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COMPARATIVE STUDY OF BETA-LACTAM MONOTHERAPY VERSUS COMBINATION OF BETA-LACTAM ALONG WITH OTHER ANTIBIOTIC THERAPY FOR THE TREATMENT OF LRTI IN PEDIATRICS

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Abstract:

Background:

This study was done to compare the effectiveness of Beta lactam monotherapy versus combination of Beta lactam along with other antibiotics therapy for treating the LRTI in Pediatrics. A total of 75 patients included in this study who are of age between 3 months to 18 years. The most frequent presenting complaints were cough, fever, and breathlessness, signifying the serious condition of the patient, requiring hospitalization. The common diagnosis are Pneumonia and Bronchiolitis.

Objectives:

The primary objective of this study is to compare the effectiveness and tolerability of β-Lactam monotherapy Vs combination of β-Lactam along with other antibiotics therapy for the treatment of LRTI in Pediatrics and to compare the duration of hospital, stay on β-Lactam monotherapy Vs combination of β-Lactam along with another antibiotics therapy.

Materials and methods:

The present study was conducted in Pediatric department of BGS Global Institute of Medical Sciences (BGS-GIMS), Kengeri, Bengaluru, Karnataka. This is a comparative study of monotherapy vs combination therapy of beta lactam antibiotics in LRTI and the study was conducted for the period of 6 months. All children within the age of 3 month to 18 years admitted with LRTI in a pediatric department were included in the study.

Results:

Our study compares the effectiveness of monotherapy vs. combination therapy with commonly prescribed antibiotics for LRTI in children, primarily Ceftriaxone, Amoxicillin + Clavulanic acid, and Azithromycin. Most children recover fully, with a small portion developing chronic symptoms due to factors like immunosuppression and environmental conditions. Hospital stays and recovery times were similar between groups, with no significant difference in duration. Monotherapy had a higher pneumonia classification rate (48.1% vs. 38.1%) and underweight status (77.8% vs. 81%) compared to combination therapy. The PRESS score showed significant differences only on the first day of follow-up.

Interpretation & Conclusions:

Over all in the comparison between the beta lactam monotherapy and combination of beta lactam along with other antibiotic therapy we concluded that there was no significant difference between the both of them. Both are effective in the patients for their respective situation and can chose based on the benefit over risk to the patient.

Key words: Beta lactam antibiotics, LRTI, monotherapy, combination therapy, PRESS score.

INTRODUCTION:

RESPIRATORY TRACT INFECTIONS (RTIs):

RTI is defined as any infectious disease of the upper or lower respiratory tract. Upper respiratory tract infections (URTIs) include the common cold, laryngitis, pharyngitis/tonsillitis, rhinitis, rhinosinusitis/sinusitis and otitis media. Lower respiratory tract infections (LRTIs) include bronchitis, bronchiolitis, pneumonia and tracheitis. [1]

CLASSIFICATION OF RTIs:

Respiratory tract infections (RTIs) are classified as upper respiratory tract infections (URIs) or lower respiratory tract infections (LRTIs). The upper respiratory tract consists of the airways from the nostrils to the vocal cords in the larynx, including the paranasal sinuses and the middle ear. The lower respiratory tract covers the continuation of the airways from the trachea and bronchi to the bronchioles and the alveoli. [2]

Common lower RTIs in infants and young children include:

Flu. The flu (influenza) is a common viral infection that occurs most often during the winter months. It can be more dangerous to your health if you are very young or elderly. Viral Bronchiolitis. Bronchiolitis is an inflammation of the lining of the bronchioles (the very small passages through which air flows to and from the lungs). This condition is very common in infants and caused by several viruses, including respiratory syncytial virus (RSV). Pneumonia. Pneumonia is an infection that causes inflammation of the air sacs in one or both of the lungs. Its symptoms can range from mild to severe enough to require hospitalization. The main symptom of a lower RTI is cough, which can be severe. Your child may have a dry cough or a wet cough. Even if it is a wet cough, he or she may not be able to cough up phlegm/mucus.

Classification of LRTI based on IMNCI Guidelines:

The Integrated Management of Newborn and Childhood Illnesses (IMNCI) case management approach offers simple and effective methods to comprehensively prevent and manage the leading causes of serious illnesses and mortality in children below five years. With IMNCI, sick children or young infants are not only treated for the signs and symptoms they present within a health facility, but are also assessed for the other disease conditions they may be suffering from. The guidelines take an evidence-based, syndromic approach to case management that supports the

rational, effective and affordable use of drugs and diagnostic tools. [22] An evidence-based syndromic approach can be used to determine the:

• Health problem(s) the child may have;

• Severity of the child's condition;

• Actions that can be taken to care for the child (e.g. refer the child immediately, manage with available resources, or manage at home). [22]

IMNCI Classification for Pneumonia [23]

IMNCI Classification	Clinical Guidelines
Severe Pneumonia or Very severe disease	Chest indrawing Any general danger sign
Pneumonia	Fast Breathing
Cough or Cold	No signs of pneumonia or very severe disease

Pediatric Respiratory Severity Score (PRESS).

It is important to evaluate the severity of respiratory infection in a timely manner to assess the emergency condition, so that further management can be planned. There are few scoring systems for evaluating respiratory infections at the bedside.

Yumiko Miyaji, K. Sugai et al. developed Pediatric Respiratory Severity Score (PRESS) score in 2010 to evaluate a new simple bedside scoring system for the rapid assessment of pediatric respiratory infections in emergency settings. It is for the assessment of severity of pediatric patients with respiratory infections and helps to classify patients into three groups: mild (0 - 1), moderate (2 - 3), severe (4 - 5) based on five parameters: respiratory rate, wheezing, accessory muscle use, SpO2, and feeding difficulties. The PRESS score is easy and simple for assessing a patient. Each parameter has a score of 0 or 1, where 1 is present, and 0 is absent. A summation of these parameters classifies the patient as mild (with score 0 to 1), moderate (with score 2 to 3), and severe (with score 4 to 5). Based on the total score the severity of the infection is identified, this consequently indicates a proper treatment with urgency. Thus, patients can be treated appropriately. [24]

ANTIBIOTIC TREATMENT FOR LRTI IN PEDIATRICS:

β-Lactam monotherapy and β-lactam plus other antibiotic combination therapy are both common empirical treatment strategies for children hospitalized with lower respiratory tract infection, but few studies have evaluated the effectiveness of these 2 treatment approaches. Empirical antibiotic use was classified according to the antibiotics received during the first 2 calendar days of hospitalization. β-Lactams included oral or parenteral second- or third generation cephalosporins (excluding anti-pseudomonas cephalosporins), as well as penicillin, ampicillin, ampicillin sulbactam, amoxicillin, and amoxicillin-clavulanate.

β-Lactam monotherapy was defined as the exclusive use of 1 or more of these antibiotics. Use of a β-lactam plus an oral or parenteral macrolide (azithromycin or clarithromycin) during the first 2 calendar days of hospitalization served as the other combination therapy group. [25]

Antibacterial were prescribed in prescriptions, of which amoxicillin/clavulanic acid and cefotaxime were the most common. Almost half of the antibacterial were prescribed by their brand name. Five antibacterial, namely amoxicillin/clavulanic acid, cefotaxime, amikacin, ceftriaxone, and ampicillin made up the DU 90% index.

To assess the appropriateness of antibacterial use, guidelines set by the Indian Academy of Pediatrics and the modified Kunin's criteria were used. It was observed that all patients received antibacterial, irrespective of the laboratory results and chest X-ray.

