

Oral and inhaled corticoid treatment for wheezing in the first year of life

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Abstract

Objective: To evaluate the prevalence of corticoid utilization for the treatment of wheezing in infants less than 12 months old and to analyze factors associated with this practice.

Methods: This was a cross-sectional study that administered the validated questionnaire from the International Study on the Prevalence of Wheezing in Infants to 1,261 infants aged 12 to 15 months in Belo Horizonte, Brazil. Proportions and 95% confidence intervals were calculated and the chi-square test was used to detect associations between variables.

Results: Six hundred and fifty-six (52%) infants, 53% male and 48.2% white, exhibited wheezing during the first year of life. Mean age at first episode was 5.11 ± 2.89 months. There was a high rate of morbidity, with many emergency visits (71%) and hospitalizations (27.8%). Also common were a family history of asthma and atopic disease (32.2 to 71%) and exposure to passive smoking (41.5%) and to mould (47.3%). The prevalence rates for corticoid use, whether via oral route (48.7%) or inhaled (51.3%), were elevated and were higher in the group that suffered three or more episodes. Children suffering greater morbidity were more likely to be prescribed a corticoid ($p < 0.05$).

Conclusion: The high frequency of corticoid use highlights the need to establish specific criteria for the treatment of wheezing in the first years of life in order to avoid extrapolation of asthma treatments to other conditions that are transitory and self-limiting and in which using corticoids could involve more risk than benefit.

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Introduction

Long-term inhaled corticoid therapy (IC) is a well-established treatment for asthma that is associated with rapid reduction of symptom severity, with significant improvement of inflammation and pulmonary function in days or weeks and with modification of hyperreactivity over the course

of several months.¹ However, it is not always possible to identify asthmatics early, especially when wheezing episodes are triggered by viral infections and as such are transitory conditions that only require symptomatic medication.¹ Around 1/3 of children exhibit recurrent wheezing episodes

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before 3 years of age, but the majority (60 to 80%) no longer exhibit symptoms of asthma in future life.¹⁻⁴

Several different classifications and phenotypes have been proposed in attempts to better understand the diversity of presentation of infant wheezing.^{1,3,5} Classic cohort studies found that there were a number of different phenotypes, differentiated by the course that symptoms take over the first years of life (transitory/persistent/late wheezing). The British Thoracic Society has compiled a classification based on trigger-factors, differentiating episodic viral wheezing from wheezing triggered by multiple factors (allergens, climatic variations, physical exercise).^{1,3,5}

If recurrent wheezing is due to a viral infection, it is unlikely to last beyond early childhood and using IC in this situation runs the probable risk of excessive treatment. On the other hand, early-onset asthma is often indistinguishable from transitory wheezing and severe cases damage children's pulmonary function, affecting their quality of life.⁶

Recurrent wheezing during the first years of life is difficult to manage because of the limited objective measures available and the small number of studies of the efficacy and safety of anti-inflammatory agents.² It is important to estimate the frequency of corticoid use in infants in order to build up a picture of what is actually happening in clinical practice in the face of the existing gaps in scientific knowledge, but few studies have investigated this subject. The objective of this study was therefore to analyze the prevalence of oral and inhaled corticoid usage for the treatment of wheezing infants less than 1 year old.

Methods

This study was part of the International Study on the Prevalence of Wheezing in Infants (Estudio Internacional de Sibilancias en Lactantes [EISL]), which is an international, cross-sectional, multicenter study designed to investigate the prevalence and severity of wheezing, and the factors associated with it, in infants in Latin America and the Iberian peninsula during their first year of life.⁷

A minimum sample size of 1,000 infants from 12 to 15 months is required for participation in the EISL protocol. The sample described here was recruited from the regions served by 47 basic healthcare centers (BHC) in the municipality of Belo Horizonte that were chosen at random. The children were identified and located by analyzing the BHCs' copies of vaccination records.

