hypertonic saline nebulization, inhalational beta2 agonists, corticosteroids, inhalational anti-cholinergics and antibiotics[3]. Prevalence of bronchiolitis and bronchopneumonia in infants and children accounts for majority of childhood morbidity and mortality that poses a huge burden on health care systems throughout the world. Several studies focusing on drug utilization pattern in bronchial asthma have been documented, but this study focuses on drug utilization of some infective causes of wheeze related respiratory infections and the efficacy and adverse effects related to drug polytherapy. The anatomical therapeutic classification (ATC)/defined daily dose (DDD) is used as a tool to enhance the quality of drug use and is advised by the WHO as the international standard for drug utilization studies[4].

World health organization (WHO, 2004) defines "pharmacovigilance" as the science and activities relating to the detection, assessment, understanding, and prevention of adverse drug reactions (ADRs), or any other medicine-related problems. ADR can also be defined as "an appreciably harmful or unpleasant reaction, resulting from intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product".[5]

This study highlights the drugs utilized in infective causes of wheeze namely Bronchiolitis, lower respiratory tract infections and bronchopneumonia.

The objectives of the study are to analyze the drug utilization pattern in infective wheeze related disorders in pediatric department and its adverse effects. And also, to analyze safety and efficacy of monotherapy (single drug) and polytherapy (fixed drug combinations). List of abbreviations used:

WALRI	Wheeze associated lower respiratory tract infections
LRI	Lower respiratory tract infections
ATC	Anatomical therapeutic chemical
PDD	Prescribed daily dose
DDD	Defined daily dose
FDC	Fixed drug combinations
WHO-UMC-	World health organization-Uppsala monitoring center
ADR	Adverse drug reactions
INRUD	International network for rational use of drugs

Materials and Methods

Study Design: The present study was a prospective, observational study of subjects with wheeze associated lower respiratory tract infections due to infective causes for a period of one year.

Study Setting: Study approval was obtained from Institutional Ethics Committee before initiating the study. The study was carried out in pediatric department of Rajah muthiah Medical College and Hospital, Chidambaram.

Study Period: Study was carried out from January 2018 to December 2018

Study Participants:

Inclusion Criteria: Children attending the outpatient and inpatient department of pediatrics in the age group of 3months to 12 years with wheeze associated lower respiratory tract infections.

Exclusion Criteria: Children with other co-morbid state such as heart problems, tuberculosis were excluded from the study. Children less than 3 months of age were not included in the study.

Data Sources: Sources of collecting data were Patient interview and Patient case sheet. Data sheets were prepared for 100 patients with consent forms. The details of age, sex, socio economic status, family history of wheeze, diagnosis and

prescription data were obtained from the case records and by interviewing the patients.

Outcomes: Telephone calls were made to assess the compliance of the patients after two weeks. From the observed data, percentages are calculated. WHO causality assessment scale was used to assess the adverse effects of the drugs.

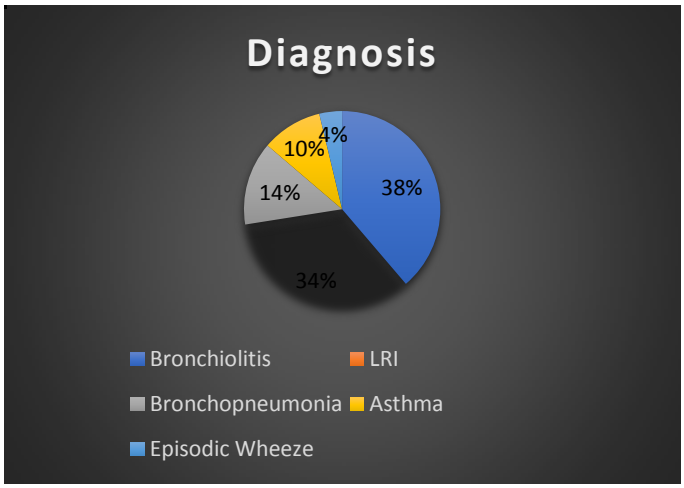
Sample Size: 100 children were taken up for the study. Finally, 80 Prescriptions of children with wheeze were analyzed due to drop outs.