As per WHO core indicators, it was observed that polypharmacy was widely practiced. Antibacterial were prescribed in all patients. Similarly, almost all patients were prescribed injections. Only half the drugs were prescribed by their generic names. A majority of the drugs prescribed were from the National Essential Medicines List (NEML) 2011 (75%) and the WHO EML 2010 (70%). [26]

Treatment of these infections is often directed towards the prevention of late complications (especially rheumatic fever and acute glomerulitis, which can be very serious)

Since GABHS are generally susceptible to a range of antibiotics, there are numerous possible treatments, although penicillin V, amoxicillin and co-amoxiclav remain popular. Nevertheless, in spite of their good activity in vitro against GABHS, a significant number of failures occur with penicillin's, which have been attributed to a number of causes. Pediatric LRTIs can also be caused by respiratory viruses, and antibiotic treatment is aimed at reducing complications such as bacterial pneumonia. Although Gram-positive 286 bacteria are often the cause of LRTI, atypical pathogens can also be involved; one of these, Mycoplasma pneumoniae, occurs more frequently in children than in adults. Empirical antibiotic therapy needs, therefore, to be effective against such penicillin-resistant organisms, and the macrolide erythromycin has been widely used as an alternative to lactams for treating LRTI.

Although erythromycin is active against many important respiratory pathogens, it has only moderate activity against Hemophilus influenzae, tolerance of the drug is often low and it also has to be given more than once a day." Azithromycin is an azalide antibacterial agent, related structurally to erythromycin, but with a number of novel features. It has improved acid stability and has far better activity against some Gram-negative organisms, including H. influenzae and Moraxella catarrhalis, whilst retaining the good Gram-positive spectrum of erythromycin.

MATERIAL & METHODS

STUDY METHOD:

Study setting: The present study was conducted in Pediatric department of BGS Global Institute of Medical Sciences (BGS-GIMS), Kengeri, Bengaluru, Karnataka 560060

Study population: All children within the age of 3 month to 18 years admitted with LRTI in a pediatric department.

Study design: It is a Comparative study.

Study duration: Study was conducted for a period of six months.

Sample size: At a 95% confidence level, 80% power, considering the effect size of 0.70 (70%), with an allocation ratio 2:1 (Monotherapy: Combination therapy). The sample size is estimated using G*Power 3.1.9.7 is, 54 Monotherapy and 21 Combination therapy.

INCLUSION CRITERIA

All pediatric patients of age between 3 months to 18 years with LRTI from inpatient department.

EXCLUSION CRITERIA

- Patients with multisystem involvement, shock, altered sensorium.
- Patients above the age of 18 years. Patients below the age of 3 month.
- Patients with aspiration pneumonia, very severe pneumonia.

COLLECTION OF DATA:

The data was collected from the pediatric department as per the inclusion criteria; and the collections of data is based on these parameters i.e , first was the patient demographic details like age, gender, date of admission and second one was the outcome parameters like improvement of signs and symptoms of LRTI, hospital length of stay (LOS), duration of antibiotic usage and discharge status, time to become afebrile, and using the series of Press Score via ANNEXURE 1: PATIENT DATA COLLECTION FORM

STATISTICAL ANALYSIS:

All the data collected were entered in a Microsoft Excel worksheet and analyzed using statistical software SPSS 20.0.

The Qualitative characteristics like Gender, Diagnosis, Procedure, scores have expressed in frequency with proportions, and compared between the groups by Chi-square test.

The Continuous study variable age, LOS, lab investigations is expressed by Mean ±SD if data follows normality, else Median with IQR (Interquartile range) in case of non-normality, based on normality t-test and Mann-Whitney U-Test is applied for comparison between the groups.

DATA CONFIDENTIALITY AND ETHICAL ISSUES:

Approval from the respective hospital – IRB was obtained prior to the study. The data collected will be accessible to the clinical guide, academic guide, and co-guide. As there is no risk to the patient the waiver of consent was approved.

REGULATORY APPROVAL AND FINDING:

Approval from the IRB and Ethical committee of BGS GIMS Hospital, Kengeri, Bengaluru, Karnataka.

CONFLICT OF INTEREST:

The research is conducted in the absence of any commercial or financial relationships that could be constructed as potential conflict of interest.

PUBLICATION AND PRESENTATION PLAN:

The study is planned to publish in reputed journals and clinical conferences. The paper will be authorized by clinical guide, academic guide, co-guide and the co-investigators.

RESULTS

Table 1: Distribution of Study Population based on Type of Therapy

Type of Therapy	n	%
Monotherapy	54	72
Combinational Therapy	21	28
Total	75	100

Among the total study population of 72% (54) received Monotherapy, while 28% (21) were prescribed Combination therapy after diagnosis.

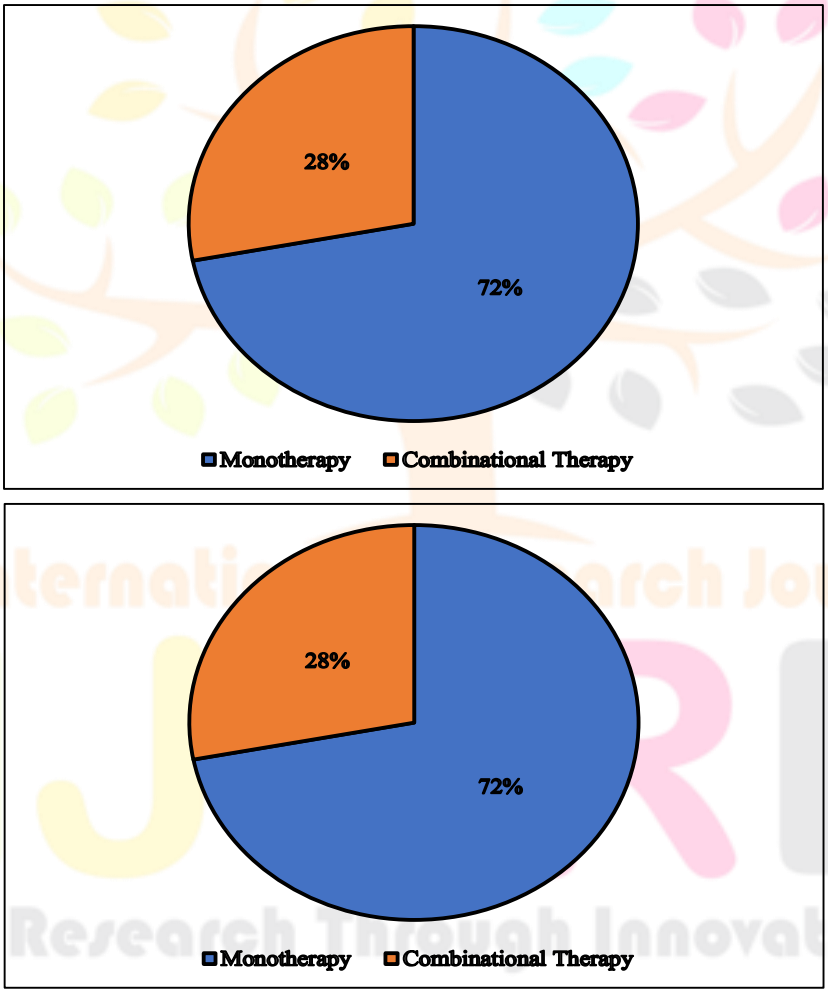

Fig 7: Distribution of Study subjects based on type of Therapy

Table 2. Age distribution among groups

Age Group (Years)	Monotherapy		Combinational Therapy		Total	
	n	%	n	%	n	%
< 4	23	42.6	13	61.9	36	48

4-8	20	37	6	28.6	26	35
8-12	7	13	2	9.5	9	12
> 12	4	7.4	0	0	4	5
Total	54	100	21	100	75	100
Comparison						
Median (Q1-Q3)	4 (2 - 6.25)		3 (2 - 5)		Mann-Whitney U	493
					p-value	0.38

The study investigated the age distribution within both groups. In both groups, most subjects were under the age of 4. 37% of study subjects in the monotherapy group fell within the age range of 4 – 8 years, compared to 28.6% in the combination therapy group for the same age group. 13% of study subjects in the monotherapy group were in the age range of 8-12 years, while the corresponding figure in the combination therapy group was 9.5%. Additionally, 7.4% of study subjects were in the age group of more than 12 years, and none were in the combination therapy group.

