

Presence and Treatment of Asthma Exacerbation in Infants and Children

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Abstract

We sought to determine that asthma exacerbation exists in infants and can be treated effectively with inhaled corticosteroids. The sample included 1500 consecutive children aged <5 years who attended a tertiary pediatric asthma clinic in 2000-2013 because of an asthma exacerbation that failed to be controlled in the community.

Clinical characteristics and response to treatment were compared between the infants and older children (age 1-5 years). Thirty-one percent of the children were infants. There was no difference between infants and older children in rate of asthma in the family, percentage of emergency department visits or hospitalizations, duration of asthma symptoms, and beta-2 agonist and oral corticosteroid use. All patients had a history of prolonged cough and were coughing during their first visit; 45% were also wheezing. During the treatment period, the rate of emergency department visits and hospitalization for asthma exacerbations decreased significantly without use of oral corticosteroids. Most patients (88%), with or without wheezing, had a good response to treatment, with no significant difference between infants and older children. Asthma is present in infants and has the same clinical characteristics as in older children. In both age groups, asthma exacerbations respond equally well to inhaled corticosteroids, regardless of the presence of wheezing.

Keywords: Asthma; Young children; Infants; Treatment; Inhaled corticosteroids

Introduction

The 2012 International Consensus (ICON) on Pediatric Asthma stated that the diagnosis of asthma in children younger than 2-3 years is difficult because of the lack of objective methods to measure suboptimal responses to medications [1]. The consensus also reported that high-dose inhaled steroids may be effective for the treatment of asthma exacerbations [1]. This was supported by a recent meta-analysis showing equal effectiveness of inhaled and oral corticosteroids in the treatment of children with asthma in the emergency department setting [2]. Azithromycin might serve as an add-on drug in severe cases [3]. Studies have shown that doctor-diagnosed wheeze might not be a mandatory criterion for the diagnosis of asthma [4]. A previous study by our group found that inhaled corticosteroids are effective in the treatment of asthma even in children as young as 5 months [5]. The main objectives of the present study were to investigate the characteristics of asthma in children aged less than 1 year (infants) compared to older children; to determine whether prolonged cough is a diagnostic symptom of asthma in infants without wheezing; to evaluate the use of inhaled corticosteroids to control asthma exacerbations also in infants; and to evaluate the benefit of add-on azithromycin.

Materials and Methods

The study group consisted of all children younger than 5 years who presented to our asthma clinic in 2000-2013 with an exacerbation of

asthma that was not controlled in the community. We included only children who had been coughing for at least 3 weeks before the present asthma exacerbation and who were coughing with or without wheezing at the first clinic visit. Children with diagnoses other than asthma, including lung (e.g., foreign body) or heart disorders, were excluded. Before the first visit of the child to our clinic parents were asked to watch on-line an educational video on asthma available on-line (www.volovitz.co.il) with basic information on asthma disease, prevention of asthma attack and asthma treatment. Children whose parents did not do so were excluded from the study, as were children whose parents failed to confirm during follow-up that they had complied with the treatment as proposed.

During the first clinic visit, background data were collected using similar questionnaire and physical examinations were performed by the same pediatric pulmonologist. If available, lung X-ray films made prior to the visit were reevaluated. Thereafter, the asthma treatment was explained to the parents, including a written treatment schedule and a demonstration of the proper technique to operate inhalers and spacers. In the event that the treatment failed to control the present or a future exacerbation, the parents were instructed to bring the child to the clinic. Asthma exacerbation was defined according to the 2006 revised Global Initiative for Asthma (GINA) guidelines as a sudden, progressive increase in asthma symptoms, including cough or wheeze [6]. All children were examined by the same specialist in pediatric pulmonology (B.V.). Treatment was provided according the severity of the exacerbation in 3 protocols that were developed in our clinic on the basis of a large series of clinical experiments previously published by our group [5,7].