Statistical Analysis: The cross- tabulation and Pearson Chi- square test were used to find out association between the diagnosis and the drug used. Data collected were entered in MS Excel and analyzed with SPSS version 23.

Results

Among the 100 prescriptions analyzed, 20 drop outs in the course of study were not evaluated. Most of the children having wheeze were related to infective causes. Thirty-one participants had Bronchiolitis, 27 children had lower respiratory tract infection, 11 children with bronchopneumonia and remaining 8 cases were due to bronchial asthma and 3 prescriptions due to seasonal wheeze as depicted in Fig 1.

Fig 1: Morbidity distribution pattern:



Demographic data analysis

1. Age wise distribution of patients

Among the study participants, 31% were in the age group 1 to 3 years as in **Table 1**.

Table1: Age wise distribution of children

Age (in months)	Male	Female	%
3 to 6	11	7	23
7 to 12	8	9	21
13 to 36 (1 to 3 yrs)	12	11	31
>36 (3 to 12 yrs)	10	12	25
Total	41	39	100

2. Gender wise distribution of children

Table 2: Gender wise distribution of disease pattern.

Diagnosis	Sex		Total
	Male	Female	
Bronchiolitis	20	11	31
LRI	2	6	8
Bronchopneumonia	13	14	27
Bronchial asthma	5	6	11
Episodic wheeze	1	2	3
	41(51.25%)	39(48.75%)	80

Among the study participants, **in table 2,** male children were 51.25% and females were 48.75%.

3. Socioeconomic status distribution:

This was derived from modified kuppusamy scale with their income, occupation and educational status. Among the study participants, 52.5% comes under lower middle class.