The EISL questionnaire has been validated for the Brazilian population and contains 45 questions about respiratory system manifestations during the infant's first 12 months - items related to wheezing, use of medications and physician-diagnosed asthma - in addition to information on family, environmental and demographic characteristics.⁸ Recurrent wheezing was defined as three or more episodes

of wheezing in the first year of life. The question used to investigate wheezing was as follows: "How many episodes of a whistling chest (bronchitis or wheezing) did your baby have during the first year of life?" Corticoid use was investigated with the following questions: "Has your baby been treated with inhaled corticoid (cortisone)? For example, Symbicort, Flixotide, Seretide, Clenil, Beclosol, Budesonide, Busonid, Pumicort, Beclomethasone, Fluticasone, etc?" and "Has your baby been treated with oral corticoid (Predsim, Prelone, Decadron)?"⁷

The aim of statistical analysis was to delineate the subset of the sample that wheezed in their first 12 months and this was accomplished using descriptive measures for the quantitative variables (means and standard deviations, medians with minimum and maximum values) and frequency distributions for qualitative variables. Oral corticoid (OC) was estimated for the whole sample and for the subset of wheezing infants. The prevalence of IC use was only analyzed for the wheezing infants. A univariate analysis was performed using the chi-square test in order to detect significant associations between qualitative variables two by two. Associations were defined as significant where $p < 0.05$. Analyses were performed using the Statistical Package for the Social Sciences, version 13.0.

This study was approved by the Research Ethics Committee at the Universidade Federal de Minas Gerais (ruling ETIC 340/07) and by the Municipal Health Department of Belo Horizonte (ruling 026/2006).

Results

A total of 1,261 children were assessed. Of these, 656 (52%) had wheezed during the first year of life and 357 (54.6%) of them had had recurrent wheezing. In the subset of wheezing infants ($n = 656$), 348 (53%) were male and 316 (48.2%) were white. Mean age at first wheezing episode was 5.11 ± 2.89 months.

Table 1 lists characteristics for those children who had at least one wheezing episode in the first year of life with relation to severity of wheezing, to the environment and to risk factors for atopic disease and airway infections. Note the elevated morbidity rate characterized, for example, by the frequency of emergency visits (71%) and hospital admissions for bronchitis (27.8%). The majority of cases were of early onset, within the first 6 months of life (73.3%) and had family history of asthma or other atopic diseases (32.2 to 71%). A significant proportion of the infants were exposed to environmental risks such as passive smoking (41.5%) and mould (47.3%).

The frequency of oral corticoid therapy in the whole sample was 24.3% (304/1,261) and 9.1% of the infants who had never wheezed had been given OC at least once. Table 2 shows the frequencies of OC and IC for the subset of wheezing infants.

Tables 3 and 4 illustrate the analysis of associations between the variables studied and use of OC and IC respectively.

Discussion

There was an elevated prevalence of corticoid use in the subset of wheezing infants studied, both via oral route (48.7%) and inhaled (51.3%). Particularly so if one considers

Table 1 - Characteristics of wheezing infants (n = 656)

| Characteristics | n (%) |
|--|------------|
| Variables related to severity | |
| Recurrent wheezing (≥ three episodes) | 357 (54.6) |
| Nighttime waking (> once per month) | 443 (67.6) |
| Emergency visits | 462 (71) |
| Intense breathing difficulties | 326 (49.9) |
| Hospital admissions for bronchitis | 181 (27.8) |
| Physician-diagnosed asthma | 170 (26) |
| First wheezing episode (by 6 months) | 473 (73.3) |
| Variables related to the environment | |
| Smoking inside at home | 272 (41.5) |
| Parent or guardian smokes | 129 (19.7) |
| Smoking during pregnancy | 107 (16.4) |
| Mould | 309 (47.3) |
| Pets | 308 (47) |
| Variables associated with a risk of atopic disease | |
| Relatives with allergic dermatitis | 208 (32.2) |
| Relatives with asthma | 383 (59) |
| Relatives with allergic rhinitis | 457 (71) |
| Baby has skin allergy | 451 (69) |
| Variables related to airway infections | |
| First cold (by 4 months) | 392 (61.7) |
| Number of siblings ≥ two | 216 (33.5) |
| Number of people living in home ≥ five | 287 (44.8) |
| Baby attended daycare | 99 (15.2) |