4-day protocol	8-day protocol*	4- & 8-day protocol	4-day protocol	8-day protocol		
At the first asthma symptom	If after 1 day no response to treatment*	First Salbutamol or Terbutaline	Followed by Budesonide 200 mcg or Fluticasone 125 mcg			
To be taken on:	To be taken on:	Number of puffs to be taken one after the other, during daytime		Times/day	Every	
Day 1	Days 1 & 2	2	1	2	4	3-4 hr.
Day 2	Days 3 & 4	2	1	2	3	4-5 hr.
Day 3	Days 5 & 6	0	1	2	3	4-5 hr.
Day 4	Days 7 & 8	0	1	1	2	12 hr.

*When 1-2 days treatment with the 4-day protocol was not associated with a 50% reduction in asthma symptoms.

Table 1: Treatment protocol 1 (inhalers and spacer) for asthma exacerbation.

Protocol 1

Inhalers and spacer (Aero chamber)

Protocol 1 included 2 subprotocols: A 4-day protocol used in children with mild exacerbations, and an 8-day protocol used in children who failed to respond to the 4-day protocol after 1-2 days (Table 1). Beta2-agonists were administered only in the first 2-4 days of each subprotocol, followed by Inhaled budesonide (200 mcg) or inhaled fluticasone (125 mcg) in decreasing doses (Table 1).

Protocol 2

Inhalation

Protocol 2 was used if 1-2 days treatment with the 8-day protocol did not achieve a significant reduction in symptoms (reduction of more than 50% in asthma symptoms). It consisted of inhalation of salbutamol or terbutaline, 0.3 ml for children <1 year or 0.5 ml for older children, + 1.5 ml saline, followed by inhalation of budesonide 1 mg/2 ml, given every 2-4 hours during the day-time for a period of 1-3 days, followed by treatment with high decreasing doses of inhaled corticosteroid: 2 puffs of inhaled budesonide or fluticasone 4 times daily for 1-2 days, then 3 times daily for 1-2 days, and then twice daily for 1-2 days.

Protocol 3

Inhalation + azithromycin

Protocol 3 was used if 2 days treatment with the inhalation protocol did not achieve a reduction in symptoms of more than 50% or when infection with atypical agents was clinically suspected.

Response to treatment was categorized as follows: good-complete cessation of symptoms followed by at least 7 symptom-free days; partial-complete cessation of symptoms followed by only 2-3 days without symptoms; none-continuation of symptoms despite treatment.

Study procedure

Data on clinical characteristics and response to treatment were collected prospectively. For the present study, the records of the participants were retrospectively reviewed, and findings were compared between infants (age <1 year) and older children (age 1-5

years). The study was approved by the Ethics Committee of Maccabi Healthcare Services, Tel Aviv, Israel.

Statistical analysis

Student's paired t-test was used to analyze differences in continuous variables between groups, and chi-square test was used for categorical variables. P values less than 0.05 were considered statistically significant.

Results

Clinical characteristics: whole cohort

The study cohort consisted of 1500 children aged <5 years who were examined in our asthma clinic for asthma exacerbations during the study period. There were 990 boys (66%) and 510 girls (34%); 463 patients (31%) were aged <1 year (infants) and 1037 (69%) were aged 1-5 years (older patients).