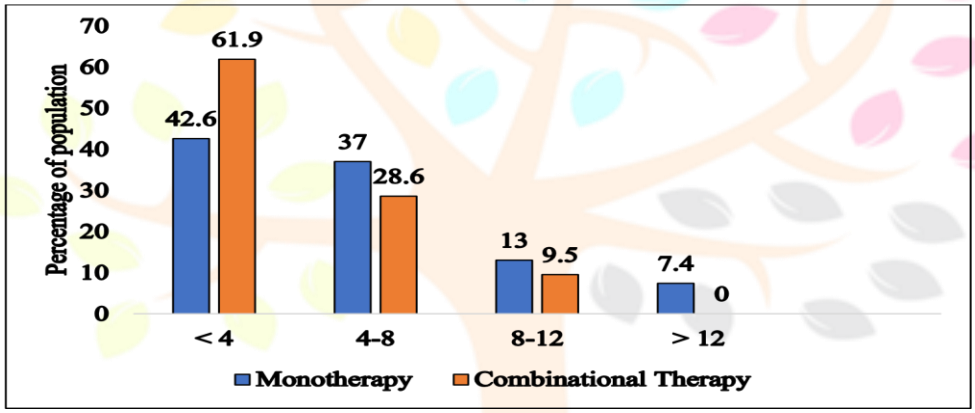

Fig 8. Age distribution among groups

Table 3: Gender Distribution among Monotherapy and Combinational Therapy Study Population

Gender	Monotherapy		Combinational Therapy		Total		Chi-square test	p-value
	n	%	n	%	n	%		
Male	27	50	10	47.6	37	49.3	0.034	0.853
Female	27	50	11	52.4	38	50.7		
Total	54	100	21	100	75	100		

In the Monotherapy group, the distribution of study subjects is equal. Among those in the Combination Therapy group, the majority are female (52.4%), followed by males (47.6%). There was no statistically significant difference

in gender associations with the groups was observed (p > 0.05).

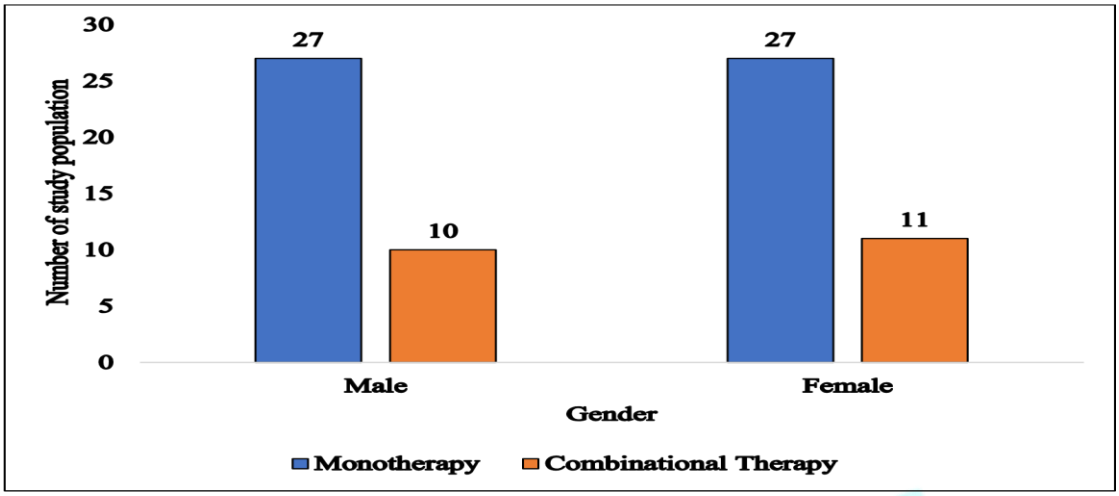

Fig 9. Gender distribution among groups

Table 4: Length of stay distribution among Monotherapy and Combinational Therapy Study Population

Duration of stay	Monotherapy		Combinational Therapy		Total	
	n	%	n	%	n	%
1-4	11	20.4	4	19	15	20
4-8	39	72.2	13	61.9	52	69.3
8-12	3	5.5	1	4.8	4	5.3
12-16	1	1.9	3	14.3	4	5.4
Total	54	100	21	100	75	100
Comparison						
Median (Q1-Q3)	5 (4- 6)		6 (4 - 6.5)		Mann-Whitney U	479.5
					p-value	0.294

The LOS (Length of Stay) distribution among subjects undergoing Monotherapy and Combination Therapy was observed. Most subjects in both the groups stayed in the hospital for 4-8 days, accounting for 72.2% and 61.9%, respectively. 20.4% in the Monotherapy group and 19% in the Combination Therapy group had a hospital stay of 1-4 days. 5.5% in the Monotherapy group and 4.8% in the Combination Therapy group stayed for 8-12 days.1.9% of subjects in the Monotherapy group and 14.3% in the Combination Therapy group stayed for more than 12 days. The test resulted in a U statistic of 479.5 and a p-value of 0.294. p > 0.05 indicates that there is no significant difference in the duration of stay between the two groups.

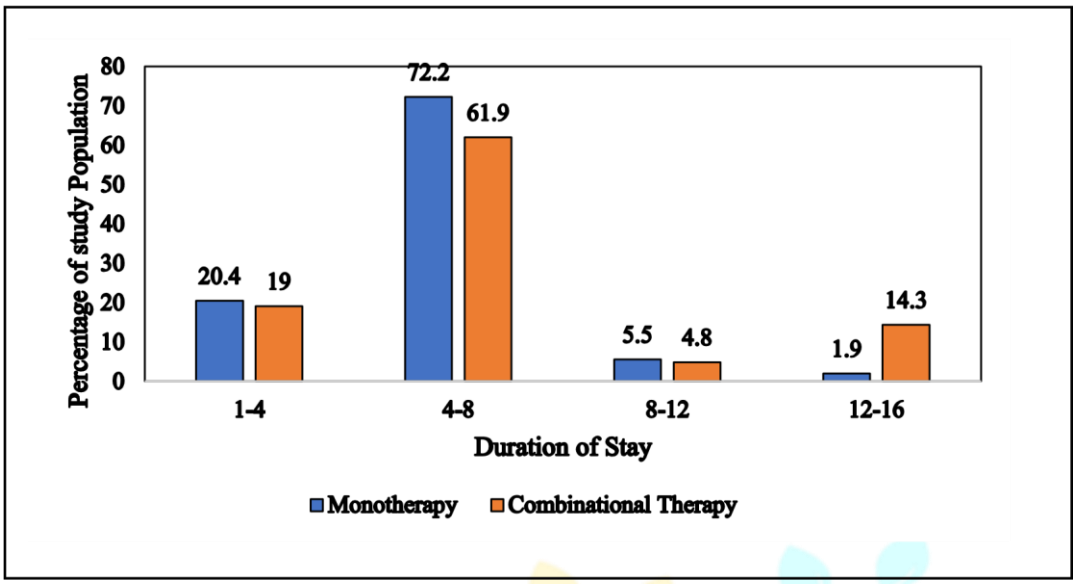

Fig 10. Distribution of Duration of stay among groups

Table 5: Distribution of the Study population receiving mono-therapy based on Diagnosis