Fig 2 – Socioeconomic status pattern

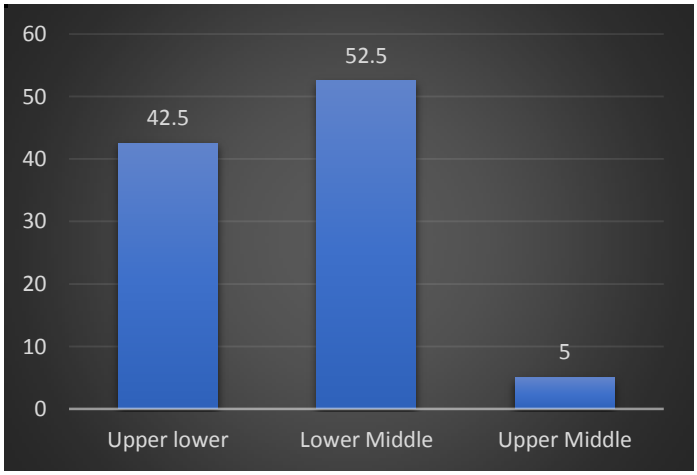


Table 3: ATC code and PDD / DDD ratio for the drugs used in prescriptions

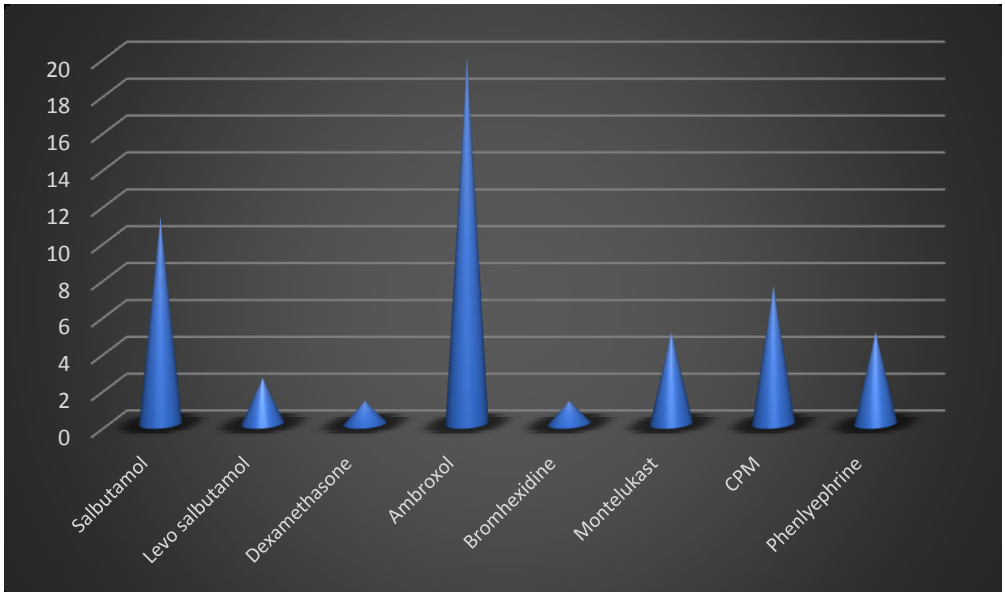
S.No	Group	Drug	ATC code	Calculated DDD for (child)	DDD (adult)	PDD	PDD/DDD
1	Bronchodilators	Levosalbutamolnebulizer	R03AC02	0.57mg (for child of 1.5 year)	0.8mg	2cc which contains 0.5mg	0.9
2	Steroids	Budesonide nebulizer	R03BA02	0.69 mg(for a child of 9months)	0.8mg	0.5mg	0.72
3	Bronchodilators	Syrup levosalbutamol	R03ACC02	0.8mg (child of 8.5kgweight)	0.8mg	0.8mg 4ml TDS	1
4	Steroids	Dexamethasone	H02AB02	6.4mgTDS (childof 3.2kg)	1.5mg	8mg TDS	0.8
5	Methyl xanthines	Montelukast	R03DC03	4mg(child of 8 yrs)	10mg	5mg	0.8
6	Mucolytics	Ambroxol	R05CB06	40mg (child of 10 yrs) 6ml	0.12gm or 120mg	3ml	0.5
7		Ceftriaxone	J010004	620mg BD (child of 5.5 yrs)	2gm	600mg BD	0.9
8		Amikacin	J01GB06	314mg(childof 5.5 yrs)	1gm	300mg	0.9
9		Cefotaxime	J01DD01	800mg (child for 3yrs)	4g	800mg	1
10	Antibiotics	Clarithromycin	J01FA09	83mg(wt of 5.5kg)	Adult 0.5gm 12H	75mg	0.9
11		Inj. Amoxiclav	J01CR02	430mg TDS	34g(parenteral)	600mg TDS	1.39
12		Inj. Ampicillin	J01CA01	1200mg	6g(parenteral)	800mg	0.7

1. PDD/DDD Ratio for the drugs Cefotaxime and syrup levosalbutamol is one.
2. The Ratio for Inj. Amoxiclav is 1.39
3. The Ratio for Levosalbutamol nebulizer, amikacin, clarithromycin, ceftriaxone were 0.9

