



# **Wheezing in infancy: epidemiology, investigation, and treatment**

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## **Abstract**

**Objective:** To perform a review of the epidemiological aspects of investigating and treating wheezing in infants.

**Sources:** A search was run on MEDLINE using the keywords "wheezing," "infants," "diagnosis," "treatment," and "children," and Google was also used to search for "Estudio Internacional de Sibilancias en Lactantes."

**Summary of the findings:** The prevalence of wheezing in infants varies greatly around the world. The factors associated with wheezing in infants are different at different research centers. Treatment of wheezing infants is still controversial and is dependent on a precise diagnosis. Clinical history and physical examination are fundamental to diagnosis.

**Conclusions:** A standardized method could reveal data of relevance to the epidemiology and treatment of wheezing in Brazil and allow comparisons between different participating centers.

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## **Introduction**

An international epidemiological study investigated more than 300,000 children and found that the prevalence of asthma among children and adolescents varies around the world.<sup>1</sup> Brazil was one of the countries with the greatest number of children affected, with a prevalence of active asthma oscillating between 19 and 24.3%.<sup>2</sup> In Curitiba, Brazil, there was no increase in the number of asthmatic children between 1995 and 2001, but the prevalence of asthma was elevated (18.4 and 18.7%, respectively).<sup>3</sup>

Asthma is an inflammatory disease that increases the airways' response to certain stimuli and causes bronchial obstruction that is reversible with or without treatment and is characterized by symptoms such as recurrent wheezing, dyspnea and coughing. It may be confused with other diseases in children less than 5 years old. This difficulty with diagnosing asthma, combined with a lack of standardized instruments to determine its prevalence in infants and

preschool children means there is a lack of data on the disease among young children.<sup>4</sup>

Many children exhibit symptoms of bronchial obstruction before they are 5, especially wheezing and coughing. The results of cohort studies show a great deal of variation and indicate that between 10 and 80.3% of infants suffer at least one episode of wheezing during their first year of life, while 8 to 43.1% have three or more episodes, with lower prevalence rates in developed countries.<sup>5-9</sup>

Children less than 2 years old who exhibit continuous wheezing for at least 1 month or at least three episodes of wheezing in a 2-month period are defined as wheezing infants. Asthma is just one of many possible causes of wheezing in this age group.<sup>10</sup> One half of children who wheeze early in life will cease to do so by 6 years of age; this is known as transient early wheezing, which is associated with reduced caliber of the airways, viral infections of the upper

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airways, maternal smoking and genetic factors. However, there is another group of patients in which the symptoms persist. Among children who continue wheezing after 3 years of age, allergic sensitization was the predominant risk factor. Exposure to older siblings, domestic animals and endotoxins and attendance at daycare were factors that protect against asthma.<sup>11</sup>

The treatment of recurrent wheezing in infants is controversial. Once other causes of wheezing that simulate asthma have been ruled out, treatment to control wheezing should be initiated. Inhaled corticosteroids (IC) are the first-line medications for controlling asthma in all age groups, assuming that the diagnosis is correct. Failure to respond after 6 weeks on IC demands prompt clinical assessment, rather than increased dosage. If treatment is started with IC, but there is no beneficial effect whatsoever, clinical guidelines recommend that they should be withdrawn.<sup>4</sup>

Despite all of the knowledge that has been accumulated about wheezing in infants, there is no standardized instrument for determining its prevalence, clinical characteristics or risk factors or for investigating how our population's wheezing infants are cared for.

### **Epidemiology and factors associated with wheezing in preschool children**

Epidemiological studies are essential for delineating the natural history and associated factors of a given disease within the population, and also for comparing different populations.

The epidemiology of asthma is known for school-age children, adolescents and adults all over the world. However, for preschool children the prevalence, clinical characteristics and factors associated with the most common symptom – wheezing and recurrent wheezing – were not established because no standardized instrument was available for either local or international investigations.

