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Efficacy and Safety of Azithromycin with Various Cephalosporins Used in Treatment of Lower Respiratory Tract Infection

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Abstract

Both macrolides as well as cephalosporins are widely used in the treatment of various lower respiratory tract infections either alone or in combination. The most commonly prescribed macrolide is azithromycin, generally in combination with different cephalosporins. The objectives of the present study were to find out the different combinations of azithromycin and cephalosporins generally prescribed, compare their efficacy, safety (adverse drug reactions) and cost. A prospective study was conducted in the medicine ward at St. Martha's Hospital, Bangalore. The data was analyzed to interpret different parameters of the study. Efficacy was determined based upon the clinical response (reduction in symptoms) and length of hospital stay. Safety was determined by assessing the occurrence of ADR and their severity. Cost of treatment was calculated by cost effective analysis. In the study period, 88 patients were included based on the inclusion criteria. Results revealed that different combinations prescribed were azithromycin + cefotaxime, azithromycin + ceftriaxone and azithromycin + cefuroxime. The most commonly prescribed combination was found to be cefotaxime with azithromycin. The cefotaxime group showed statistically significant difference in the reduction of clinical symptoms thereby indicating greater efficacy. 18% of the patients experienced ADRs which were mild in nature with none severe indicating that all the combinations were safe. The cost effective analysis showed that combination of azithromyin and cefotaxime is most economical.

Key words: *Antibiotics, Organisms, Antibiotic use, Pediatrics*

INTRODUCTION

Respiratory tract infections (RTI) are very common in the community and are one of the major reasons for visiting to primary care physicians[1]. The broad diagnosis of RTI includes the two principal sub-diagnoses of lower respiratory tract infection (LRTI) and upper respiratory tract infection (URTI) [2]. Community-acquired lower respiratory tract infection is a common cause of acute illness in adults. The spectrum of disease ranges from mild mucosal colonization or infection, to acute bronchitis or acute exacerbation of chronic bronchitis (AECB) or chronic obstructive pulmonary disease (COPD), to overwhelming parenchymal infection in patients with community-acquired pneumonia (CAP) [3]. The term LRTI includes a wide range of diseases which have different underlying pathologies and etiologies, *e.g.* acute bronchitis and pneumonia[4, 5]. In the out-patient setting, LRTI account for the majority of all antibiotics prescribed, burdening healthcare drug budgets. In most of the adults with LRTI, the illness is self-limiting and its course will not be modified by antibiotic therapy, representing viral or clinically non-relevant bacterial diseases. However, failure to initiate antibiotic therapy within four hours in cases of community acquired pneumonia is already associated with an increased mortality.[6] The major problem in the management of the LRTI is the inability to determine the causative micro-organism in majority of patients[7].

There are great systematic differences in the prescription of antibiotics, both overall and for LRTI, between countries and between different healthcare providers in the same country[8]. The "first generation" of guidelines was mostly consensus-based, whereas those published in 2000/2001 are at least partly evidence-based. However, there is still a lack of evidence in many areas of the LRTI field, and, in addition, interpretation of the available evidence is variable in some cases[9].

MATERIALS AND METHODS

The present study was conducted at medicine wards of St. Martha's Hospital, Bangalore which is 850 bedded

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tertiary care teaching hospital providing specialized health care services. Ethical clearance was obtained from the Institutional review board, St. Martha's Hospital, and an Informed consent was taken from the patients before starting the study. The period of study was 8 months. All adult and geriatric hospitalized patients of medicine department who were diagnosed with lower respiratory tract infection being prescribed with combination of azithromycin and cephalosporin during the study period and who were willing to participate in the study were included. Out patients, Pregnant/lactating patients, Pediatric patients, Non consenting patients were categorized under exclusion group.

In this prospective study, data was collected from case sheets of in-patients diagnosed with LRTI. A detailed description of demographic details, Presenting complaints, Past History, Personal History, Family History, Drug history, Laboratory parameters was taken. Patient follow up was carried out until discharge.

Efficacy was determined based upon the clinical response i.e. reduction in the symptoms such as sputum production, cough, wheezing, dyspnoea, fever, discolored sputum and length of hospital stay. The patients were monitored throughout till discharge and the symptoms were noted at regular intervals of three days. The patients were also monitored for any adverse drug reactions during the treatment.

Table No.1

Gender	n	%
Male	52	59
Female	36	41

Table No.2

Age	n	%
20-29	4	5
30-39	16	18
40-49	19	22
50-59	29	33
60-69	10	11
≤ 70	10	11

Cost of treatment was calculated by "cost effective analysis". It is an economic evaluation method of pharmacoeconomics where cost is measured in monetary terms and consequences are measured in non-monetary units. Cost effective analysis is used when there is single measurable dimension of effectiveness for both treatments. This method is used when it is necessary to measure both cost and clinical outcomes of drugs.