Diagnosis	n	%
Acute Bronchopneumonia	1	1.8
Bronchiolitis	5	9.3
Bronchiolitis with secondary bronchopneumonia	1	1.9
Bronchopneumonia	18	33.2
Bronchopneumonia with moderate respiratory distress with no complications	2	3.6
Bronchopneumonia with mild respiratory distress	2	3.6
Bronchopneumonia with moderate respiratory distress	1	1.9
Bronchopneumonia with respiratory distress	2	3.7
Bronchopneumonia with severe acute malnutrition	1	1.9
community-acquired pneumonia	2	3.8
community acquired pneumonia - left lower lobe with no respiratory distress with no complications	1	1.9
Lower Lobe Pneumonia	1	1.9
LRTI	7	13
LRTI(Bronchiolitis)	1	1.9
Mild laryngotracheal bronchitis	1	1.8
pneumonia	3	5.6
pneumonia with URTI	1	1.8
Right middle lobe pneumonia	1	1.8
Viral Pneumonia	3	5.6
Total	54	100

Table 6: Distribution of the Study population receiving Combination therapy based on Diagnosis

Diagnosis	n	%
Atypical pneumonia	5	23.8
Bronchiolitis	1	4.8
Bronchopneumonia	3	14.3
Bronchopneumonia with moderate respiratory distress	1	4.7
Bronchopneumonia with respiratory distress	1	4.7
Left Lobar Pneumonia with left pleural effusion	1	4.7
Left Lobar Pneumonia (community-acquired)	1	4.7
Lower Respiratory Tract Infection	1	4.8
LRTI (Pneumonia)	1	4.8
Pneumonia	2	9.5
Right lower Lobe Pneumonia with pleural effusion	1	4.8
Right Lower Lober Pneumonia with pleural effusion	1	4.8
right upper Lobe Pneumonia	1	4.8
Viral Pneumonia	1	4.8
Total	21	100

Table 7: Distribution based on Clinical Signs among groups

Clinical signs	Monotherapy		Combinational Therapy		Total	
	n	%	n	%	n	%
Chest indrawing	1	1.8	1	4.8	2	2.7
Crept sounds (+)	3	5.6	0	0	2	4
Crept sounds (+), fast breathing	1	1.8	1	4.8	2	2.7
Crepitations (+)	1	1.8	0	0	1	1.3

Crepts is present	2	3.7	0	0	2	2.7
Crepts (+)	3	5.6	0	0	3	4
Difficulty in breathing	1	1.8	0	0	1	1.3
Fast breathing	8	14.9	6	28.5	14	18.7
Fast breathing, coarse crepts (+)	1	1.8	0	0	1	1.3
Fast breathing and crepts (+)	6	11.2	1	4.8	7	9.3
Fast breathing (40cpm), coarse crepts	0	0	1	4.8	1	1.3
Hurried breathing	2	3.7	0	0	2	2.7
NA	25	46.3	11	52.3	36	48
Total	54	100	21	100	75	100

Table 8: IMNCI classification among Monotherapy and Combination therapy study population

IMNCI Classification	Monotherapy		Combinational Therapy		Total	
	n	%	n	%	n	%
Non-severe Pneumonia	2	3.7	1	4.8	3.0	4
Pneumonia	26	48.1	8	38.1	34.0	45.3
Severe Pneumonia	1	1.9	1	4.8	2.0	2.7
NA	25	46.3	11	52.3	36.0	48
Total	54	100.0	21	100.0	75.0	100

The distribution of IMNCI classifications among subjects undergoing Monotherapy and Combination Therapy was analyzed. In the Monotherapy group, 3.7% of subjects were classified as having Non-severe Pneumonia, while in the Combination Therapy group, this figure was 4.8%. The combined total for Non-severe Pneumonia across both groups was 4.0%. For subjects undergoing Monotherapy, 48.1% were classified as having Pneumonia, compared to 38.1% in the Combination Therapy group. The combined total of Pneumonia across both groups was 45.3%. Severe Pneumonia was observed in 1.9% of subjects in the Monotherapy group and 4.8% in the Combination Therapy group. The combined total of Severe Pneumonia across both groups was 2.7%. In the Monotherapy group, 46.3% of subjects lacked available information, while in the Combination Therapy group, this percentage was 52.3%.

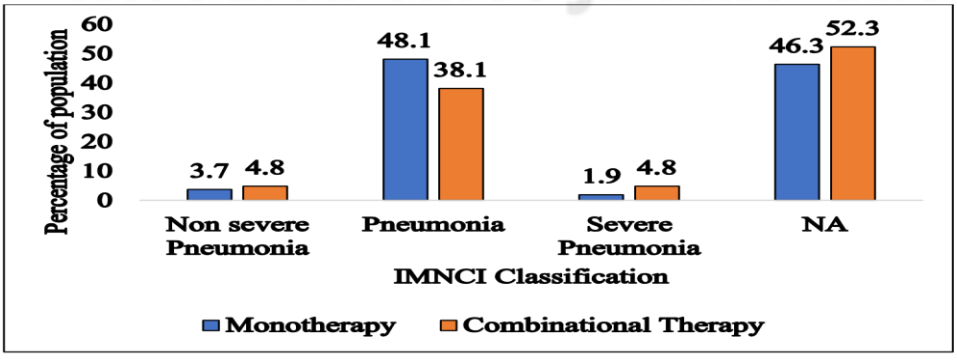

Fig 11. IMNCI classification among groups

Table 9: BMI classification among study groups

BMI Classification	Monotherapy		Combinational Therapy		Total	
	n	%	n	%	n	%
Underweight	42	77.8	17	81.0	59	78.7
Normal	7	13.0	3	14.3	10	13.3
Overweight	3	5.6	0	0	3	4
Class 1 Obese	0	0.0	1	4.8	1	1.3
Class 2 Obese	2	3.7	0	0	2	2.7
Total	54	100	21	100	75	100
Comparison						
Median (Q1-Q3)	15.04 (13.28- 17.46)		13.31 (12.71 - 14.76)		Mann-Whitney U	400.5
					p-value	0.049

In the Monotherapy group, 77.8% of subjects were classified as Underweight, while in the Combination Therapy group, this percentage was 81.0%. For subjects undergoing Monotherapy, 13.0% fell into the Normal BMI classification, compared to 14.3% in the Combination Therapy group. Overweight subjects were observed in 5.6% of the Monotherapy group, while none were recorded in the Combination Therapy group. No subjects in the Monotherapy group were classified as Class 1 Obese, whereas 4.8% of subjects in the Combination Therapy group fell into this category. Class 2 Obese subjects were identified in 3.7% of the Monotherapy group, while none were recorded in the Combination Therapy group. The Mann-Whitney U test yielded a U statistic of 400.5 with a p-value of 0.049, indicating a statistically significant difference in BMI between the two groups.

