



## Efficacy of amoxicillin-clavulanic acid versus ceftriaxone in children hospitalized under 5 years of age with uncomplicated community acquired pneumonia.

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**ABSTRACT... Objectives:** The aim of current study was to compare efficacy of amoxicillin-clavulanic acid versus ceftriaxone among children under 5 years of age, hospitalized having uncomplicated CAP. **Study Design:** Randomized Controlled trial (RCT). **Setting:** Department of Pediatric Medicine, The Children Hospital and Institute of Child Health, Lahore. **Period:** 01/01/2019 to 30/06/2019. **Material & Methods:** A total of 210 (105 in each group) children aged between 2 to 60 months, diagnosed having CAP were randomly allocated into either Group-A (received IV amoxicillin-clavulanic acid) or Group B (received IV ceftriaxone). Efficacy in terms of response of both treatment groups was noted after 5 days treatment. **Results:** Overall, mean age was noted as  $14.68 \pm 15.7$  months. Majority ( $n=131$ , 32.4%) were male and aged between 1 to 12 months ( $n=135$ , 64.3%). Mean duration of symptoms was noted as  $3.60 \pm 1.69$  days. Efficacy was significantly higher in children treated with ceftriaxone as compared to those treated with Amoxicillin/Clavulanic acid (96.2% vs. 76.2%;  $p < 0.001$ ). This difference was significant across all age, gender and duration of symptom groups ( $p < 0.05$ ). **Conclusion:** The efficacy was significantly higher in children treated with ceftriaxone as compared to Amoxicillin/Clavulanic acid.

**Key words:** Amoxicillin, Ceftriaxone, Community Acquired Pneumonia, Efficacy.

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## INTRODUCTION

Pneumonia is described as an inflammation of the parenchyma of the lungs.<sup>1</sup> Pneumonia is killing more children than any other type of infectious disease. Every year, pneumonia is estimated to claim the lives of more than 800,000 children under the age of 5 years. Greatest incidence of pneumonia is observed among South Asian countries where 2500 per 100000 children are affected with it.<sup>2,3</sup> In Pakistan, pneumonia is the leading reason of mortality among children, contributing to 33% of all deaths in infants and 37% of all deaths in children 1 to 4 years.<sup>4</sup> It has also been estimated that around 70% of global under 5 years of age deaths are being reported from only 15 countries while about 50% from 5 countries (that includes Pakistan as well).<sup>5</sup> According to UNICEF, in 2018, an estimated 58000 children died due to pneumonia in Pakistan.<sup>2</sup>

Under the age of 5 years, around 1 out of 500 children are hospitalized every year having community acquired pneumonia (CAP).<sup>6</sup> CAP may be caused by many pathogens yet commonest are known to be bacteria and viruses. In children less than 2 years of age, viral pathogens are more common while bacterial infections are more frequently seen among older children. In developing countries, streptococcus pneumonia is noted to be the commonest cause among children less than 5 years of age, followed by haemophilus influenza type b (Hib) and respiratory syncytial virus (RSV).<sup>7</sup>

WHO emphasized early diagnosis as well as assessment of severity of pneumonia based on clinical grounds and endorse antibiotics as foundation of treatment in suspected cases of bacterial CAP. Cotrimoxazole, penicillins, macrolides, aminoglycosides and cephalosporins

are some of the most commonly used antibiotics regarding CAP.<sup>8,9</sup> For in-patient management of CAP, WHO recommends amoxicillin (or benzylpenicillin)-gentamicin as 1<sup>st</sup> line of treatment while ceftriaxone, cloxacillin and gentamicin are endorsed as 2<sup>nd</sup> line treatment options.<sup>10</sup>

A study comparing ceftriaxone and amoxicillin-CA monitoring resolution of symptoms of pneumonia, clinical cure rate and therapy failure noted cure rate of 97% with the use of ceftriaxone while amoxicillin-CA resulted in 88% of cure rate at the end of the treatment period. The difference was not statistically significant between both treatment groups for cure rates.<sup>11</sup>

To the best of our knowledge, no local study is available comparing efficacy of ceftriaxone and amoxicillin-CA in children having CAP so this study was conducted to compare efficacy of amoxicillin/clavulanic acid versus ceftriaxone among children under 5 years of age, hospitalized having uncomplicated CAP.

## MATERIAL & METHODS

This randomized controlled trial (RCT) was done at the Pediatric Medicine Ward, The Children Hospital and Institute of Child Health, Lahore, from 01/01/2019 to 30/06/2019.

Written informed consent was taken from parents/guardians of all the study participants. Approval from Institutional Ethical Committee was taken for this trial. No conflict of interest was involved in this study and no financial grant or support was taken from the institution or any pharmaceutical company.