Maternal habits and conditions during pregnancy are related to the onset of wheezing in infants. Children born to asthmatic mothers exhibit greater risk of developing asthma.<sup>12</sup> Mothers who smoked while pregnant gave birth to children with a greater risk of wheezing and asthma, and it was found that they had elevated IgE and IL-13 levels, but low IL-4 and IFN- $\gamma$  levels, in cord blood, reduced airway caliber and reduced pulmonary function.<sup>13-15</sup>

During the perinatal period, exclusive breastfeeding for the first 4 months of life may be a protective factor against wheezing; other studies have not however confirmed this hypothesis.<sup>16,17</sup>

Respiratory viruses, such as syncytial respiratory virus, rhinovirus, metapneumovirus, parainfluenza type 3 and influenza are associated with increased risk of wheezing among preschool children.<sup>18,19</sup> In low-income

populations, pneumonia has been associated with recurrent wheezing.<sup>5</sup>

The risk of developing wheezing at the start of life is greater among male infants, children who attend daycare, children exposed to cigarette smoke and children in contact with high levels of endotoxins and allergens in room air, such as those produced by mites, cockroaches and animal hair.<sup>8,20-25</sup>

Infants vaccinated in accordance with the local immunization program did not exhibit increased chances of developing wheezing than those who had not been vaccinated in accordance with the recommended schedule.<sup>26</sup>

The factors that are associated with recurrent wheezing are the result of interactions between genes and the environment. This assessment demands population studies with representative samples and standardized methodology, which are expensive. Longitudinal studies determined the prevalence of recurrent wheezing among infants in Pelotas, Brazil, (58%) and in São Paulo, Brazil, (52%), but at that point in time there was no standardized research method.<sup>27,28</sup> Cohorts are more robust, following individuals throughout a given period in their lives, but they are more difficult to carry out because of patients being lost to follow-up.

The International Study of Wheezing in Infants (EISL) was born of the need to trace the epidemiology of wheezing among infants. In Brazil, the project had participating centers in Belém, Belo Horizonte, Curitiba, Fortaleza, Porto Alegre, Recife, and São Paulo.<sup>29,30</sup>

The standardized instrument has already been validated for the Portuguese and Spanish languages, can be administered to the parents of children aged up to 36 months, is capable of identifying infants who wheeze during the first year of life, whether recurrently or not, with a good level of precision, and identifies these children's clinical characteristics, risk factors and treatments.<sup>31-34</sup>

In common with the results of the International Study of Asthma and Allergies in Childhood (ISAAC), the prevalence of wheezing among infants has exhibited great variation in the few cohort studies that have been published.<sup>1,5-9</sup> Cohort studies are difficult to conduct because they require greater commitment from infants' parents/guardians, which opens the door to the possibility of losing them to long-term follow-up. The EISL questionnaire was administered to 3,003, 1,014 and 1,261 individuals in Curitiba, São Paulo and Belo Horizonte respectively. It was observed that approximately half of the infants assessed exhibited at least one episode of wheezing (Curitiba: 45.4%, São Paulo: 46%, and Belo Horizonte: 52%), and that around 1/4 (Curitiba: 22.6%, São Paulo: 26.6%, and Belo Horizonte: 28.4%) of these infants suffered recurrent episodes of wheezing (three or more), with a mean age at onset of 5 months. These children with recurrent wheezing ( $\geq$  three episodes) exhibited increased use of short-acting bronchodilators

and of inhaled corticosteroids, a greater frequency of symptoms and of nighttime waking, a greater number of unscheduled consultations at emergency/walk-in services, more hospitalizations due to asthma and more medical diagnoses of asthma than those who exhibited less than three wheezing episodes.<sup>35-37</sup> While it is not possible to state that these infants are all asthmatic, considering that these figures are very close to the prevalence rates of asthma among schoolchildren and adolescents, and taking into account the natural history of wheezing (in the majority of cases the different phenotypes of wheezing have onset before 3 years of age), it is probable that they are in fact asthmatics (Table 1).