Table 10: Comparison between study groups

Comparison	Monotherapy	Combinational Therapy	Test Statistic		p-value
HB(g/dl)					
Mean ± SD	11.17±1.34	10.6±1.5	t-test	0.974	0.184
WBC (mm^3)					
Median(Q1-Q3)	10300 (5812.5 - 14450)	13600 (5687.5 - 23095)	Mann-Whitney U	265	0.223
PLT(µL)					
318000 343000 Median(Q1-Q3) (241000 - 457000) U	Mann- 372.5 0.582 (214000 -	471000) Whitney			
CRP (mg/L)					
Median(Q1-Q3)	14.3 (3.5 - 56.9)	21.2 (5.2 - 120.2)	Mann-Whitney U	200	0.233

The comparison of parameters (HB, WBC, PLT, and CRP) between subjects undergoing Monotherapy and Combination Therapy is summarized. The test statistics and p-values indicate no significant difference between the two groups in relation to these parameters.

Table 11: Distribution of monotherapy study subjects based on generic drug name

GENERIC Drug	n	%
Inj. Amikacin	2	3.7
Inj. Ceftriaxone	17	31.4
Inj. Amoxicillin + clavulanic acid	30	55.6
Syp. Azithromycin	4	7.4
Tab. Ceftriaxone	1	1.9
Total	54	100.0

In the context of Monotherapy, Inj. Amoxicillin + Clavulanic Acid (55.6%) was prescribed to most subjects, followed by Inj. Ceftriaxone (31.4%). Other prescribed medications include Inj. Amikacin (3.7%), Syp. Azithromycin (7.4%), and Tab. Ceftriaxone (1.9%).

Table 12: Distribution of Combination Therapy study subjects based on generic drug name

GENERIC Drug	n	%
Inj. Ceftriaxone & Inj. Amikacin	2	9.5
Inj. Ceftriaxone & Inj. Linezolid	2	9.5
Inj. Amoxicillin + clavulanic acid, Syp. Azithromycin, Inj. Ceftriaxone& Inj. Tazobactam + piperacillin	1	4.8
Inj. Amoxicillin + clavulanic acid & Syp. Azithromycin	2	9.5
Inj. Amoxicillin + clavulanic acid & Tab. Azithromycin	1	4.8
Inj. Amoxicillin + Clavulanic acid & Inj. Amikacin	1	4.8
Inj. Amoxicillin + Clavulanic acid & Inj. Ceftriaxone	2	9.5
Inj. Amoxicillin + Clavulanic acid & Syp. Azithromycin	2	9.5
Inj. Ceftriaxone & Syp Azithromycin	7	33.4
Inj. Ceftriaxone & Syp Azithromycin &Inj. Amikacin	1	4.7
Total	21	100.0

The study population received various combinations of generic drugs. Notable combinations included Inj. Ceftriaxone & Syp. Azithromycin (33.4%) and Inj. Ceftriaxone & Inj. Amikacin (9.5%), Inj. Ceftriaxone & Inj. Linezolid (9.5%), Inj. Amoxicillin + Clavulanic Acid & Syp. Azithromycin (9.5%), Inj. Amoxicillin + Clavulanic acid & Inj. Ceftriaxone (9.5%), and others.

Table 13: Number of days to become Afebrile among monotherapy and Combinational therapies

Number of Days	Monotherapy		Combinational Therapy		Total	
	n	%	n	%	n	%
1	10	18.5	4	19	14	18.7
2	14	25.9	4	19	18	24
3	15	27.8	6	28.7	21	28
4	6	11.1	4	19	10	13.4
5	4	7.4	0	0	4	5.3
6	2	3.7	2	9.5	4	5.3
NA	3	5.6	1	4.8	4	5.3
Total	54	100	21	100	75	100
Comparison						
Median (Q1-Q3)	3 (2 - 3)		3 (2 - 4)		Mann-Whitney U	400.5
					p-value	0.0494

The distribution of the number of days to achieve Afebrile status among subjects undergoing Monotherapy and Combination Therapy was analysed. Most of study subjects in both Monotherapy (27.8%) and Combination Therapy (28.7%) groups became afebrile within 3 days. In the Monotherapy group, 25.9% of subjects attained Afebrility in 2 days, while in the Combination Therapy group, 19% achieved the same within the same timeframe. 18.5% and 19% of subjects in Monotherapy and Combination Therapy, respectively, recovered from fever within 1 day. The remaining subjects took 4 days or more to become Afebrile. The statistical comparison indicated a significant difference in the median number of days to achieve Afebrile status between the two groups (p-Value < 0.05).

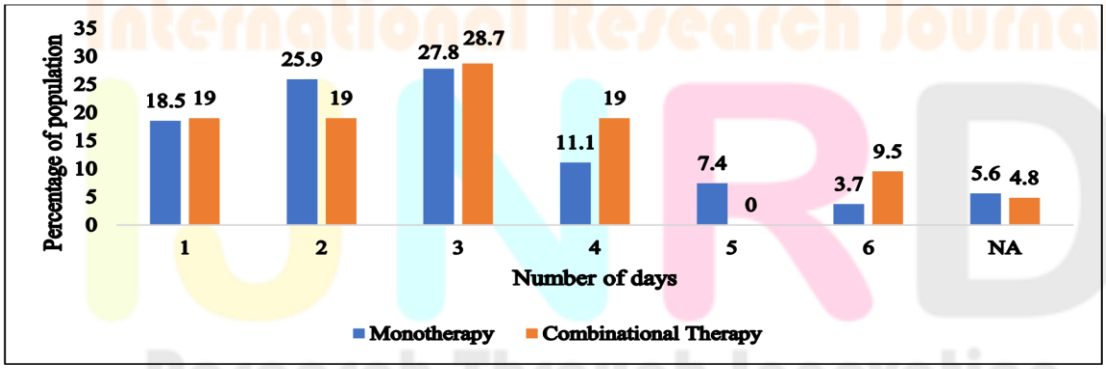

Fig. 12: Number of days to become Afebrile among study groups

Table 14: Distribution of Study population based on Discharge Status among Monotherapy and Combinational Therapy

DISCHARGE Status	Monotherapy		Combinational Therapy		Total	
	n	%	n	%	n	%
Afebrile, hemodynamically stable, satisfactory	0	0	1	4.8	1	1.3

he child is afebrile and emodynamically stable	2	3.7	0	0	2	2.7
Getting DAMA	0	0	1	4.8	1	1.3
Hemodynamically stable, symptomatically better	11	20.4	4	19	15	20
Hemodynamically stable	1	1.9	1	4.8	2	2.7
Hemodynamically stable, No respiratory distress	1	1.9	0	0	1	1.3
Satisfactory	34	63	10	47.6	44	58.7
Stable	2	3.7	0	0	2	2.7
Symptomatically better	1	1.8	4	19	5	6.7
Symptomatically better & and stable	1	1.8	0	0	1	1.3
Symptomatically better but DAMA	1	1.8	0	0	1	1.3
Total	54	100	21	100	75	100

The distribution of the study population based on discharge status was studied for both groups. Notable categories include 'Satisfactory' (Monotherapy: 63%, Combination Therapy: 47.6%), 'Hemodynamically Stable, Symptomatically Better' (Monotherapy: 20.4%, Combination Therapy: 19%), and 'Afebrile, Hemodynamically Stable, Satisfactory' (Overall: 1.3%).

