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Original Research Article

Antibiotics in children with bronchial asthma

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ABSTRACT

Background: This study was conducted to determine if oral antibiotics started at presentation reduce the duration of acute exacerbations of bronchial asthma by comparing the durations of mild to moderate exacerbations of asthma managed with or without antibiotics in children below 12 years.
Methods: In this systematic trial, we allocated the eligible children to antibiotic group (who also received standard of care and control (the standard of care) group (n=40 in each group) and compared the duration of acute asthma exacerbation between the two groups.
Results: The mean difference of duration of mild and moderate exacerbations between the antibiotic and control group was 4.76 hours (95% Confidence Interval (CI) of -36.76 to 28.84) which was found not to be statistically significant (p value- 0.482).
Conclusions: There was no significant reduction in the duration of mild to moderate exacerbations of asthma in children below 12 years by the administration of empirical antibiotics.

Keywords: Childhood asthma, Empirical antibiotics, Mild to moderate exacerbations

INTRODUCTION

Bronchial asthma is one of the most common chronic illnesses of childhood.[1] The most common kind of asthma in children is the viral-induced episodic asthma, in contrast to adults in whom atopic asthma is common.[2] The role of various viruses (respiratory syncitial virus, for example) in the causation of childhood asthma is well established.

Though viruses have been established as important in the pathogenesis of childhood asthma and its exacerbations, there is emerging pathological and microbiological evidence for the role of bacteria in childhood wheezing.[3-5]

Streptococcus pneumoniae, *Hemophilus influenzae* and *Moraxella catarrhalis* have been found in a significant proportion of children with acute wheezing in a study by Bisgaard et al.[6] Thumerelle et al implicated atypical bacteria in asthma with poorly controlled symptoms and recommended active investigation and treatment of these bacteria in children with persistent clinical symptoms.[7] Friedman et al did a study on management of sinusitis with antibiotics in children who had both asthma and sinusitis and found that effective antibiotic management of sinusitis resulted in a clinical improvement in the symptoms of asthma.[8]

Antibiotics are commonly used in outpatient settings in children with acute wheeze but there is a lack of robust evidence to back this practice.

We hypothesized that empirical antibiotic therapy made no difference in the duration of exacerbations of asthma in children.

The aim of this study was to test this null hypothesis by comparing the durations of mild to moderate exacerbations of asthma managed with or without antibiotics in children below 12 years.

METHODS

Subjects and setting

We conducted this systematic allocation study in the pediatric outpatient department of a tertiary care hospital in Maharashtra, India. The study population was children who were known asthmatics who presented with mild to moderate acute exacerbation to the asthma clinic. Exacerbation was defined as recent worsening symptoms (shortness of breath, cough, increased chest activity and wheezing) and increase in the frequency of reliever medication (i.e., inhaled short acting β2 agonists). The severity of asthma exacerbations was graded as per the guidelines in Global Strategy for Asthma Control and Prevention, GINA, 2012 (Table 1).[9]

Table 1: Parameters used for classification of severity of acute asthma exacerbations (selected criteria mentioned in global strategy for asthma control and prevention, GINA 2012).

Parameter	Mild	Moderate	Severe
Breathless on	Walking	Talking Infant- short, soft cry and feeding difficulty	At rest Infants stop feeding
Speech	Sentences	Phrases	Words
Alertness	May be agitated	Usually agitated	Usually agitated
Respiratory rate	Increased	Increased	Increased
Normal respiratory rates for various age groups (/min) <2months- 60 2mths-1year-<50 1-5 years- <40 6-12 years- <30			
Accessory muscles and suprasternal retractions	Usually not	Usually present	Usually present
Wheeze	Moderate, often only end expiratory	Loud	Usually loud
Heart rate	Normal for age	Increased	Markedly increased
Normal heart rates for various ages <1 year- <160 1-2 years- <120 2-8 years-<110 8-12 years- <100			

Children who had acute severe exacerbation of asthma, high fever or clinical or radiological evidence of pneumonia were excluded from the study.

Study sample size

We examined the existing data from our hospital and found that the average duration of an episode of mild to moderate asthma exacerbation in children below 12 years without antibiotics was 96 (+/- 48) hours. Our hypothesis was that antibiotics in addition to inhaled short acting β2 agonist would not reduce the duration of these exacerbations by a minimum of 24 hours. To detect this with 80% power and α error of 0.05 we needed a sample size of 40 children (after allowing for 10 % dropout rate) in each group. Thus, a total of 80 children were enrolled in the study.