It is evident that wheezing in infants is related to certain risk factors. For asthma in schoolchildren and adolescents these factors have been identified. In view of the difficulties involved in diagnosing asthma in preschool children, a predictive index has been proposed for this age group. Even with the aid of the index, a diagnosis of asthma is probable in just 80% of children when the index is administered before 5 years of age.<sup>38,39</sup> Since diagnosis is difficult, but prevalence is elevated, it is of fundamental importance to identify the risk factors for wheezing in infants. Male sex, family history of asthma (mother, father and siblings), other domestic animals (birds, rabbits, etc.) present during the

pregnancy, frequency of daycare attendance, six or more episodes of cold symptoms, a personal history of dermatitis and mold in the family home were risk factors for at least one episode of wheezing during the first year of life, while up-to-date immunization was a protective factor.<sup>40</sup> There is disagreement on whether parents' socioeconomic and cultural status are a factor associated with wheezing in infants.<sup>41</sup> When factors associated with recurrent wheezing were analyzed in Curitiba, it was observed that a parental history of asthma, maternal smoking while pregnant, dogs at home, frequency of attendance at daycare and bronchopneumonia were risk factors, while onset of cold symptoms after 4 months and a high maternal educational level were protective factors.<sup>42</sup> In São Paulo, the risk factors for recurrent wheezing were pneumonia, eating processed foods, cats at home and frequent upper airway infections with early onset.<sup>36</sup> In Belo Horizonte, male infants were at greater risk of wheezing, and those who had had three or more episodes were more likely to seek medical care and be hospitalized because of asthma.<sup>37</sup> Some factors are also known to cause asthma in schoolchildren and adolescents, but due to the different study design we cannot state that these are risk factors for asthma. Some risk factors are intrinsic to the infants themselves, while others are extrinsic and can change. We must intervene in the set of children

**Table 1** - Comparison between children who suffered three or more episodes of wheezing and those who suffered less than three episodes, plus wheezing characteristics (adapted from Chong Neto et al.<sup>35</sup>)

Wheezing characteristics	≥ 3 crises (n = 678) n (%)*	< 3 crises (n = 682) n (%)*	p
Nighttime symptoms <sup>†</sup>			
Never	54 (4)	131 (9.7)	
Rarely	128 (9.4)	244 (18)	
Sometimes	241 (17.8)	209 (15.4)	
Frequently	254 (18.8)	93 (6.9)	< 0.0001
Emergency visit(s) <sup>‡</sup>			
Yes	470 (34.7)	310 (22.9)	
No	208 (15.3)	368 (27.1)	< 0.0001
Given β2 agonists <sup>§</sup>			
Yes	608 (45.8)	539 (40.6)	
No	58 (4.4)	123 (9.2)	< 0.0001
Severe symptoms**			
Yes	402 (29.6)	226 (16.7)	
No	274 (20.2)	454 (33.5)	< 0.0001
Hospital admission(s) due to asthma <sup>††</sup>			
Yes	116 (8.6)	56 (4.1)	
No	560 (41.4)	622 (45.9)	< 0.0001
Medical diagnosis of asthma <sup>‡‡</sup>			
Yes	110 (8.1)	38 (2.8)	
No	567 (41.8)	642 (47.3)	< 0.0001

\* 4 responses missing.

† 6 responses missing.

‡ 6 responses missing.

§ 6 responses missing.

\*\*6 responses missing.

†† 8 responses missing.

‡‡ 5 responses missing.

for whom we know the risk factors in order to reduce the elevated rates of wheezing. If clinicians or specialists are aware of these data they will then be in a position to select the most likely diagnosis and the best available treatment for it (Figures 1 and 2).

**The phenotypes of wheezing**

Epidemiological studies suggest that there are several distinct phenotypes of wheezing/asthma with heterogeneous conditions, but which follow a common pathway, characterized by bronchial obstruction.