A sample of size of 210 (105 in each group) was calculated taking 80% power of test, 5% level of significance, and by taking expected efficacy of Ceftriaxone as 97% and Amoxicillin/CA as 88%.<sup>12</sup>

Study participants were children of both genders, aged 2 months to 5 years, having CAP and admitted through OPD and Emergency department in pediatric ward. CAP was labeled as per WHO guidelines<sup>13</sup> as no hospitalization in the last 1 month, presence of consolidations or other

infiltrates, on chest x-ray and the presence of minimum one out of the following: I) fever, II) cough, III) respiratory rate > 50 per minute in 2 months to 11 months of age, > 40 above 12 months to 59 months of age, IV) chest in-drawing, V) crepitation or wheeze on auscultation. Uncomplicated CAP was defined as CAP without complications on imaging study i.e. pneumothorax or blunting of costophrenic angles (air-fluid level) or necrosis on chest X-Ray. Children requiring intensive care unit (having cyanosis  $spO_2 < 85\%$  requiring intubation within first 24 hours of admission, having hospital-acquired pneumonia (that develops within 48 hours of admission), or with conditions like congenital heart or lung diseases, chronic kidney disease, developmental delays, severe malnutrition, asthma, immunodeficiency, already taking antibiotics, or having sign and symptoms related to system other than respiratory, were excluded from this study.

All the patients were divided into 2 groups adopting computer generated random numbers. Group-A received IV amoxicillin/CA as dose of 100mg per kg per day in 3 divided doses) while Group-B received IV ceftriaxone as dose of 75mg per kg per day in 2 divided doses. Total period for receiving study drug was 5 days. Response to treatment was assessed after 5 days and efficacy was labeled as absence of CAP (as per operational definition). All study information was recorded on a predesigned proforma.

All the collected data was analyzed employing SPSS version 24.0. Quantitative variables like age (months) and duration of symptoms (days) was presented in terms of mean and standard deviation (SD) while qualitative variables like gender and efficacy were presented in terms of frequency and percentages. Chi square test was applied to compare the qualitative variables while student's t-test was applied to compare age. P value less than or equal to 0.05 was taken as significant.

## RESULTS

Out of total 205 study participants, age ranged between 2-60 months while mean age was  $14.68 \pm 15.66$  months. Majority (n=135, 64.3%)

of the patients were aged between 1-12 months followed by 1-3 years (n=47, 22.4%) and 3-5 years (n=28, 13.3%). There were 131 (62.4%) male and 79 (37.6%) female, representing a male to female ratio of 1.66. Amongst all, duration of symptoms ranged from 1 day to 7 days and mean as  $3.60 \pm 1.69$  days. No significant difference was noted between both study groups regarding baseline characteristics (Table-I).

The frequency of efficacy was significantly higher in children treated with ceftriaxone (96.2% vs. 76.2%;  $p < 0.001$ ) in comparison to those treated with Amoxicillin/CA. The difference was significant across all age, gender and duration of symptom groups (Table-II).

## DISCUSSION

High prevalence of CAP among children emphasizes clinicians to always update their knowledge about the current trends and efficacy of antibiotics used for treating CAP. As no previous study has been conducted in Pakistan to compare the efficacy of ceftriaxone and amoxicillin-CA in children with CAP, aged less than 5 years, this study was planned to help clinicians for choosing a better option.

In the present study, overall mean age was  $14.68 \pm 15.66$  months. Munir S<sup>14</sup> in a local study reported similar mean age of  $13.78 \pm 12.06$  months among children presenting with CAP at Pakistan Institute of Medical Sciences (PIMS), Islamabad.

Characteristics	Total (n=210)	Group-A (n=105)	Group-B (n=105)	P-Value
<b>Age (months), Mean+SD</b>	14.68+15.7	14.47+15.6	14.90+15.8	0.843
<b>Age Groups</b>				
2-12 months	135 (64.3%)	68 (64.8%)	67 (63.8%)	0.918
1-3 years	47 (22.4%)	24 (22.9%)	23 (21.9%)	
3-5 years	28 (13.3%)	13 (12.4%)	15 (4.3%)	
<b>Gender</b>				
Male	131 (62.4%)	66 (62.9%)	65 (61.9%)	0.887
Female	79 (37.6%)	39 (37.1%)	40 (38.1%)	
<b>Duration of Symptoms (days), Mean+SD</b>	3.60+1.69	3.60+1.71	3.59+1.61	0.968
<b>Duration of Symptoms</b>				
1-3 days	107 (51.0%)	54 (51.4%)	53 (50.5%)	0.890
4-7 days	103 (49.0%)	51 (48.6%)	52 (49.5%)	

Table-I. Baseline characteristics of study participants.