Table 2 - Frequency of oral and inhaled corticoid treatment for wheezing infants during the first year of life

| Corticoid given | n | % | % of valid responses | 95%CI |
|-------------------|-----|------|----------------------|-----------|
| Oral corticoid | | | | |
| Yes | 249 | 38.0 | 48.7 | 44.3-53.1 |
| No | 262 | 39.9 | 51.3 | |
| Don't know | 145 | 22.5 | | |
| Inhaled corticoid | | | | |
| Yes | 296 | 45.1 | 51.3 | 47.1-55.4 |
| No | 281 | 42.8 | 48.7 | |
| Don't know | 79 | 12.0 | | |

95%CI = 95% confidence interval

that around 60 to 70% of wheezing infants will not continue to exhibit symptoms of asthma.¹⁻⁵

The rates of corticoid use in this population were higher than those found by a study using the same questionnaire and conducted in Curitiba.⁹ The prevalence of OC use in Curitiba was 24.3% and for IC it was 18.5%. It is important to point out that the population of wheezing infants from Belo Horizonte had a greater degree of severity in terms of emergency visits (71 vs. 57.6%) and hospital admissions for bronchitis (27.8 vs. 12.7%). Additionally, asthma diagnoses were more common in Belo Horizonte (26 vs. 10.9%), the prevalence of wheezing was higher (52 vs. 45.4%) and so was the proportion of recurrent wheezing (28.4 vs. 22.6%). It is therefore possible that these differences led to the increased prevalence of OC and IC use. An alternative hypothesis to explain the difference is that in Belo Horizonte there is a public health program that has been in place for more than 15 years and which provides inhaled beclomethasone to treat asthma, making prescriptions more likely and increasing access for the population.

Castro-Rodrigues et al.¹⁰ administered a questionnaire to pediatricians (specialists or not) in Spain, asking them how they would proceed in a clinical case of a first mild-to-moderate wheezing episode in a 5-month-old boy with a history of atopic disease and a family history of allergy. The result was that 31.3% chose to prescribe OC and 27.6% chose IC. While methodological differences make comparison of that result with our study problematic, it is of interest to note that this was a case of a child at high risk of developing asthma in the future and yet the percentage of corticoid use was lower than observed in this study.

As would be expected, the prevalence of corticoid use was greater in the subset of infants with recurrent wheezing, when compared with those who suffered less than three episodes, whether by oral route (63.5 vs. 36.5%) or via inhaler (51.3 vs. 35.7%). Recurrent episodes of wheezing may be associated with an increased risk of developing asthma.¹⁻⁵ Ly et al.,¹¹ followed a cohort up to 7 years concluded that children with parents with a history of asthma or allergy who also have early recurrent wheezing, defined as more than two reports of wheezing per year for the first 3 years of life, have a significantly higher risk of asthma and merit clinical follow-up.

Analysis of the factors associated with corticoid use for wheezing during the first year of life showed that children with greater morbidity had an increased chance of being prescribed OC and IC. This observation is coherent with the recommendations contained in the majority of consensus papers on asthma, which state that the uncertainty related to diagnosis and to efficacy of treatment mean that corticoids should be reserved for the most serious cases.¹² A family history of asthma, considered an important predictor of the risk of asthma, was only associated with IC prescriptions.

Studies that have investigated IC for treatment of wheezing in infants have used different criteria to select the children studied, different treatment strategies and different data collection methods and have investigated different outcomes.^{8,13-25} Nevertheless, it can still be concluded that giving IC to infants can, in certain circumstances, offer better control of symptoms, although this improvement does not outlast withdrawal of treatment; i.e. it does not

interfere in the natural history of asthma. Furthermore, the majority of studies did not observe any positive effect on pulmonary function test results, which are considered the most specific measure for diagnosis of asthma, even in children at high risk of developing asthma in the future. It is not recommended that IC be prescribed to infants with intermittent wheezing of less severity, which is the case with the majority of patients. There is some evidence