Analysis of the background characteristics yielded the following findings: asthma in the family, 75% of patients; first sign of asthma (usually prolonged cough) before age 1 year, 84%; mean interval from first sign of asthma to examination by a specialist in pediatric pulmonology, 1 year and 2 months; median number of asthma exacerbations in the year before the first visit (or since the first symptom, if it occurred less than 1 year before), 5.3/child/year (1-4 exacerbations in 42% of patients, 5-9 in 33%, >10 in 24%). In the 12-week period before the first visit, the mean duration of asthma symptoms was 8.4 ± 4.2 weeks; mean beta2-agonist use, 4.0 ± 3.0 weeks; proportion of patients who used oral corticosteroids, 48%; mean duration of oral corticosteroid use, 6.1 ± 5.6 days/child and 1.7 ± 1.2 times/child. Most of the children (65%) presented at the clinic between October and March (winter months in Israel), with a peak in December-January. Before presentation at our clinic a total of 1848 lung X-ray films were performed in 1118 children. Pneumonia had been diagnosed on 18.5% of the films. Reevaluation of the available lung-X-rays failed to confirm most of the diagnoses of pneumonia made initially. During the first visit, all children were coughing, but only 40% were wheezing and 5% had suspected wheeze. There was no difference between children with wheezing/suspected wheeze and children without wheezing in any of the clinical parameters evaluated except sex ratio, with a higher percentage of boys with wheezing (Table 2).

	Without wheezing	Wheezing/Suspected wheezing	P value
Number of children (%)	822 (55%)	678 (45%)	<0.001
Mean age (years)	1.9	1.6	NS
Percent boys	63%	70%	<0.01
Percent with asthma in family	73%	76%	NS
Mean (± SD) number of weeks with			
Asthma symptoms	8.23 ± 2.87	8.38 ± 2.86	NS
Beta2-agonist use	3.94 ± 2.99	3.99 ± 2.98	NS
Mean (± SD) number of days with:			
Oral steroid use	6.06 ± 1.12	6.12 ± 1.22	NS
Percent of children who			
Visited the emergency department	24%	23%	NS
Were hospitalized	10%	8%	NS
NS = Not significant			

Table 2: Clinical characteristics of children with wheezing/suspected wheezing or without wheezing during physical examination on entry to the study (n=1500).

	<1 year	1-5 years	P value
Percent of children with asthma in family	76%	65%	0.75
Percent of children who*			
Visited the emergency department	47%	55%	0.959
Were hospitalized	23%	30%	0.454
Percent of children who used**			
Beta2-agonists	92%	93%	0.908
Oral corticosteroids	48%	48%	0.997
Mean ± SD weeks/child with**			
Asthma symptoms	8.4 ± 3.0	8.5 ± 2.8	0.666
Beta2-agonist use	4.0 ± 3.1	3.9 ± 2.9	0.49
Mean number of days/child with**			
Oral corticosteroid use	5.9 ± 6.0	6.2 ± 5.5	0.463
*Data since 2010 only. **In the 12 weeks before the first visit.			

Table 3: Characteristics of asthma and asthma severity with no significant difference between infants (age <1 year) and older children (age 1-5 years).

Comparison of infants and older children

The infant group had a significantly higher rate of patients with wheezing than the older group (55% vs 41%, p<0.001). The percent of children with wheezing decreased significantly with age: 55% at 0-1

years, 45% at 1-2 years, and 37% at 2-5 years (p<0.01). The infant group also had a slightly higher proportion of boys (70% vs 64%, p<0.04), underwent significantly fewer lungs X-rays (0.8 vs 1.4 lung X-ray/child), and had a significantly lower rate of diagnosed pneumonia (12% vs. 20%, p<0.001). There were no between-group differences in

any of the other clinical parameters, namely, rate of asthma in the family, number of visits to the emergency department, number of hospitalizations for asthma exacerbation, and in the 12-week period prior to the first visit, weeks with asthma symptoms, use of beta2-agonists, and use of oral corticosteroids (Table 3). Thirty percent of all the children received azithromycin, with no significant difference between infants (31%) and older children (29%).

Response to treatment with inhaled corticosteroids

All children were treated with inhaled corticosteroids. There was no difference in the percentage of patients with a good response by

specific corticosteroid used (budesonide 90% of patients, fluticasone 10%) or by method of delivery (inhalers + spacers 80%, inhalation 20%). Owing to their higher rate of wheezing, the infants required significantly more inhalations than the older children (22% vs.18%, $p < 0.001$) and more inhalations + azithromycin compared to inhalers + azithromycin (62% vs. 47%, $p = 0.01$). Nevertheless, because the treatment protocols were adjusted to the severity of the exacerbation, both age groups showed a similar good response. This was true regardless of the presence of wheezing and of the addition of azithromycin (Table 4).