Methodology

Approval by the institutional ethics committee and consent of parents was taken. Children with asthma exacerbations who satisfied the inclusion criteria were enrolled and systematically allocated to test (odd days) or control groups (even days). Both groups were administered the standard of care for management of acute exacerbations i.e., reliever medications in the form of short acting β2 agonists (salbutamol was used in the study). In addition, the test group was given oral antibiotics. Children less than 6 years received oral amoxicillin (40 mg/kg/day in three divided doses for 5 days) and children aged 6 to 12 years were administered oral azithromycin (10 mg/kg/day for 3 days). The study population was not investigated at baseline to rule out bacterial infections. However, children who developed fever or worsening of symptoms after induction were asked to come back and were assessed for infection by Chest X-Ray and CBC for addition or change in antibiotics as required.

Both the groups were followed up till the time of resolution of exacerbation as per the study protocol. Resolution was defined by the reduction in frequency of use of inhaled salbutamol to less than two in the preceding 24 hours to remain symptom-free. Daily contact with the patient was maintained to determine

when this happened either by physical contact or by phone. The duration of the episode was calculated from the time of induction into the study to the time of resolution of the acute episode.

Statistical analysis

SPSS Version 20 was used for statistical analysis. Characteristics were compared using unpaired t test for quantitative data and chi square test for proportions.

RESULTS

A total of 106 children below 12 years presenting with acute asthma exacerbations were assessed for eligibility during the course of the study (Figure 1).

Amongst them, 26 children were excluded (16 had acute severe asthma, 7 had high clinical suspicion of a bacterial infection and 3 cases refused consent). 80 children were allocated to the two groups.

Clinical and baseline characteristics of the study population are depicted in the Table 2.

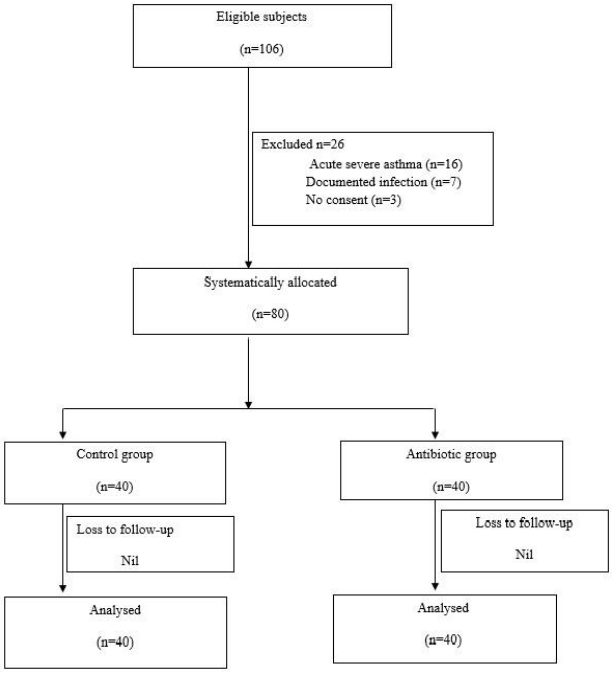

Figure 1: Study flow.

Table 2: Baseline demographic and clinical characteristics of study subjects.

No.	Characteristic	Control group (n=40)	Antibiotic group (n=40)	p value
1	Age (n)			
	< 6 yrs	10	14	
	6 -12 yrs	30	26	0.36
2	Sex (n)			
	Male	28	31	
	Female	12	9	0.56
3	Age of onset of asthma (years) Mean (SD*)	3.60 (2.46)	3.05 (2.56)	0.34
4	Category of asthma (n)			
	Mild intermittent	18	17	
	Mild Persistent	14	14	
	Moderate Persistent	8	9	0.48
5	Prior treatment (n)			
	Intermittent SABA**	10	13	
	Low dose ICS***	20	18	
	Moderate dose ICS	10	9	
	ICS and LABA****	0	0	0.34
6	Number of prior exacerbations (n)			
	<5	20	16	
	5-10	4	6	
	>10	16	18	0.79
7	Duration from onset of symptoms to presentation (days) Mean (SD*)	2.90 (2.39)	2.45 (2.35)	0.80
8	Severity of current exacerbation (n)			
	Mild	16	22	
	Moderate	24	18	0.88