The cost effective ratio for each treatment option is calculated. This ratio is total cost of the drug divided by the number of units of output (benefit). In this case, the output is reduction in the symptoms on the seventh day of the treatment. Preferred drug is the one with lower cost per unit of output or health improvement. The difference in the reduction of symptoms in different treatment groups was statistically analyzed by Chi- square test.

RESULTS

After appropriate scrutiny 88 patients met the inclusion criteria and were enrolled for the study during a period of July 2007 to February 2008. Among the 88 patients that were included, 52 (41%) were male and 36 (59%) were female. The range of age of patients was between 23 to 88 years. Maximum number of patients 29 (33%) were in the age group of 50-59 years, depicted in table nos 1 & 2.

Patients were addicted to different habits such as smoking, alcohol and tobacco which affect the state of disease. Smoking was found to be the commonest among all the patients who accounted for 51.14% followed by tobacco 29.55% and alcohol consumption 26.13%.

Different LRTI diagnosed are given in table no.3 of which pneumonia was the form of illness in 40% of patients making it highest among others.

Table No.3

Diagnosis	n	%
Pneumonia	35	40
AECOPD	20	23
AEBA	13	14
BRONCHITIS	20	23

Co-Morbid conditions were accounted for the use of different combinations of antibiotics, of which hypertension was the most common followed by Diabetes Mellitus. Table no.4 gives the details of the different combinations used for different co-morbidities.

Table.No.4

Co-Morbid Conditions	No. of Patients			Total
	Azithromycin + Ceftriaxone	Azithromycin + Cefotaxime	Azithromycin + Cefuroxime	
HTN	16	21	7	44
DM	14	13	6	33
BA	5	9	2	16
ANAEMIA	4	5	1	10
COPD	3	8	1	12
UTI	6	5	4	15
RD	7	11	3	21
FEVER	7	13	3	23

The complaints presented by the patients are listed in table no.5, Majority of the patient (84.09%) complained of cough followed by sputum production (82.95%). The other symptoms observed were discolored sputum (73.86%), wheezing (53.40%), headache (43.18%), myalgia (39.77%) fever (36.36%), nausea (35.22%) and vomiting (23.86%).

Table No.5

Clinical Symptoms	No. of Patients (%)			Total
	Azithromycin + Ceftriaxone	Azithromycin + Cefotaxime	Azithromycin + Cefuroxime	
sputum production	84.37	83.72	76.92	82.95
cough	81.25	88.37	76.92	84.09
wheezing	46.87	62.79	38.46	53.40
dyspnoea	25	30.23	23.08	27.27
headache	43.75	44.19	38.46	43.18
myalgia	37.5	39.53	46.15	39.77
fever	37.5	37.21	30.77	36.36
nausea	34.37	34.88	38.46	35.22
vomiting	25	23.25	76.92	23.86
oxygen used	21.87	20.93	30.77	22.72
discolored sputum	75	79.06	53.85	73.86

The various laboratory parameters which were evaluated were WBC, ESR, Platelet count, PaO_2, $PaCO_2$, HCO_3, and SaO_2. The combinations of Macrolide and cephalosporin therapy prescribed to the patients for the treatment of their relevant conditions are given in Table No.6.

Table No.6

COMBINATIONS	n	(%)
Azithromycin + Ceftriaxone	32	36
Azithromycin + Cefotaxime	43	49
Azithromycin + Cefuroxime	13	15

Treatment details based on the type of ailment are listed in table no 7.

Table No.7

Diagnosis	No. of Patients (%)			
	Azithromycin + Ceftriaxone	Azithromycin + Cefotaxime	Azithromycin + Cefuroxime	Total
PNEUMONIA	37	43	20	40
AECOPD	40	45	15	23
AEBA	38	54	8	14
BRONCHITIS	30	60	10	23

The length of hospital stay of patients ranged from 2 to 12 days as shown in Table No.8, minimum stay was observed in azithromycin + ceftriaxone combination.