Protocol	1-5 years		< 1 year		P value
	Wheezing/Suspected wheezing	Without wheezing	Wheezing/Suspected wheezing	Without wheezing	
Inhalers + spacer	*89%	**88%	*86%	**87%	*0.983 **0.931
Inhalations	*89%	**89%	*83%	**88%	*0.369 **0.984
Azithromycin inhalers +	*91%	**94%	*86%	**89%	*0.735 **0.788
Azithromycin inhalation +	*95%	**88%	*86%	**94%	*0.150 **0.754

None of the between-group differences were statistically significant. The presence of wheezing had no effect on the outcome of treatment (which was adjusted to the severity of the exacerbation).

Table 4: Percent of infants (<1 year) and other children (1-5 years) with good response to treatment, with or without wheezing, by protocol*.

Other outcomes

Items regarding emergency department visits and hospitalizations were included in our questionnaires only for 403 of the 1500 children who had attended the clinic within the last 3 years of the study (2010-2013). Between the first sign of asthma and the first visit to our clinic (mean interval 14.9+12.2 months per child), 201 of the 403 children (50%) had visited an emergency department (total, 501 visits) and 78 (19%) had been hospitalized (total 106 hospitalizations). During the follow-up period after the clinic visit (mean 2.9 ± 2.6 months/child), only one child visited the emergency department and was hospitalized.

In the 3-month period before the start of our treatment, corticosteroids were used by 714 of the 1500 children (48%) (Total 1208 episodes over 4532 days). During the treatment period (mean duration 3 months/child), children were given only inhaled corticosteroids; oral corticosteroids were never used by any of the children.

Discussion

Asthma presence and diagnosis in infancy

Asthma is rarely reported in children before age 1 year because of the lack of sufficiently accurate objective measures. To prove that asthma exists in infants, we had to show that infants have the same clinical characteristics as older children and respond similarly to anti-asthma treatment. Accordingly, on statistical analysis, the present study yielded no significant differences in rates of family history of asthma,

symptoms and signs of asthma, use of anti-asthma drugs, emergency department visits, hospitalizations, and response to treatment with inhaled corticosteroids between the 463 infants aged <1 year and the 1037 asthmatic children aged 1-5 years. The only difference was the higher rate of wheezing in infants which is probably attributable to the smaller diameter of their airways. This finding in our large cohort confirms a similar observation reported in an earlier study of 201 children [4].

Prolonged cough as a diagnostic factor of asthma

The typical pattern of asthma in young children consists of short, recurrent exacerbations of cough and wheeze usually triggered by a viral respiratory tract infection [8]. Indeed, both nocturnal dry cough and wheeze in early childhood have been independently associated with asthma at school age [9]. A recent study found that doctor-diagnosed wheeze in young children may not necessarily be a prerequisite for the diagnosis of asthma, and that in the first 3 years of life, global assessment of significant troublesome lung symptoms is a better predictor of asthma than assessment of wheeze [4]. In line with these findings, the present study shows that regardless of the presence of wheezing, both infants and older children with a history of prolonged cough have similar clinical characteristics (Table 3) and a similar good response to treatment with inhaled corticosteroids (Table 4). Wheezing was associated with young age and male sex, which could be explained by the higher rate of boys and of wheezing in the infant group. Wheezing, if present, may be an indicator of a more severe asthma exacerbation, as suggested by the greater use of the inhalation protocol by the wheezing infants. As the treatment protocols were

adjusted to the severity of the exacerbation, a good response to treatment was observed regardless of wheezing (Table 4).