All the baseline characteristics were found to be comparable. There were more children in the age group 6 to 12 years as compared to below 6 years (56 and 24 respectively). Male children outnumbered female children (59 and 21 respectively). Average duration from onset of symptoms to presentation at our centre was 2.45

days in the antibiotic group and 2.9 days in the control group. Control group had more number of children with moderate grade exacerbations compared to antibiotic group (24 vs 18). Table 3 depicts the comparative analysis of the durations of exacerbations between the antibiotic and the control groups. In children below 6 years of age the mean duration in the antibiotic group was 116.6 hours (SD-16.6) and in the control group was 121.8 hours (SD-17.7). The mean difference between the two groups was 5.2 hours (95% CI= -23.96 to 12.3) and the p value was 0.504. The difference was not statistically significant.

Table 3: Duration of exacerbations of asthma in children below 6 years.

	Control group (n= 20)	Antibiotic group (n=14)
Duration of exacerbation (hours) Mean (SD)	121.80 (17.7)	116.6 (16.6)
Mean Difference in duration of exacerbation between the two groups (hours) (95% CI)	5.2 (-23.96 to 12.3)	
p value	0.504	

The mean duration of exacerbations of asthma in the antibiotic group in children >6 -12 years of age was 118.2 hours (SD-35.9) and in the control group was 123.1 hours (SD-52.4). The mean difference between the two groups was 4.9 hours (95% CI= -42.52 to 36.92) and the p value was 0.820. There was no statistically significant difference between the test and control groups (Table 4).

Table 4: Duration of exacerbations of asthma in children above 6 years.

	Control group (n= 20)	Antibiotic group (n=26)
Duration of exacerbation (hours) Mean (SD)	123.10 (52.4)	118.2 (35.9)
Mean Difference in duration of exacerbation between the two groups (hours) (95% CI)	4.9 (-42.52 to 36.92)	
p value	0.82	

Other observations

During the study intervention, no child progressed to develop acute severe asthma. No child from the control group developed overt features of bacterial infection requiring sepsis screen and chest X ray and administration of antibiotics. No child from the antibiotic group developed features of bacterial infection requiring change of antibiotics.

DISCUSSION

In this study, we evaluated the role of empirical antibiotics in the control of mild to moderate exacerbations of childhood asthma in children below 12 years at a tertiary care hospital. Our study subjects were predominantly boys in both antibiotic and control groups. The difference in the sex distribution is likely due to the higher incidence or prevalence of asthma amongst male children as shown by various epidemiological data.[2,10] Choice of antibiotics was made based on the existing literature on the airway microbiome in children with asthma.

Huang et al found out in their study that colonisation with *Streptococcus pneumonia, Hemophilus influenza* and *Moarxella catarrhalis* was associated with persistence of wheeze in the first five years of life and higher risk of asthma at five years.[3] Studies on atypical bacteria like Chlamydia and Mycoplasma have demonstrated increasing prevalence in school going children as compared to pre-school children. However, the subgroup analysis shows that administration of antibiotics had no role in reducing the duration of acute asthma exacerbations in both the age groups.[4,5]

Broad spectrum antibiotics administered in children with acute asthma exacerbation without clinical evidence of bacterial infection was not found to be beneficial by Shapiro et al.[11] However, a major difference between that trial and our study involved the study population. Shapiro et al, studied hospitalized children with acute severe asthma, whereas we studied well children with mild and moderate exacerbations in outpatient setting.

A Cochrane meta-analysis by McCallum et al showed insufficient evidence for the use of antibiotics in persistent cough or wheeze following an episode of acute bronchiolitis.[12] A descriptive study by Kozyrskyj et al demonstrated a declining trend for the use of antibiotics in children with wheezing due to all causes.[13]

Our study, which showed no effect for antibiotics in reducing asthma exacerbations endorse this declining

trend. Our study had a few limitations. Firstly, it was a non-randomized trial. Secondly no information on the baseline airway microbiome of the study subjects and its alterations during acute asthma exacerbations was obtained during the study.

CONCLUSION

To conclude, the study did not reveal any significant reduction in the duration of mild to moderate exacerbations of asthma in children below 12 years by the administration of empirical antibiotics on an OPD basis.

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