Table 3 - Factors related to administration of oral corticoid to wheezing infants during their first year of life

| Factors | Oral corticoid | | | |
|-----------------------------------|----------------|------------|-----------|---------|
| | Yes (%) | No (%) | OR/95%CI | p |
| Recurrent wheezing | | | | |
| Less than 3 | 91 (36.5) | 150 (57.7) | 0.42 | < 0.001 |
| More than 3 | 158 (63.5) | 110 (42.3) | 0.29-0.60 | |
| Emergency visit | | | | |
| Yes | 202 (81.1) | 159 (61.2) | 2.73 | < 0.001 |
| No | 47 (18.9) | 101 (38.8) | 1.82-4.08 | |
| Hospital admission for bronchitis | | | | |
| Yes | 98 (39.5) | 37 (14.1) | 3.97 | < 0.001 |
| No | 150 (60.5) | 225 (85.9) | 2.58-6.11 | |
| Physician-diagnosed asthma | | | | |
| Yes | 92 (37.1) | 42 (16) | 3.08 | < 0.001 |
| No | 156 (62.9) | 220 (84) | 2.03-4.69 | |
| Relatives with asthma | | | | |
| Yes | 157 (63.6) | 144 (55.6) | 1.39 | 0.07 |
| No | 90 (36.4) | 115 (44.4) | 0.97-1.99 | |

95%CI = 95% confidence interval; OR = odds ratio.

Table 4 - Factors related to administration of inhaled corticoid to wheezing infants during their first year of life

| Factors | Inhaled corticoid | | | |
|-----------------------------------|-------------------|------------|-----------|---------|
| | Yes (%) | No (%) | OR/95%CI | p |
| Recurrent wheezing | | | | |
| Less than 3 | 105 (35.7) | 157 (55.9) | 0.43 | < 0.001 |
| More than 3 | 189 (64.3) | 124 (44.1) | 0.31-0.61 | |
| Emergency visit | | | | |
| Yes | 235 (79.9) | 170 (60.7) | 2.57 | < 0.001 |
| No | 59 (20.1) | 110 (39.3) | 0.77-3.74 | |
| Hospital admission for bronchitis | | | | |
| Yes | 124 (42.3) | 31 (11) | 5.91 | < 0.001 |
| No | 169 (57.7) | 250 (89) | 3.81-9.18 | |
| Physician-diagnosed asthma | | | | |
| Yes | 102 (34.6) | 49 (17.4) | 2.50 | < 0.001 |
| No | 193 (65.4) | 232 (82.6) | 1.69-3.69 | |
| Relatives with asthma | | | | |
| Yes | 186 (63.1) | 151 (54.3) | 1.43 | 0.03 |
| No | 109 (36.9) | 127 (45.7) | 1.02-2.00 | |

95%CI = 95% confidence interval; OR = odds ratio.

for prolonged IC use in cases of greater severity with risk factors for development of asthma.¹²

The principal limitation of this study is the fact that the frequencies of OC and IC use were estimated from parents or guardians' reports and not from medical records, which would have been more trustworthy. Nevertheless, there are very few studies that have estimated the prevalence of OC and IC use in infants with a history of wheezing. Prospective studies are needed to evaluate the criteria that are being used to guide the decision on whether or not to prescribe corticoid to infants who exhibit wheezing.

This study highlights the need to establish specific criteria and guidelines for the treatment of wheezing in the first years of life. While none exist, what is observed is extrapolation of asthma treatment to other conditions that are transitory and self-limiting and in which corticoid could be more of a risk than a benefit. It is important to remember that the concern about frequent prescription of corticoid to children is related to the possibility of negative effects on growth.

The major merit of this study is that it illustrates in figures what many professionals who treat infants and children have already suspected: that corticoid is being used excessively to treat wheezing in infancy. With regard to OC, although the short treatment cycles offer a degree of safety, concern is aroused by the cumulative effect of repeated doses over the lives of small children, particularly if we remember that they can suffer as many as 10 viral infections per year. With regard to IC, the issue of unnecessary expenditure on medication in situations in which real benefit has not been proven should also be considered.

Recurrent wheezing is a common problem in children under 3 in many parts of the world. Implications of this study that should be acted on immediately are the need to evaluate the side effects of corticoids and to implement ongoing education programs including discussion of the possible risks of this practice of general and indiscriminate prescription of corticoids.

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