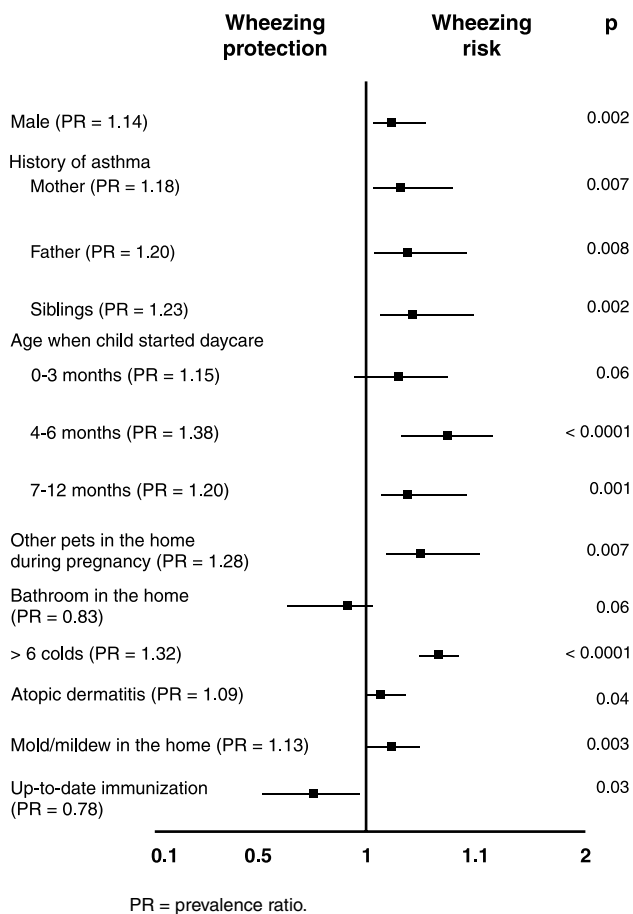
Martinez et al. performed a longitudinal study and identified a number of different wheezing phenotypes in children followed from birth until 6 years of age. There are children who suffer wheezing episodes until 3 years of age, among whom the principal characteristic is an absence of a personal or family history of atopic disease. They are born with reduced pulmonary function when compared with children who have never wheezed and do not exhibit increased bronchial hyperreactivity measured after methacholine challenge, nor large variations in peak

flow measurements at 11 years of age. It is a reduction in airway resistance, rather than airway lability, that causes these children’s predisposition to wheezing when they have symptoms of acute respiratory infections. Prematurity is another risk factor for transitory wheezing, because premature infants have a smaller caliber airways and, when exposed to siblings or other children at daycare, they are more susceptible to respiratory infections. Passive tobacco exposure, particularly when occurring during gestation, reduces pulmonary function and is associated with transitory wheezing.<sup>11,19</sup>

Another phenotype presents with recurrent wheezing, late onset of symptoms and a tendency to disappear during pre-adolescence. These children do not have a personal or family history of atopic disease/allergy and are defined as non-atopic persistent wheezing infants. The obstructive symptoms are primarily triggered by respiratory infections, particularly by rhinovirus and syncytial respiratory virus. Although these children suffer from a mild loss of pulmonary function, they do not exhibit airway hyperreactivity to methacholine nor variations in peak expiratory flow measurements. The physiopathologic mechanism of this phenotype is probably triggering wheezing by functional changes to the regulation of airway tonus.<sup>11,19</sup>

The third phenotype is made up of children whose obstructive symptoms have onset before 3 years of age and who continue to wheeze up to school age. These children do have a personal and family history of atopic disease, but with normal pulmonary function, similar to those who have never wheezed, although their pulmonary function will decline as they age. They are defined as persistent atopic wheezing infants.<sup>11,19</sup>