Table No.8

No. of Days	No. of Patients (%)			
	Azithromycin + Ceftriaxone	Azithromycin + Cefotaxime	Azithromycin + Cefuroxime	Total
1 - 4	0	4.65	7.7	3.4
5 - 8	56.25	69.77	15.38	56.82
9 - 12	43.75	25.58	76.92	39.78

Further evaluation of symptoms was done individually to assess their severity. The results are depicted in the following table no 9, 10, 11, 12, 13 & 14

Table No. 9 CHANGE IN SPUTUM PRODUCTION

TREATMENT	PATIENTS (%)						
	Day 0 (Base line)			Day 7			
	Severe	Mild/ Moderate	Absent	Discharged	Severe	Mild/Moderate	Absent
Azithromycin + Ceftriaxone	84.4	12.5	3.1	21.9	43.8	9.4	25.0
Azithromycin + Cefotaxime	83.7	9.3	7.0	34.9	25.6	0	39.5
Azithromycin + Cefuroxime	84.6	0	15.4	7.7	46.2	30.8	15.4

$\chi 2 = 3.635$ P = 0.458 $\chi 2 = 19.844$ P = 0.003

Table No. 10 CHANGE IN COUGH

$\chi 2 = 2.901$ P = 0.574 $\chi 2 = 9.892$ P = 0.129

Table No. 11 CHANGE IN WHEEZING

TREATMENT	PATIENTS (%)						
	Day 0 (Base line)				Day 7		
	Severe	Mild /Moderate	Absent	Discharged	Severe	Mild/ Moderate	Absent
Azithromycin + Ceftriaxone	46.9	12.5	40.6	21.9	9.4	18.8	50.0
Azithromycin + Cefotaxime	62.8	11.6	25.6	34.9	0	14.0	51.2
Azithromycin + Cefuroxime	61.5	23.1	15.4	7.7	23.1	23.1	46.2

$\chi 2 = 4.325$ P = 0.364 $\chi 2 = 12.075$ P = 0.060

Table No. 12 CHANGE IN DYSPNOEA

TREATMENT	PATIENTS (%)						
	Day 0 (Base line)			Visit 2			
	Severe	Mild/ Moderate	Absent	Discharged	Severe	Mild/ Moderate	Absent
Azithromycin + Ceftriaxone	25.0	50.0	25.0	21.9	6.2	31.2	40.6
Azithromycin + Cefotaxime	30.2	39.5	30.2	34.9	0	16.3	48.8
Azithromycin + Cefuroxime	53.8	30.8	15.4	7.7	23.1	46.2	23.1

$\chi 2 = 4.290$ P = 0.368 **$\chi 2 = 18.069$ P = 0.006**

Table No. 13 CHANGE IN FEVER

TREATMENT	PATIENTS (%)				
	Day 0 (Base line)		Day 7		
	No	Yes	Discharged	No	Yes
Azithromycin + Ceftriaxone	62.5	37.5	21.9	56.2	21.9
Azithromycin + Cefotaxime	62.8	37.2	34.9	53.5	11.6
Azithromycin + Cefuroxime	38.5	61.5	7.7	53.8	38.5

$\chi 2 = 2.686$ P = 0.261 **$\chi 2 = 7.091$ P = 0.131**

Table No. 14 Change in color of sputum

TREATMENT	PATIENTS (%)				
	Day 0 (Base line)		Day 7		
	No	Yes	Discharged	No	Yes
Azithromycin + Ceftriaxone	25.0	75.0	21.9	40.6	37.5
Azithromycin + Cefotaxime	20.9	79.1	34.9	46.5	18.6
Azithromycin + Cefuroxime	23.1	76.9	7.7	30.8	61.5

$\chi 2 = 0.174$ P = 0.917 $\chi 2 = 10.079$ P = 0.039

Table No. 15 Cost Effectiveness ratio

Cost Effective ratio = Cost of treatment for 7 days / Reduction of symptoms by 100%
Cost of Treatment = Cost of Drug + Other associated costs (Syringe)

TREATMENT	Cost Effective Ratio*						
	Sputum Production	Cough	Wheezing	Dyspnoea	Fever	Discoloured Sputum	Average
Azithromycin + Ceftriaxone	1497	1497	1621	3234	3897	1621	2230
Azithromycin + Cefotaxime	1251	1042	1158	2408	2841	1202	1650
Azithromycin + Cefuroxime	1822	2272	1822	2280	3043	4545	2631

*in Rs for 100% decrease in symptoms

Azithromycin + Cefotaxime has least cost effective ratio and is therefore most cost effective

DISCUSSION

During the study period, a total of 143 LRTI patients were admitted to the medicine units. Out of these, 88 patients (61.5%) met the inclusion criteria and were included in the study. Out of total 88 patients, 52 (59%) were male and 36 (41%) were female as shown in Table No. 1.The age of patients ranged from 23 to 88 years. Maximum number of patients 29 (33%) were in the age group of 50-59 years whereas 4 (5%) patients belonged to the age group of 20-29 years as shown in Table No. 2.Out of 88 patients 35 (40%) were diagnosed with Pneumonia followed by 20 patients with AECOPD (23%), 20 patients with bronchitis (23%) and 13 patients with AEBA (14%). The subjects were presented with different co-morbid conditions such as hypertension, diabetes mellitus, fever, bronchial asthma, renal disorder, chronic obstructive pulmonary disease, urinary tract infection and anemia. Among these co-morbid conditions, the most common conditions were hypertension (44 patients) and diabetes (33 patients).