Effectiveness of inhaled corticosteroids in infants

The potential benefits of inhaled corticosteroids for the treatment of acute asthma exacerbations include direct delivery to the airways and reduced systemic exposure. Previous reports have shown that high-dose inhaled corticosteroids are effective in controlling asthma exacerbations [5,9-11] and safe [7,10]. This is true in both the community [5,12] and the emergency department [9,11,12]. However, almost all the children in these studies were older than 2 years. The present study is the first to show that infants (<1 year) have a similarly good response to inhaled corticosteroids, whether delivered by inhaler or inhalation, in the presence or absence of wheeze (Table 4).

Azithromycin for uncontrolled asthma exacerbations

Atypical pathogens, such as *Mycoplasma pneumoniae*, are associated with asthma exacerbation in children. Two studies of asthmatic children reported *M. pneumoniae* infection rates of 20-50% and 36.5% [13,14]. Macrolides such as azithromycin exert both antimicrobial effects and anti-inflammatory/anti-asthma effects [5]. Treatment with azithromycin has been found to significantly alleviate asthma symptoms and improve lung function in asthmatic patients with *Chlamydia pneumoniae* infection [15]. We added azithromycin to the inhaled corticosteroid protocol of children with a severe asthma exacerbation (30% of the cohort). We found that the add-on effect of azithromycin totally replaced the need for oral corticosteroids, thereby sparing patients their potentially adverse effects, such as aggressive behaviors and anxiety [16] as well as hypothalamic-pituitary-adrenal axis suppression [9,17].

Study Limitations

Our study is not a randomized trial. However, it derives significant power from the fact that all the children started our treatment protocols after failing to respond to other anti-asthma treatment given in the community immediately before the study and from the quick good response they had to our treatment (after 1-4 days). Furthermore, the study offers a comprehensive set of data collected from a very large cohort of young children (N=1500 children) in the age group for which very little information on asthma is currently available.

How can we be sure our young children had asthma exacerbation and not another pathology such as viral infection? And how can we know that the exacerbation did not stop spontaneously? Viral infection is the most common trigger of asthma exacerbation in young children, and in most of the children in our study, the asthma attack started after a viral infection. Furthermore, it is possible that some of the exacerbations could have stopped spontaneously. However, several important findings in the cohort support our suggestion that the diagnosis was asthma exacerbation and that the resolution of the signs and symptoms was due to our treatment: In the 12 weeks before the study, the children had asthma symptoms 70% of the time (mean 8.4 weeks/child) and took beta2-agonists 33% of the time (mean 4 weeks/child); 48% of the children were treated with oral corticosteroids, 50% visited the emergency department, and 19% were hospitalized for asthma exacerbation; all the children were coughing at onset of the study, and 45% were wheezing; 88% responded well to treatment after 1-3 days. Asthma is the only disease in young children with such a history and such good response to anti-asthma treatment.

Conclusion

This is the first study of a large cohort of young children <5 years old with asthma exacerbation that was effectively controlled with inhaled corticosteroids. The findings support several assumptions. (1) Asthma may be present and can be diagnosed in infants <1 year. (2) Children with prolonged cough should be considered to have asthma and treated accordingly, even in the absence of wheeze. (3) Inhaled corticosteroids are very effective in controlling acute asthma exacerbations, equally in infants and older children. (4) Azithromycin may have an important role in the treatment of uncontrolled asthma exacerbations. The administration of our treatment protocols with inhaled corticosteroids for asthma exacerbation in young children was associated with a significant reduction in emergency department visits and hospitalizations, without the use of oral corticosteroids.

Early diagnosis of asthma and asthma exacerbation in infants and the ability to control asthma with inhaled corticosteroids contribute significantly to the health of the children while reducing the burden of the disease on the parents and healthcare system.

Author Contributions

B. Volovitz initiated and performed the study, conducted the analysis, and wrote the manuscript.

M. Nussinovitch served as an advisor during the study and critically reviewed the final draft of the manuscript.

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