Characteristics	Total n (%)	Group-A (n=105)	Group-B (n=105)	P-Value
<b>Overall</b>	181/210 (86.2%)	80/105 (76.2%)	101/105 (96.2%)	<0.001
<b>Age Groups</b>				
2-12 months	116/135 (85.9%)	52/68 (76.5%)	64/67 (95.5%)	0.001
1-3 years	40/47 (85.1%)	18/24 (75.0%)	22/23 (95.7%)	0.047
3-5 years	25/28 (89.3%)	10/13 (76.9%)	15/15 (100%)	0.049
<b>Gender</b>				
Male	112/131 (85.5%)	50/66 (75.8%)	62/65 (95.4%)	0.001
Female	69/79 (87.3%)	30/39 (76.9%)	39/40 (97.5%)	0.006
<b>Duration of Symptoms</b>				
1-3 days	92/107 (86.0%)	41/54 (95.9%)	51/53 (96.2%)	0.002
4-7 days	89/103 (86.4%)	39/51 (76.5%)	50/52 (96.2%)	0.004

Table-II. Efficacy in between participants of both study groups.

Dinur-Schejter Y et al<sup>12</sup> noted similar mean age of  $14.2 \pm 4.4$  months among such children. Relatively higher mean age of  $29.7 \pm 8.9$  months was reported previously by Hassan M et al<sup>15</sup> in a local finding. Majority ( $n=135$ , 64.3%) of our patients were aged between 1-12 months followed by 1-3 years ( $n=47$ , 22.4%) and 3-5 years ( $n=28$ , 13.3%). Our findings were similar to what Bari A et al<sup>16</sup> reported where frequency of age groups 2-12 months (74.9%), 1-3 years (20.6%) and 3-5 years (4.5%). Hassan M et al<sup>15</sup> (51.57%), Hamid MH et al<sup>17</sup> (46%) and Simbalista R et al<sup>18</sup> (24.7%) also reported 2-12 months being the most frequent age group among children with CAP.

We noted majority, 62.4% of the patients to be male giving a male to female ratio of 1.7:1 which was very similarly to Bari A et al<sup>16</sup> (2:1), Munir S<sup>14</sup> (1.8:1), Simbalista R et al<sup>18</sup> (1.5:1) and Hamid MH et al<sup>17</sup> (1.2:1). Hassan M et al<sup>15</sup> found much higher male predominance with a male to female ratio of 3:1 while Amir J et al<sup>19</sup> reported a female prominence with a male to female ratio of 1:1.6. Our results stood similar to most findings with regards to age<sup>14-17</sup> and gender<sup>16-18</sup> distribution.

Overall, mean duration of symptoms was noted as  $3.60 \pm 1.69$  days. A similar mean duration of symptoms before presentation at hospital has been reported by Dinur-Schejter Y et al<sup>12</sup> ( $3.5 \pm 2.9$  days) and Munir S<sup>14</sup> ( $4.5 \pm 3.10$  days).

As no significant difference was seen among participants of both study groups, so randomization proved effective without showing any sort of bias in between both the groups.

A study from Bangladesh<sup>20</sup> noted ceftriaxone to be the most common antibiotic used in about 50% of the admitted children having pneumonia. Ceftriaxone seem to be a popular choice for treating pneumonia in this region. In the present study, the frequency of efficacy was significantly higher in children treated with ceftriaxone (96.2% vs. 76.2%;  $p < 0.001$ ) in comparison to Amoxicillin-CA. This difference was significant across all age, gender and duration of symptom groups. Amir J et al<sup>19</sup> observed efficacy of amoxicillin-CA to be 88.0%. However, the researchers only had a

total of 62 patients in two study groups assessing different drugs. The observed difference in their series could be due to very limited sample size of study ( $n=62$ ) as compared to the present study ( $n=210$ ) which make current research more reliable. Similar to current findings, Zarinfar N et al from Iran<sup>21</sup> reported similar findings where they reported efficacy of amoxicillin-CA to be 79% in CAP. They however only included adult patients of community acquired pneumonia with a mean age of  $48.12 \pm 17.96$  years. In a local RCT from Lahore<sup>22</sup>, IV ceftriaxone was compared with IV penicillin for children admitted with CAP. Ceftriaxone showed significantly better efficacy than the comparator (84.7% versus 71.8%,  $p = 0.04$ ). Cetinkaya F et al<sup>23</sup> found ceftriaxone to be equally effective when compared to a combination of parenteral penicillin and chloramphenicol.

A study done by Salih KM et al<sup>24</sup> treating patients with CAP, noted efficacy of amoxicillin-CA, ceftriaxone and penicillin as 86%, 90% and 79%. Those results supported that ceftriaxone was the most effective drug for the treatment of CAP while Roson B et al recorded efficacy of ceftriaxone to be 88.9%.<sup>25</sup>

The present study is the first research aimed at finding our experience of studied drugs in the local population. Good sample size is the strength of this study while randomization showed no bias. A limitation to the present study was that we did not evaluate side effects of treatment which could be important and need to be considered in future studies.

## CONCLUSION

Among children with CAP, efficacy was significantly higher in children treated with ceftriaxone in comparison to amoxicillin/clavulanic acid. This difference was significant across all age, gender and duration of symptom groups.

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


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3	Irfan Naeem	Data collection, Data analysis.	
4	Aysha Mansoor Lodhi	Data collection, Data analysis.	
5	Muhammad Nasir Rana	Supervision, Proof reading.	