Table: 4 Assessment of prescription as per WHO/INRUD Drug use indicators

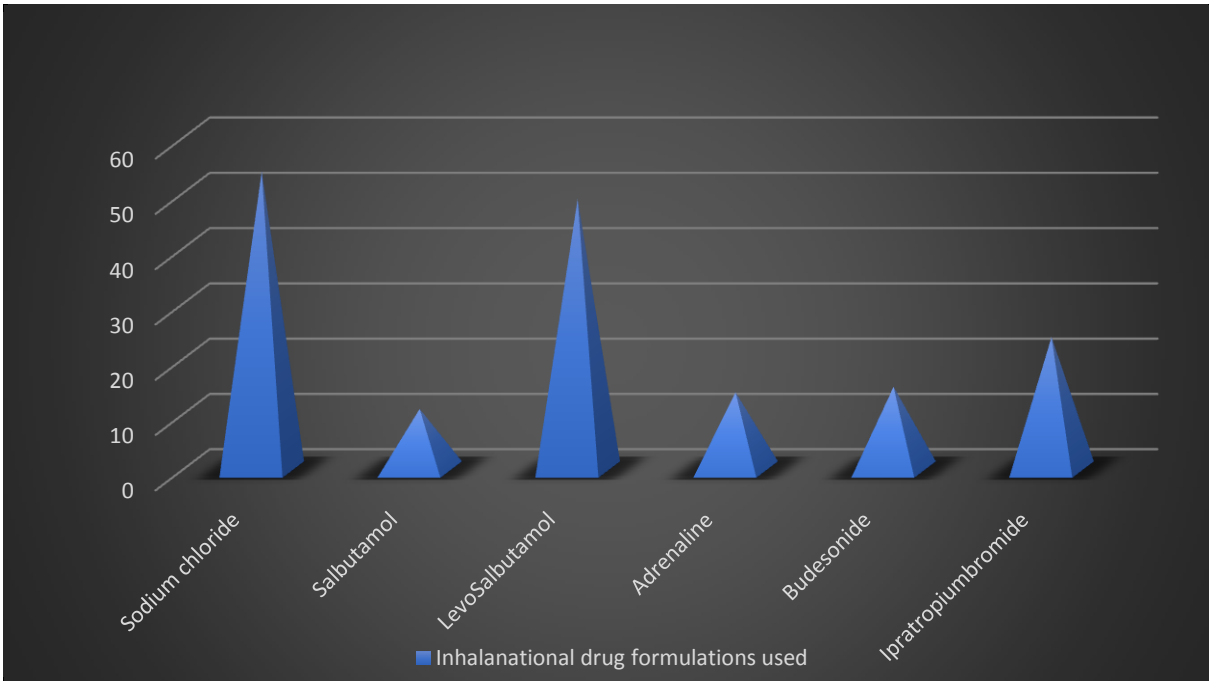
S.No	Drug use indicators	Result
1	Average number of drugs per prescription	3.3
2	Average of each group of drugs per prescription	
	Adrenergic drugs	0.9
	Steroids	0.3
	Anticholinergics	0.2
	Mucolytics	0.7
	Antibiotics	1
	Leukotriene inhibitors	0.05
	Antihistamines	0.08
	Total	3.3
3	% of drugs prescribed by generic names	12.5
4	% of drugs contain FDC'S	63.7
5	Percentage of drugs prescribed from the Tamilnadu essential drug list	36.3%
6	Percentage of drugs dispensed from hospital drug store at free of cost	36.3%
7	Percentage of drugs purchased by patients at cost	63.7%

Fig 3: Oral drugs prescribed-its Drug utilization



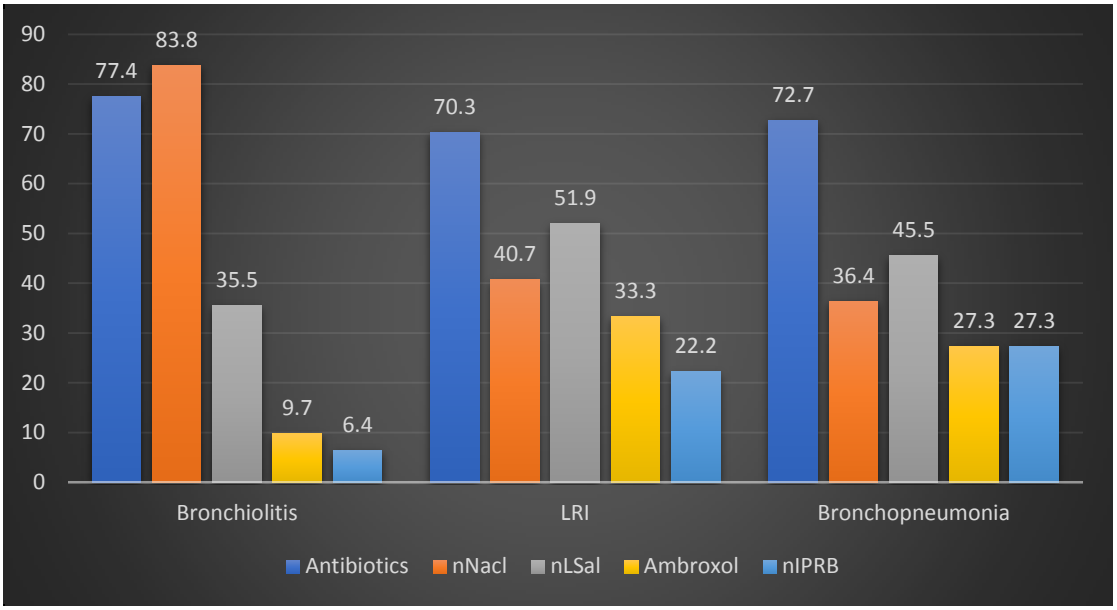
From **fig 3**, among the oral drugs prescribed, the mucolytic ambroxol was utilized in 20% children, salbutamol in 11.25% children, chlorpheniramine maleate in 7.5% children, montelukast and phenylephrine in 5% children.