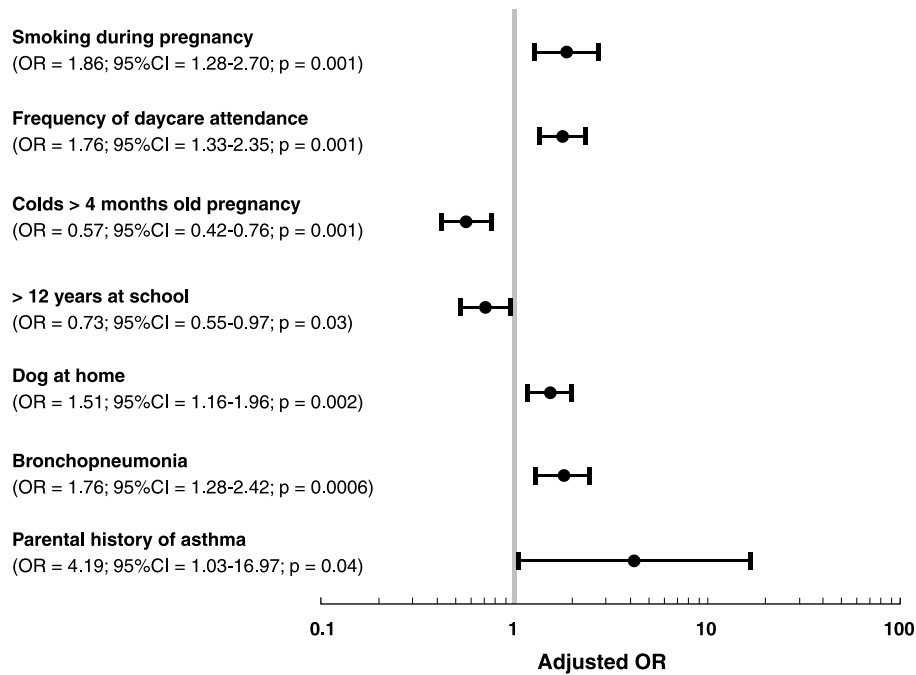
Castro-Rodríguez & Garcia-Marcos suggested that there is yet another wheezing phenotype: in the Tucson cohort, girls (but not boys) who became obese or overweight between 6 and 11 years of age were seven times more likely to develop asthma. Even when at a healthy weight and irrespective of physical activity level and allergy status, they respond more to bronchodilators (as measured by the forced expiratory volume in 1 second). Prevalence was even greater among those whose menarche began before 11 years of age and, because of this, this group are defined as obese/overweight wheezing children with early menarche. This was later confirmed in French, Mexican and Spanish children. Obesity changes the production of hormones related to puberty in girls and these girls would appear to increase production of female hormones which can alter pulmonary development and regulation of airway tonus.<sup>43-47</sup>



**Figure 1** - Risk factors for at least one episode of wheezing during the first 12 months of life (adapted from Chong Neto et al.<sup>40</sup>)

**Assessing wheezing preschool children**

The objective of taking the clinical history and performing the physical examination is to confirm wheezing in young



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

**Figure 2** - Protective and risk factors for recurrent wheezing during the first 12 months of life (adapted from Chong Neto et al.<sup>42</sup>)

children, identify its severity, the symptoms and their characteristics and possible trigger factors and to investigate characteristics suggestive of other diagnoses or associated conditions.

The patient history is the principal diagnostic instrument when assessing wheezing preschool children who are not wheezing when they are examined. Accurately identifying wheezing on the basis of history alone can be difficult for parents and health professionals.<sup>48</sup> In a study of 209 infants aged 12 to 15 months presenting at emergency services with respiratory symptoms, parents were asked, "Is your baby wheezing now?" Wheezing was then confirmed or ruled-out during the physical examination by thoracic auscultation performed by an examiner blind to the protocol (a specialist physician), and it was observed that concordance between the physical examination and parents' replies was good (Kappa = 0.74), leading to the conclusion that parents are able to identify wheezing in their children.<sup>31</sup>