Table 15: Distribution of Study population among Monotherapy and Combinational Therapy comparison based on Day 1 of follow-up

Day 1	Monotherapy		Combinational Therapy		Total	
	n	%	n	%	n	%
0	2	3.7	1	4.8	3	4
1	16	29.6	2	9.5	18	24
2	29	53.7	11	52.4	40	53.3
3	7	13	7	33.3	14	18.7
Total	54	100	21	100	75	100
Comparison						
Median (Q1-Q3)	2 (1 - 2)		2 (2 - 3)		Mann-Whitney U	402
					p-value	0.032

Distribution of the study population among individuals undergoing Monotherapy and Combination Therapy, with a specific focus on the first day of follow-up. On Day 1, 3.7% (n=2) of Monotherapy subjects and 4.8% (n=1) of Combination Therapy subjects attended follow-up, constituting a total of 4% (n=3) of the study population. The breakdown of followup days reveals that most subjects attended on Day 2, with 53.7% (n=29) in the Monotherapy group and 52.4% (n=11) in the Combination Therapy group, making up 53.3% (n=40) of the overall study

population. The Mann-Whitney U test, with a test statistic of 402 and a p-value of 0.032, signifies a significant difference in the distribution of the study population between Monotherapy and Combination Therapy on the first day of follow-up.

Table 16: Distribution of Study population among Monotherapy and Combinational Therapy and comparison based on Day 3 of follow-up

Day 3	Monotherapy		Combinational Therapy		Total	
	n	%	n	%	n	%
0	18	42.9	5	33.3	3	4
1	17	40.5	7	46.7	18	24
2	6	14.3	3	20	40	53.3
3	1	2.4	0	0	14	18.7
Total	42	100	15	100	75	100
Comparison						
Median (Q1-Q3)	1 (0 - 1)		1 (0 - 1)		Mann-Whitney U	285.5
					p-value	0.563

Distribution of the study population among individuals undergoing Monotherapy and Combination Therapy, focusing specifically on the third day of follow-up. On Day 3, 42.9% (n=18) of Monotherapy subjects and 33.3% (n=5) of Combination Therapy subjects attended follow-up, constituting a total of 18.7% (n=14) of the study population. The breakdown of follow-up days reveals that most subjects attended for 1 day, with 40.5% (n=17) in the Monotherapy group and 46.7% (n=7) in the Combination Therapy group, making up 24% (n=18) of the overall study population. The Mann-Whitney U test, with a test statistic of 285.5 and a p-value of 0.563, suggests no significant difference in the distribution of the study population between Monotherapy and Combination Therapy on the third day of follow-up.

Table 17: Distribution of Study population among Monotherapy and Combinational Therapy and comparison based on Day 5 of follow-up

Day 5	Monotherapy		Combinational Therapy		Total	
	n	%	n	%	n	%
0	15	83.3	12	92.3	27	87.1
1	2	11.1	1	7.7	3	9.7
2	1	5.6	0	0	1	3.2
Total	18	100	13	100	31	100
Comparison						
Median (Q1-Q3)	0 (0 - 0)		0 (0 - 0)		Mann-Whitney U	106
					p-value	0.449

Distribution of the study population among individuals undergoing Monotherapy and Combination Therapy, with a specific emphasis on the fifth day of follow-up. On Day 5, a significant proportion of subjects attended follow-up,

with 83.3% (n=15) in the Monotherapy group and 92.3% (n=12) in the Combination Therapy group, making up a total of 87.1% (n=27) of the study population. The breakdown of follow-up days indicates that most subjects attended on the same day, with 83.3% (n=15) in the Monotherapy group and 92.3% (n=12) in the Combination Therapy group, constituting 87.1% (n=27) of the overall study population. The analysis, utilizing the Mann-Whitney U test with a test statistic of 106, suggests no significant difference in the distribution of the study population between Monotherapy and Combination Therapy on the fifth day of follow-up.

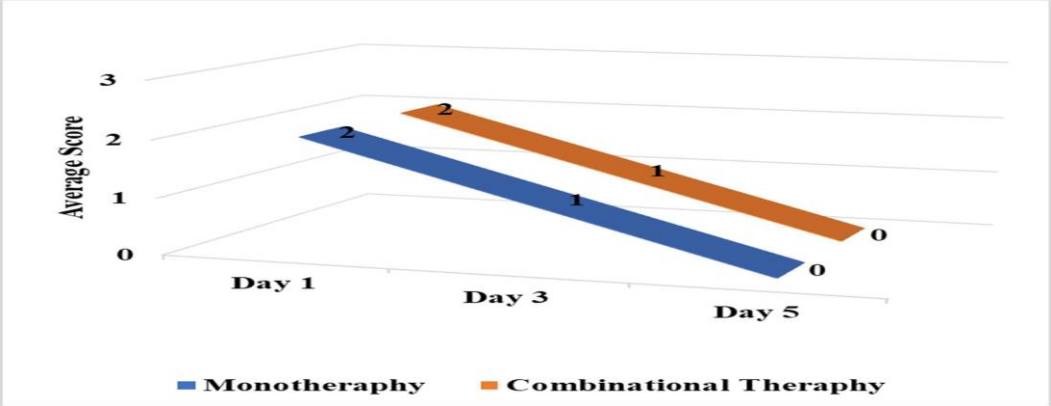

Fig. 13: DAY-WISE PRESS SCORE AMONG THE GROUPS

DISCUSSION

This study was done to compare the effectiveness of Beta lactam monotherapy versus combination of Beta lactam along with other antibiotics therapy for treating the LRTI in Pediatrics. A total of 75 patients included in this study who are of age between 3 months to 18 years. The most frequent presenting complaints were cough, fever, and breathlessness, signifying the serious condition of the patient, requiring hospitalization. The common diagnosis are Pneumonia and Bronchiolitis.

Among antibiotics Ceftriaxone, Amoxicillin + Clavulanic acid are the most prescribed Beta lactam antibiotics for the treatment of LRTI in our study. Along with beta lactam other antibiotics like Macrolide antibiotics, in that Azithromycin is most widely used in this study. So our study mainly compare the effectiveness of monotherapy versus combination therapy of these prescribed antibiotics.

Most children with LRTI fully recover, a proportion develop chronic respiratory symptoms; Reasons include host factors (immunosuppression, poor secretion clearance, airway abnormalities or genetic factors), infectious causes (TB or adenovirus), and adverse environmental factors.

The substantial decline in the burden of childhood community acquired lower respiratory tract infections (LRTI) over the last decades is associated with improvements in immunization, nutrition, socioeconomic control.

The distribution of study subjects in the monotherapy group is equal. Among combination therapy group, the majority are females (52.4%), followed by males (47.6%). Which is different than the study conducted by Mohamed Azmi Ahmad Hasali, Mohamed Izham Mohamed
Ibrahim, Syed Azhar Syed sulaiman, Zhari Ahmad and Jameela Banu Ahmad Hasali, (Males 55% & Females – 45%).