Fig 4: Inhalational drugs prescribed- its Drug utilization



In the inhalational drugs used, from **fig 4,** hypertonic saline nebulization (53.75%)was utilized more in children followed by levosalbutamol nebulization (48.7%), ipratropium bromide nebulization was used in 23,75% children, budesonide nebulization in 15% children, adrenaline nebulization in 13.7% children followed by salbutamol nebulization in 11.25% children.

Fig 5: Drug Distribution pattern in wheeze associated disorders

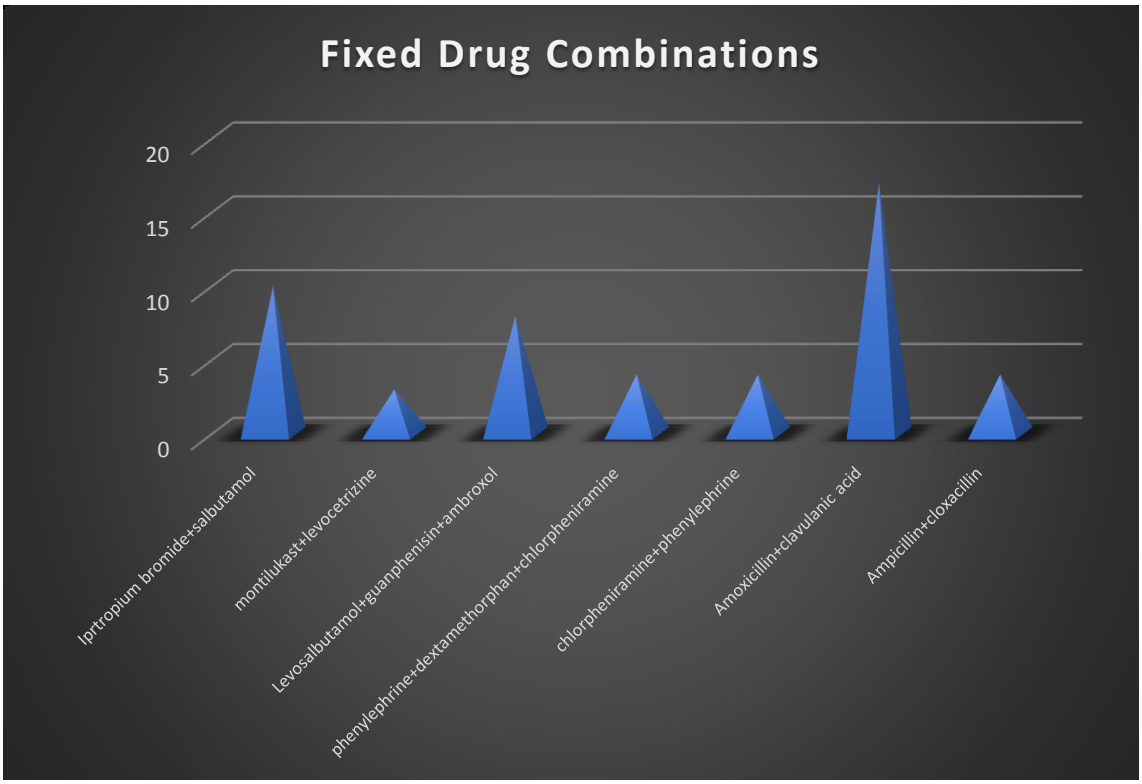


With a significant p value<0.05

From fig 5, we infer that antibiotics are used in infective wheeze associated disorders with a higher percentage in bronchiolitis (77.4%) and bronchopneumonia (72.7%) than LRI.

Hypertonic saline nebulization was efficacious in bronchiolitis (83.8%) and LRI (40.7%) than in bronchopneumonia (36.4%). Levo salbutamol nebulization and Ipratropium bromide nebulization were of maximal benefit in LRI and Bronchopneumonia respectively.