During the physical examination, bronchial obstruction is estimated from respiratory work (intercostal retraction, flared nostrils, and use of accessory muscles) and the degree of wheezing is estimated from chest auscultation. The primary objective of the physical examination of the chest is to identify atypical or uncommon features that suggest that other conditions are also present.<sup>49</sup>

Invasive examinations are dependent on the degree of morbidity and the level of doubt about the diagnosis, being primarily justifiable in cases with persistent or severe symptoms. Viral cultures and PCR are reserved for research and for identifying respiratory viruses, since there is no evidence of their benefit for short or long-term clinical management.<sup>50</sup> Testing for sensitization to allergens is recommended in children with recurrent wheezing, whatever their age group, and this can be done using prick tests with standardized extracts, or by assaying specific immunoglobulin E using modern techniques that are sensitive and minimally-invasive, such as microarrays that require just 10 µL of serum.<sup>51</sup> Chest X-rays contribute little to defining diagnoses of recurrent wheezing in preschool children. In uncommon or severe cases only, the improvements in the quality of imaging techniques offer details about the structure, wall thickness and caliber of the airways.<sup>52</sup> Although gastroesophageal reflux disease (GERD) is common among children in this age group with recurrent wheezing, there is no evidence of better treatment of infants with GERD and wheezing.<sup>53</sup> Pulmonary function tests will aid in distinguishing between episodic wheezing and wheezing caused by multiple trigger factors when infants have nonspecific symptoms, while a positive bronchodilator response helps to separate wheezing preschool children from those with other clinical conditions.<sup>54,55</sup> Fractional

exhaled nitric oxide (FeNO) levels were elevated in primarily atopic infants and reduced after pharmacological treatment for asthma. Standardized normal levels are only available for children over 4 years of age because of the need for cooperation.<sup>56,57</sup> Induced sputum was not studied in all groups of preschool children. Bronchoalveolar lavage and biopsy of the airway wall are used little, because of their invasive nature and ethical risk-benefit considerations must be taken into account.<sup>58</sup>

### Treatment of wheezing/asthma in preschool children

This is one of the most-debated topics within the subject of infant wheezing. Much is known about the treatment of schoolage children, adolescents and adults with asthma and a fair proportion of what is used for treatment of recurrent wheezing/asthma in preschool children comes from findings with older patients, as is the case of long-acting  $\beta_2$  agonists. Diagnosing asthma in this population is difficult and confusion with other diseases is possible. For this reason, a clinical index to predict asthma was produced, designed to be capable of identifying probable asthma sufferers with a good degree of precision. One major criterion or two minor criteria aid in diagnosing asthma. The major criteria are personal medical diagnosis of atopic dermatitis and medical diagnosis of parental asthma. The minor criteria are wheezing with no cold symptoms, personal medical diagnosis of rhinitis and eosinophilia in peripheral blood  $\geq 4\%$ . The addition of allergic sensitization to aeroallergens, such as dust mites, increased the index's accuracy. Additionally, the addition of sensitization to dietary antigens, such as milk and eggs, together with one major criterion or two minor criteria emphasizes further the probable diagnosis of the modified clinical asthma prediction index (API<sub>m</sub>).<sup>38,39</sup>

Treatment is based on reducing inflammation, maintaining pulmonary function and quality of life, preventing exacerbations and providing drugs free from

adverse events or with minimal adverse events. National and international guidelines recommend inhaled corticosteroids as the first choice treatment (level of evidence: A) and, as an alternative, leukotriene receptor antagonists (level of evidence: A). Although they also have an A evidence level for the treatment of asthma, long-acting  $\beta_2$  agonists are not recommended for this age group because there is a lack of studies proving their efficacy and safety. Oral corticosteroids (level of evidence: D) and slow release theophylline are occasionally used to control severe asthma in patients under 5 (level of evidence: D). The recommendation is to treat for 8 to 12 weeks and, if the response is negative, increase the medication dose, change the drug combination or review the diagnosis.<sup>4,59</sup>