In this study the distribution of subjects with length of stay undergoing monotherapy and combination therapy was observed. 20.4% in the monotherapy group and 19% in the combination group had a hospital stay of 1-4 days and 5.5% of monotherapy and 4.8% of combination therapy group stayed for 8-12 days. 1.9% of subjects in the monotherapy group and 14.3% in the combination therapy group stayed for more than 12 days. The test resulted in a U statistic of 479.5 and a p-value of 0.294. $p > 0.05$ indicates that there is no significant difference in the duration of stay between the two groups, which is similar to the study conducted by the Derek J Williams, Kathryn M Edwards, Wesley H Self, Yuwei Zhu, Sandra R Arnold, Janathan A McCullers, et al. [25]

In this study based on IMNCI guidelines, for subjects undergoing monotherapy, 48.1% were classified as having pneumonia, compare to 38.1% in the combination therapy group. The combined total of pneumonia across both groups was 45.3%.

In monotherapy group 77.8% of subjects were classified as underweight, while in the combination therapy group this percentage was 81%. For subjects undergoing monotherapy, 13.0% fell into the normal BMI classification compared to 14.3% in the combination therapy group. Overweight subjects were observed in 5.6% of the monotherapy group, while none were recorded in the combination group.

The comparison of parameters (Hb, WBC, PLT and CRP) between subjects undergoing monotherapy and combination therapy is summarized.

In the context of monotherapy, Inj. Amoxicillin + Clavulanic acid was prescribed to most of the subjects (55.6%) followed by Inj. Ceftriaxone (31.4%). Other prescribed medications include Inj. Amikacin (3.7%), Syp. Azithromycin (7.4%), and Tab. Ceftriaxone (1.9%), which is similar to the study conducted by Geetha S. Iyer, Prakruti P. Patel, Jigar R. Panchal, R.K Dikshith.

The study population received various combinations of generic drugs. Notable combinations include Inj. Ceftriaxone and Syp. Azithromycin (33.4%), and Inj. Ceftriaxone and Inj. Amikacin (9.5%), Inj. Ceftriaxone & Inj. Linezolid (9.5%), Inj. Amoxicillin + Clavulanic acid & Syp. Azithromycin (9.5%), Inj. Amoxicillin + Clavulanic acid & Inj. Ceftriaxone (9.5%) and others.

Most of study subjects in both monotherapy (27.8%) and combination therapy (28.7%) groups became afebrile within 3 days. In the monotherapy group, 25.9% of subjects attend afebrility in 2 days, while in the combination therapy group 19% achieved the same within the same time frame.18.5% & 19% of subjects from both monotherapy and combination therapy respectively, recovered from fever within one day. The remaining subjects took 4 days or more to became afebrile. Which shows a significant difference between the both groups. Which is study not similar to the study conducted by, Mohamed Azmi Ahmad Hasali, Mohamed Izham Mohamed Ibrahim, Syed Azhar Syed sulaiman, Zhari Ahmad and Jameela Banu Ahmad Hasali where it states there is a no significant difference between the groups in terms of time of afebrile.

The study population based on discharge status was studied for both groups. The categories included in this study are satisfactory (Monotherapy:63%, Combination therapy: 47.6%), hemodynamically stable, symptomatically better (Monotherapy: 20.4%, Combination therapy :19%) and afebrile.

Distribution of study population based on PRESS SCORE, indicates with a test-statistics of 402 and a p- value of 0.032, signifies a significance difference in the distribution in the study population between monotherapy and combination therapy on the first day of follow-up. For the third day follow-up the test statistics of 285.5 and a p-value of 0.0563, suggests no significant difference in distribution of the study population between monotherapy and combination therapy. On the fifth day of follow-up, the test statistic of 106, suggests no significant difference in the distribution of the study population between monotherapy and combination.

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None

BIBLIOGRAPHY

1.Respiratory Tract Infections - Antibiotic Prescribing: Prescribing of Antibiotics for Self-limiting Respiratory Tract Infections in Adults and Children in Primary Care. London: National Institute for Health and Clinical Excellence (NICE); 2008 Jul. (NICE Clinical Guidelines, No. 69.)

2.Simoes EAF, Cherian T, Chow J, et al. Acute Respiratory Infections in Children. In: Jamison DT, Breman JG, Measham AR, et al., editors. Disease Control Priorities in Developing Countries. 2nd edition. Washington (DC): The International Bank for Reconstruction and Development / The World Bank; 2006. Chapter 25

3.Dasaraju PV, Liu C. Infections of the Respiratory System. In: Baron S, editor. Medical Microbiology. 4th edition. Galveston (TX): University of Texas Medical Branch at Galveston; 1996. Chapter 93.

4.Troeger C, Blacker B, Khalil IA, Rao PC, Cao J, Zimsen SR. Estimates of the global, regional, and national morbidity, mortality, and etiologies of lower respiratory infections in 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Infect Dis. (2018) 18:1191–210.

5.Nanoo A, Izu A, Ismail NA, Ihekweazu C, Abubakar I, Mametja D, et al.. Nationwide and regional incidence of microbiologically confirmed pulmonary tuberculosis in South Africa, 2004-12: a time series analysis. Lancet Infect Dis. (2015) 15:1066–76.

6. Smylie J, Adomako P, editors. Indigenous children health report, assessed April 22, 2009.

7. Gupta GR. Tackling pneumonia and diarrhea: the deadliest diseases for the world's poorest children. Lancet. 2012 Jun 09;379(9832):2123-4.

8. Rudan I, O'Brien KL, Nair H, Liu L, Theodoratou E, Qazi S, Lukšić I, Fischer Walker CL, Black RE, Campbell H., Child Health Epidemiology Reference Group (CHERG). Epidemiology and etiology of childhood pneumonia in 2010: estimates of incidence, severe morbidity, mortality, underlying risk factors and causative pathogens for 192 countries. J Glob Health. 2013 Jun;3(1):010401.

9. Arif F. Updated Recommendations of Rcog On Prevention Of Early Onset Neonatal Group B Streptococcus Infection. J Ayub Med Coll Abbottabad. 2018 Jul-Sep;30(3):490.

10. Chen JC, Jenkins-Marsh S, Flenady V, Ireland S, May M, Grimwood K, Liley HG. Earlyonset group B streptococcal disease in a risk factor-based prevention setting: A 15-year population-based study. Aust N Z J Obstet Gynaecol. 2019 Jun;59(3):422-429.

11. Al Hazzani AA, Bawazeer RAB, Shehata AI. Epidemiological characterization of serotype group B Streptococci neonatal infections associated with interleukin-6 level as a sensitive parameter for the early diagnosis. Saudi J Biol Sci. 2018 Nov;25(7):1356-1364.

12.Verhoeven D. Influence of Immunological Maturity on Respiratory Syncytial Virus-Induced Morbidity in Young Children. Viral Immunol. 2019 Mar;32(2):76-83.

13. GBD 2016 Lower Respiratory Infections Collaborators. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Infect Dis. 2018 Nov;18(11):1191-1210.

14. Omer SB, Sutanto A, Sarwo H, Linehan M, Djelantik IG, Mercer D, Moniaga V, Moulton LH, Widjaya A, Muljati P, Gessner BD, Steinhoff MC. Climatic, temporal, and geographic characteristics of respiratory syncytial virus disease in a tropical island population. Epidemiol Infect. 2008 Oct;136(10):1319-27

15. Gessner BD, Sutanto A, Linehan M, Djelantik IG, Fletcher T, Gerudug IK, Ingerani, Mercer D, Moniaga V, Moulton LH, Moulton LH, Mulholland K, Nelson C, Soemohardjo S, Steinhoff
M, Widjaya A, Stoeckel P, Maynard J, Arjoso S. Incidences of vaccine-preventable Haemophilus influenzae type b pneumonia and meningitis in Indonesian children: hamletrandomised vaccine-probe trial. Lancet. 2005 Jan 1-7;365(9453):43-52.