Fig 6: Distribution of fixed drug combinations:



Among the fixed drug combinations observed in **fig 6,** antibiotics most commonly used was amoxicillin with clavulanic acid (34%) and among bronchodilators Ipratropium bromide with levosalbutamol (20%).

Fig 7: Pharmacovigilance

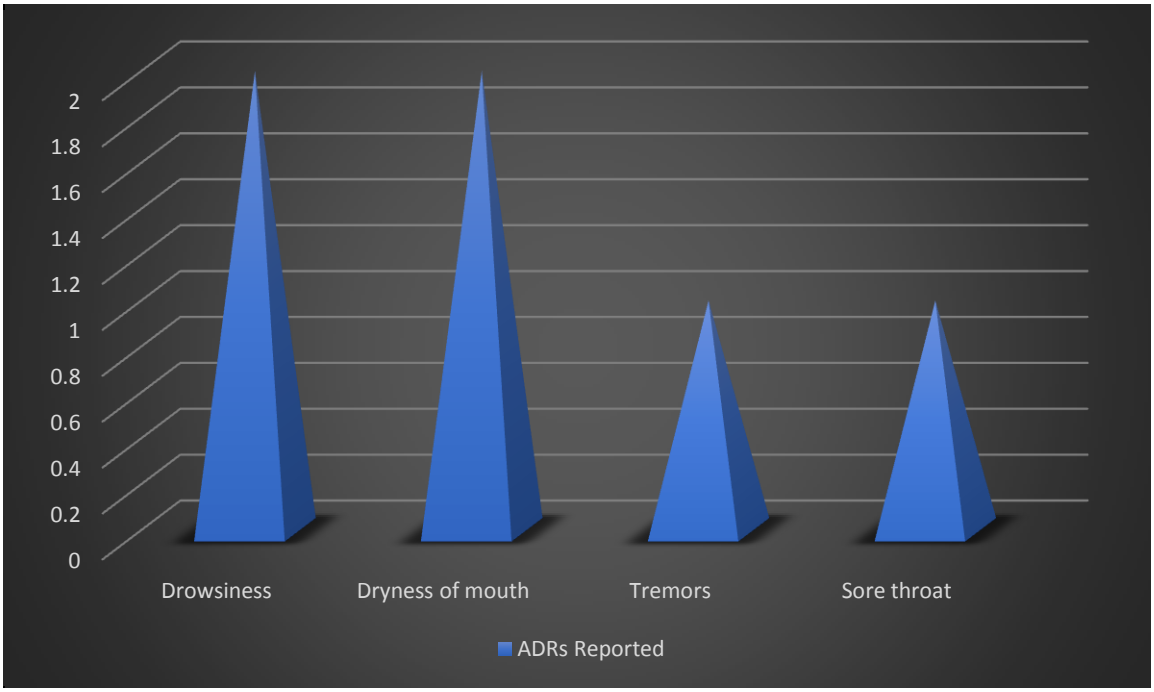


Table 5 WHO-UMC Causality Categories

Causality term	No of ADRs	% of ADRs
Certain	1	1.25
Probable	3	3.75
Possible	2	2.5
Unlikely	0	0
Conditional	0	0
Unassessable	0	0

Discussion

Drug Utilization Review helps the healthcare system to understand and improve the prescribing pattern for optimal drug use. The World Health Organization (WHO) addressed drug utilization as the marketing, distribution, prescription and use of drugs in a society, considering its consequences, either medical, social, and economic.

Drug utilization review is designed

- To detect &help prevent drugs interactions.
- To detect the potential drugs toxicity.
- To develop criteria & standards which prescribe optimal drug use.
- To detect the potential drug toxicity.
- To provide feed-back of results to clinicians.[6]

From **table 1,** we understand that wheeze associated disorders were more common in age group1-3 years which is in par with the study by Martinez et al[1]**. Table 2** showed male children (51.25%) predominance as mentioned in the study by Masters et al[7].

From **fig 2** we infer that wheeze is more in children in lower socioeconomic status which was similar to the study by Almqvist et al[8].

Anatomical therapeutic code (ATC) classification

When the Prescribed daily dose and defined daily dose ratio (PDD/DDD)is less than one it represents underutilization and more than one represents over utilization of drugs[4].