One meta-analysis reviewed 29 randomized studies, controlled with placebo, involving 3,592 infants and schoolchildren taking inhaled corticosteroids for at least 4 weeks. The primary outcome was exacerbation of wheezing/asthma and the secondary outcome was exclusion from the study due to exacerbation of wheezing/asthma, changes in asthma score, pulmonary function or need for salbutamol during crises. The children on inhaled corticosteroids had significantly fewer exacerbations of wheezing/asthma than those on placebo (18 vs. 32.1%), being withdrawn from the study due to less frequent exacerbations, higher clinical score, better pulmonary function and reduced salbutamol use. Because of this, preventative treatment with inhaled corticosteroids is recommended for infants and preschool children with recurrent wheezing and asthma.<sup>60</sup>

In contrast, studies undertaken with children less than 3 years old using nebulized budesonide or oral Montelukast intermittently demonstrated that there was no significant improvement in primary outcomes, such as days free from symptoms, persistence of wheezing or reduced oral corticosteroid use.<sup>61,62</sup> Nevertheless, Bacharier et al. observed that among patients with a positive API<sub>m</sub> result, treatment for 1 week with nebulized budesonide or Oral Montelukast resulted in less oral corticosteroid use, significant reduction in severe episodes of wheezing and

**Table 2** - Treatment of infants according to frequency of wheezing episodes in Curitiba, Brazil (adapted from Rosário & Chong Neto<sup>64</sup>)

Medication	$\geq 3$ episodes (n = 678)	$< 3$ episodes (n = 682)	p
	n (%)	n (%)	
Inhaled short-acting $\beta_2$ agonists*	608 (89.6)	539 (79)	< 0.0001
Inhaled corticosteroids <sup>†</sup>	160 (23.6)	90 (13.2)	0.003
Leukotriene modifiers <sup>‡</sup>	47 (6.9)	26 (3.8)	0.42
Oral corticosteroids <sup>§</sup>	126 (18.6)	109 (16)	0.2

\* 6 responses missing.

† 12 responses missing.

‡ 10 responses missing.

§ 20 responses missing.

improved respiratory score, when compared with children with a negative APIIm result.<sup>62</sup>

According to the guidelines, continuous or intermittent inhaled corticosteroids will not alter the severity or course of the disease in preschool children with recurrent wheezing or asthma, but can be used to control symptoms and improve quality of life.<sup>4,59</sup>

The scarcity of studies of the treatment of recurrent wheezing/asthma means that there is no consensus on how to treat this group of children. In Curitiba, medication for preventative treatment of asthma is available to the pediatricians working at public Health Centers. This contributed to a reduction in hospitalizations and better control of the disease at one public center of excellence.<sup>63</sup> For infants, these data are reduced or nonexistent, because of the diagnostic difficulties and absence of standardized studies. In Curitiba, the EISL detected that a large proportion of children were treated for asthma (inhaled corticosteroids and bronchodilators), disproportionate to the real need for these medications.<sup>64</sup> It is known that 70% of asthma patients have mild forms and in this age group preventative medication is still not the consensus. Even with the high rate of recurrently wheezing infants, a high proportion of them are treated for asthma. This is due to the accessibility of asthma drugs, or to the fact that international guidelines for asthma treatment are probably not being respected (Table 2).

In conclusion, the prevalence of recurrent wheezing is elevated among infants. The factors associated with recurrent wheezing can be useful when diagnosing asthma in very young children. These factors vary from one research center to the next, even when using standardized instruments, demonstrating that the situation in Brazil is different to that observed in other countries. Despite the widely-publicized recommendations and guidelines, the treatment of wheezing in infants must be made criteria-based to avoid unnecessarily prescribing inhaled or systemic corticosteroids to many children.

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