From Table No.6, it was observed that maximum patients (43 patients and 49 %) were prescribed with the combination of azithromycin + cefotaxime followed by azithromycin + ceftriaxone (32 patients and 36 %) and azithromycin + cefuroxime axetil (13 patients and 15%).

EFFICACY

Azithromycin was the common antibiotic prescribed along with the cephalosporin to the enrolled patients at a dose of 500mg O.D. The minimum dose of cefotaxime prescribed to the patients was 1g B.I.D and the maximum dose was 2g Q.I.D. In case of ceftriaxone, the minimum dose was 1g B.I.D and the maximum dose was 2g T.I.D. In case of cefuroxime, the minimum dose prescribed to the patients was 1g B.D and the maximum dose prescribed was 2g Q.I.D.

The efficacy of medications was evaluated mainly by observing the reduction of symptoms from the time of admission up to the 7^{th} day of treatment. According to the Table Nos. 9,10,11,12,13 & 14, it was found that reduction in symptoms was greater in case of the combination of azithromycin with cefotaxime group compared to the other two groups. As the percentage of reduction in severe symptoms was greater in combination of Azithromycin with cefotaxime (58%), compared to ceftriaxone (40.6%) and cefuroxime (36.9%) group of patients, cefotaxime combination seems more effective in reducing the symptoms.

Statistically there was a significant difference found in the reduction of sputum production and dyspnea between the treatment groups. However, there was no statistically significant difference in the symptoms namely cough, wheezing and fever with different combinations.

The length of hospital stay ranged from 2 days to 12 days, according to Table No.8, maximum patients (56.82%) got discharge between 5 – 8 days. In case of cefotaxime and ceftriaxone group maximum patients i.e. 69.77% and 56.25% respectively got discharge between 5 – 8 days whereas in case of cefuroxime group maximum patients (76.92%) got discharged between 9 – 12 days. Based on the number of days for discharge, the patients of cefotaxime group were found to have improved and discharged earlier compared to the other two groups. Thus the combination of azithromycin and cefotaxime seemed most effective.

Safety of the treatment was evaluated by monitoring the adverse drug reactions of the treatment groups throughout the study period. 21.59% of patients had complaints of ADRs. Cefotaxime group of patient experienced lesser number of ADRs compared to the ceftriaxone and cefuroxime group. In case of patients given the combination of azithromycin with cefotaxime, there was no complaint of arthralgia, gingivitis, abdominal pain and heart burn, but CNS side effects such as agitation and dizziness were found. However, none of the ADRs were severe and life threatening. Hence, we can say that all the three combinations were safe.

The cost of the therapy was calculated by cost effective analysis. According to the Table No. 15, cefotaxime combination was found to be more economic compared to the ceftriaxone and cefuroxime combination. The average cost effective ratio of the cefotaxime combination was found to be Rs. 1650.00, whereas in case of ceftriaxone and cefuroxime combination the average cost per treatment for 100 % reduction in symptoms was found to be Rs. 2230.33 and Rs. 2631.27 respectively.

CONCLUSION

The various cephalosporins used along with the azithromycin for the treatment of LRTI in the medicine wards of the hospital were cefotaxime (3rd generation), ceftriaxone (3rd generation) and cefuroxime axetil (2nd generation). The combinations prescribed were appropriate with respect to the diagnosis. All the three combinations showed a decrease in the clinical symptoms of the patients, but cefotaxime group of patients showed a faster decrease compared to the other two groups. Length of the hospital stay was also less in the patients treated with cefotaxime and azithromycin combination.

Thus it can be concluded that combination of azithromycin with cefotaxime was more efficacious than azithromycin with ceftriaxone and azithromycin with cefuroxime axetil.

Azithromycin with cefotaxime showed a lesser number of adverse drug reactions than the other two combinations. However, ADRs observed in patients taking all the three different combination were mild in nature and none of them were serious and life threatening.

From the cost effective analysis azithromycin with cefotaxime combination was found to be more cost effective.

Thus, it can be concluded that combination of azithromycin with cefotaxime was the best among the three combinations in treating the LRTI.

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