Table 4 -WHO/ INRUD Drug use indicators showed that all patients with wheeze associated disorder were prescribed multiple drug therapy at an average of 3.3 drugs per prescription. It is similar the study done by T. Rajathilagam et al in treating Bronchial asthma where the average was 3.632 per prescription.[9] This trend may be attributed to minimize the symptoms, prevent recurrent exacerbations and reduce the need for hospitalization. Hence polytherapy was needed with nebulization and antibiotics to cure the infection and to maintain the pulmonary function. It is found that only a small proportion 12.5% of drugs are prescribed in their generic names.

Generic names of drugs reduces the cost of therapy and will be beneficial provided there is adequate quality control[10]. Among the prescribed drugs 36.3% were from the state essential list of medicines and were available free of cost. Addition of related drugs to the essential list of medicines, could help patients with financial constraints to overcome the economic burden of the disease and also improves the compliance of treatment.

Analysis from our study showed that doctors preferred inhalational preparations than oral formulations probably because the study population was between age group of 3 months to 12 years. In analysis of prescriptions among the multidrug therapy antibiotics contribute 30.3% followed by adrenergic drugs (27.3%) as depicted in **table 4**. Nebulizer produces an aerosol from a solution to produce droplets which requires little coordination from the patient as the drug is inhaled through a face- mask or a mouth piece using normal tidal breathing. Thus, it is useful in patients who are unable to use conventional inhaler. The disadvantages of using a nebulizer include the long time commitment to maintenance and lack of portability.[11]

The most commonly prescribed drug in treating infective wheeze related disorders was nebulized Hypertonicsaline (HS)(53.7%) followed by levosalbutamol nebulization (48.7%).While considering individual diseases in our study in Fig:5 the preferred drug for treating bronchiolitis was nebulized HS (83.8%) followed by levosalbutamol nebulization (35.5%) which is in par with the study by Linjie Zhang et al where hypertonic saline 3% is preferred more in bronchiolitis in children in combination with bronchodilator.[12] In addition, adrenaline nebulization is used in 22.6% cases in bronchiolitis which increases the effectiveness of HS nebulization as per Tal G et al[13]. Budesonide nebulization is used in 19.4 % which is efficacious in bronchiolitis[14].Similarly, in treating LRI the preferred drug observed in our study was levosalbutamol nebulization (51.9%) followed by nebulized HS (40.7%). In case of bronchopneumonia since only 11 patients were treated for the same, no specific choice pattern was identified.

The major usage of Hypertonic saline nebulization in prescriptions is the documentation of its ability to improve mucus rheologic properties (elasticity and viscosity) and accelerating mucus transport. Also nebulized HS significantly decreased both the frequency and the duration of hospitalization in conditions like bronchiolitis among pediatric patients, improving efficacy and cost-effectiveness. Its good safety profile and low cost makes nebulized HS a potential attractive therapeutic modality for bronchiolitis in infants.[15]

Prescription-based study evaluates the rationality of the prescriptions and guidelines for rational prescribing practices which are put forth to improve the standards of prescribing.

Single drug therapy versus fixed drug combination

In this study, **fig:6** showed the fixed drug combination was used in 62.5% of the prescriptions. Among that amoxicillin with clavulanic acid (34%) was the preferred antibiotic followed by Ipratropium bromide with salbutamol (20%). This trend may be because fixed drug combination usage reduces the risk of medication noncompliance and help reduce rates of polypharmacy.[16,17]

Pharmacovigilance

Oral salbutamol (11.25%) over inhalational salbutamol (11.25%) have caused adverse effects with tremors 1.25%. Inhalational Salbutamol did not cause any side effects like sinus tachycardia in this study which correlates with the study done by Neville et al .[18]There were no side effects observed with levosalbutamol nebulization.

Budesonide nebulization (15%) caused sore throat in (1.25%) cases.

Adrenaline nebulization was used in 13.7 % patients and its safety and efficacy is better than salbutamol which is in par with Abroug et al[19]. All adverse effects (7.5%) were evaluated according

to WHO Causality scale in table 5. Among them 3.75% events were found to be probable ADR (dryness of mouth due to ipratropium and tremors due to oral salbutamol), 2.5% events were found to be possible ADR (drowsiness due to chlorpheniramine) and 1.25 % events were found to be certain ADR (sore throat due to budesonide).