16.Saraya T. Mycoplasma pneumoniae infection: Basics. J Gen Fam Med. 2017 Jun;18(3):118125.

17. Akashi Y, Hayashi D, Suzuki H, Shiigai M, Kanemoto K, Notake S, Ishiodori T, Ishikawa H, Imai H. Clinical features and seasonal variations in the prevalence of macrolideresistant Mycoplasma pneumoniae. J Gen Fam Med. 2018 Nov;19(6):191-197

18. Markowitz RI, Ruchelli E. Pneumonia in infants and children: radiological-pathological correlation. Semin Roentgenol. 1998 Apr;33(2):151-62

19. Jadavji T, Law B, Lebel MH, Kennedy WA, Gold R, Wang EE. A practical guide for the diagnosis and treatment of pediatric pneumonia. CMAJ. 1997 Mar 01;156(5):S703-11.

20. Hall CB, Powell KR, Schnabel KC, Gala CL, Pincus PH. Risk of secondary bacterial infection in infants hospitalized with respiratory syncytial viral infection. J Pediatr. 1988
Aug;113(2):266-71

21.Wagner T. Bronchiolitis. Pediatr Rev. 2009 Oct;30(10):386-95; quiz 395

22.Integrated Management of Neonatal and Childhood Illness,
main.mohfw.gov.in/sites/default/files/7091371954Mod%201%20INTRODUCTION%20R

23Facility Based Integrated Management of Neonatal and Childhood Illness ..., www.nhm.gov.in/images/pdf/programmes/child-health/guidelines/imnci_chart_booklet.pdf

24. Janjira Thokngaen, Wissaroot Karoonboonyanan, Pediatric respiratory severity score evaluates disease severity of respiratory tract infection in children, Chula Med J Vol. 63 No. 1 January - March 2019; 41 – 46.

25. Williams DJ, Edwards KM, Self WH, Zhu Y, Arnold SR, et.al. Effectiveness of β-Lactam Monotherapy vs Macrolide Combination Therapy for Children Hospitalized With Pneumonia. JAMA Pediatr. 2017 Dec 1;171(12):1184-1191.

26. Geetha S. Iyer, Prakruti P. Patel, Jigar R. Panchal1 , R. K. Dikshit. An analysis of the pharmacological management of respiratory tract infections in pediatric in-patients at a tertiary care teaching hospital. Emphasis on proper diagnosis and treatment, education and availability of locally effective guidelines may help in a better and judicious use of drugs in children.

27. Dunn CJ, Barradell LB: Azithromycin. A review of its pharmacological properties D V A Lauvau, L Verbist and the Paediatric Azithromycin Study Group Azithromycin and coamoxiclav for RTI in children and use as 3-day therapy in respiratory tract infections. Drugs 1996; 51: 483 – 505'

28. Baldwin DR, Wise R, Andrews JM, et a1: Azithromycin concentrations at the sites of pulmonary infection. Eur Respir J 1990; 3: 886 – 890.

29. Vandaux BP, Cherpillod J, Dayer P: Concentration of azithromycin in tonsillar and/or adenoid tissue from paediatric patients. J Antimicrob Chemather 1996; 37 (suppl C): 45 – 52.

30. Hamill J: Multicentre evaluation of azithromycin and penicillin V in the treatment of acute streptococcal pharyngitis and tonsillitis in children. J Antimicrab Chemather 1993; 37 (suppl E): 89 – 94.

31. O'Doherty B: Azithromycin versus penicillin V in the treatment of paediatric patients with acute streptococcal pharyngitis/tonsillitis. Eur J CUn Microbial Infect Dis 1996; 15: 718 - 724.

32. Schaad DB, Heynen G and the Swiss Tonsillopharyngitis Study Group: Evaluation of the efficacy, safety and toleration of azithromycin vs penicillin V in the treatment of acute streptococcal pharyngitis in children: results of a multicenter, open comparative trial. Pediatr Infect Dis J1996; 15: 791 – 795.

33. Weippl G: Multicentre comparison of azithromycin versus erythromycin in the treatment of paediatric pharyngitis or tonsillitis caused by group A streptococci. J Antimicrob Chemather 1993; 37 (suppl E): 92 – 101.

34. Hasali MA, Ibrahim MI, Sulaiman SA, Ahmad Z, Hasali JB. A clinical and economic study of community-acquired pneumonia between single versus combination therapy.
Pharm World Sci. 2005 Jun;27(3):249-53.

35.Fiore M, Corrente A, Pace MC, Alfieri A, Simeon V, Ippolito M, et,al. CeftolozaneTazobactam Combination Therapy Compared to Ceftolozane-Tazobactam Monotherapy for the Treatment of Severe Infections: A Systematic Review and Meta-Analysis. Antibiotics (Basel). 2021 Jan 15;10(1):79.

36. Paul M, Benuri-Silbiger I, Soares-Weiser K, Leibovici L. Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy for sepsis in immunocompetent patients: systematic review and meta-analysis of randomised trials. BMJ. 2004 Mar 20;328(7441):688

37. Leyenaar JK, Shieh MS, Lagu T, Pekow PS, Lindenauer PK. Comparative effectiveness of ceftriaxone in combination with a macrolide compared with ceftriaxone alone for pediatric patients hospitalized with community-acquired pneumonia. Pediatr Infect Dis J.
2014 Apr;33(4):387-92.

38.Same RG, Amoah J, Hsu AJ, Hersh AL, Sklansky DJ, Cosgrove SE, Tamma PD. The Association of Antibiotic Duration With Successful Treatment of Community-Acquired Pneumonia in Children. J Pediatric Infect Dis Soc. 2021 Apr 3;10(3):267-273.

39. Kogan R, Martínez MA, Rubilar L, Payá E, Quevedo I, et.al. Comparative randomized trial of azithromycin versus erythromycin and amoxicillin for treatment of communityacquired pneumonia in children. Pediatr Pulmonol. 2003 Feb;35(2):918.

40. Chiappini E, Mazzantini R, Bruzzese E, Capuano A, Colombo M, Cricelli C, et.al , Rational use of antibiotics for the management of children's respiratory tract infections in the ambulatory setting: an evidence-based consensus by the Italian Society of Preventive and Social Pediatrics. Paediatr Respir Rev. 2014 Sep;15(3):231-6.

41. Bottone E, Baldini G, Macchia P, Soldateschi M, Fridlevski A. Evaluation of the clinical efficacy of erythromycin, amoxicillin and co-trimoxazole in the treatment of acute respiratory tract infections in paediatric patients. Curr Med Res Opin. 1982;8(2):67-74.

42. Shapiro DJ, Hall M, Lipsett SC, Hersh AL, et.al.. Short- Versus Prolonged-Duration Antibiotics for Outpatient Pneumonia in Children. J Pediatr. 2021 Jul;234:205-211.e1

43. Li JZ, Winston LG, Moore DH, Bent S. Efficacy of short-course antibiotic regimens for community-acquired pneumonia: a meta-analysis. Am J Med. 2007 Sep;120(9):783-90

44. Mathur NB, Murugesan A. Comparison of Four Days Versus Seven Days Duration of Antibiotic Therapy for Neonatal Pneumonia: A Randomized Controlled Trial. Indian J Pediatr. 2018 Nov;85(11):963-967. doi: 10.1007/s12098-018-2708-y. Epub 2018 May 21.
PMID: 29781043.