Conclusion

The study highlighted the interesting fact that polytherapy (FDC) was the main stay of treatment than monotherapy (single drug) in infective wheeze associated disorders in children. Formulations such as hypertonic saline nebulization and levo salbutamol nebulization was found to be most commonly used in children. Among the bronchodilators, FDC of salbutamol with ipratropium bromide was more frequently used.

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References

1. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and Wheezing in the First Six Years of Life. N Engl J Med . 1995 Jan 19;332(3):133–8.
2. Weiss LN. The Diagnosis of Wheezing in Children. American family physician 2008; 77(8):1110-1114
3. Wright AL: Epidemiology of Asthma and Recurrent Wheeze in Childhood, Arizona,2002;22:33-34
4. Utilization D, Alto P, Trykk LH, Aksidenstrykkeri N, Isbn AS. Introduction to Drug Utilization Research .Drug classification system, 2003:33-39.
5. Jamali AN, Aqil M, Alam MS, Pillai KK, Kapur P. A pharmacovigilance study on patients of bronchial asthma in a teaching hospital. Journal of pharmacy and bioallied sciences 2010;2(4):333-336.
6. Shimpi RD, Salunkhe PS. Drug utilization evaluation and prescription monitoring in asthmatic patients.Journal of pharmacy and biological sciences 2012;2(1)117-122.
7. Masters IB, Chang AB, Patterson L, Wainwright C, Buntain H, Dean BW, et al. Series of laryngomalacia, tracheomalacia, and bronchomalacia disorders and their associations with other conditions in children. Pediatric Pulmonology 2002;34(3):189–195.
8. Almqvist C, Pershagen G, Wickman M. Low socioeconomic status as a risk factor for asthma, rhinitis and sensitization at 4 years in a birth cohort. Clincal and Experimental Allergy 2005 1;35(5):612–8.
9. T.Rajathilagam, Tasneem Sandozi , A.D. Nageswari, P.Paramesh, R.Jamuna Rani:Drug utilisation study in bronchial asthma in a tertiary care hospital. International journal of Pharmaceutical applications 2012;3(2):297–305.
10. Mathew P. Generic drugs : Review and experiences from South India. Journal of family medicine and primary care 2015;4(3):319–323.
11. Cochrane G Mac et al. Compliance and Outcomes in Patients with Asthma. Department of allergy and respiratory medicine 1996;12–13.
12. Zhang L, Mendoza-sassi RA, Klassen TP, Wainwright C. Nebulized Hypertonic Saline for Acute Bronchiolitis : A

Systematic Review. 2015;136(4):688-701.
13. Tal G, Cesar K, Oron A, Houri S, Ballin A, Mandelberg A. Hypertonic Saline / Epinephrine Treatment in Hospitalized Infants with Viral Bronchiolitis Reduces Hospitalization Stay : 2 Years Experience. 2006;8:3–7.
14. Richter H, Seddon P. Early nebulized budesonide in the treatment of bronchiolitis and the prevention of postbronchiolitic wheezing. The Journal of Pediatrics 1998;132(5):849–853.
15. Wills PJ, Hall RL, Chan W, Cole PJ, Cook P, Hooper P, et al. Rapid Publication Sodium Chloride Increases the Ciliary Transportability of Cystic Fibrosis and Bronchiectasis Sputum on the Mucus-depleted Bovine Trachea. American society for clinical investigation 1997:99(1):9-13
16. Press D. Polypharmacy in pediatric patients and opportunities for pharmacists involvement. Integrated pharmacy research and practice 2015;4:113–126.
17. Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-Dose Combinations Improve Medication Compliance : A Meta-Analysis. The American journal of medicine 2007;120(8)713–719.
18. Neville A, Palmer BD, May CS, Palmer KN V, Murchison LE. Metabolic effects of salbutamol : comparison of aerosol and intravenous administration. British medical journal 1977;1:413-414.
19. Abroug F, Nouira S, Bchir A, Boujdaria R, Elatrous S, Bouchoucha S. A controlled trial of nebulized salbutamol and adrenaline in acute severe asthma. Intensive Care Medicine 1995 ;21(1):18–23.