

CORRESPONDENCE

Treatment of wheezing in Brazilian infants in the first year of life

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To the Editor,

Wheezing disorders in infants are a significant global public health problem, with high morbidity (1), and are responsible for overuse of health resources. The first year of life is when the majority of wheezing infants present their first wheezing episode (2). However, it is difficult to distinguish the different wheezing phenotypes in this age group, such as post-viral wheezing and asthma, which delays the use of appropriate treatment.

Asthma-like symptoms are particularly common in the first years of life but represent heterogenic diseases, with little to differentiate the clinical presentations. This heterogeneity is the main problem in both research and daily clinical practice and results in inappropriate treatments in young children (3).

The *Estudio Internacional de Sibilancias en Lactentes* (EISL), or International Study of Wheezing in Infants, held in Latin America, the Netherlands, and Spain, was developed in order to study the impact of wheezing in infants in the first year of life and to identify its prevalence and associated risk factors (1). Parents of infants aged between 12 and 15 months, who attended health centers for routine visits or immunization, answered the validated written questionnaire (WQ)(4) on demographic characteristics, respiratory symptoms (including wheezing), use of medications, medical diagnosis, and possible risk factors for wheezing in the first year of life, such as gender; history of previous respiratory infections; parents or siblings with asthma, rhinitis, or eczema; daycare attendance; exposure to tobacco smoke; presence of pets, carpet, or mold at home; skin allergies; breastfeeding; consumption of processed food. In Brazil, seven centers participated in this study, and the prevalence of wheezing ranged from 43 to 63.6% and recurrent wheezing (three or more episodes in the first year of life) ranged from 21.9 to 36.3% between them (1). The aim of this study was to evaluate the use of drugs for the treatment of occasional and recurrent wheezing among Brazilian centers of EISL.

Methods

We applied the standardized WQ of EISL in all centers. It includes questions on upper respiratory tract infections (URTI); treatment modalities such as inhaled bronchodilators (BD), inhaled corticosteroids (ICS), and leukotriene receptor antagonists (LTRA); severe episodes of wheezing; sleep disturbance; emergency department (ED) visits/admissions to hospital due to wheezing; physician-diagnosed asthma, among others. One additional question was added for our population: 'Has your son/daughter ever taken oral corticosteroids (OCS)?'

The questions on wheezing had been previously validated in Portuguese (4). Parents or guardians completed the questionnaire when they attended the health centers for routine visits or

immunizations. The Brazilian centers involved in this study were São Paulo, Recife, Fortaleza, Maceió, Curitiba, and Belém.

Recurrent wheezing (RW) was defined as three or more episodes of ever wheezing in the first 12 months of life, and occasional wheezing (OW) was defined when the infant had presented <3 episodes of wheezing in that period of time. Infants with physician-diagnosed asthma were considered asthmatics.

Non-parametric statistical analyses were performed, and $p < 0.05$ was considered as a statistically significant value.

Results

The study included 12,027 infants. The average OW and RW observed in the whole group were 21.7% (18.1–24.2) and 21.3% (16.3–26.6), respectively. Table 1 shows the need for medication and the clinical characteristics of the wheezing infants who were classified according to the frequency of episodes. There were an increased frequency of visits to emergency services and more severe symptoms among RW infants at all centers, also a higher asthma diagnosis and use of medication for symptom control in this group. There were also significant differences between groups as regards the use of inhaled bronchodilators, history of pneumonia (Table 1), and hospitalization for pneumonia (data not shown).

Discussion

We observed that the use of medication for relief during episodes of wheezing was very frequent, but the use of maintenance therapy was more common in the RW group, where asthma diagnosis was also more common, and the disease more severe. Nevertheless, diagnosis of asthma in this population was low, as only 20.8% of RW group were considered asthmatics. However, the percentage of patients who received prophylactic treatment does not differ much from what could be characterized as asthmatics.

The diagnosis of asthma in young children is difficult and based on clinical assessment of symptoms and results of physical examination. Viral-triggered wheezing episodes, gastroesophageal reflux, rhinitis, foreign body aspiration, cystic fibrosis, or structural abnormalities of the upper and lower airways are some possible differential diagnoses of asthma in children with wheezing disorders.

In some centers, the use of OCS was more common than asthma diagnosis, especially among RW. According to the guidelines for the treatment of childhood wheezing (5), the use of oral corticosteroids is recommended only for severe attacks of wheezing. It is possible that this medication has been

Table 1 Clinical characteristics and need for medication of the wheezing infants stratified according to the frequency of episodes (n = 12,027)

Variables	Belém (n = 3024)		Fortaleza (n = 2732)		Recife (n = 1071)		Maceió (n = 1183)		São Paulo (n = 1014)		Curitiba (n = 3003)		Total (n = 12027)	
	OW (n = 732)	RW (n = 662)	OW (n = 580)	RW (n = 444)	OW (n = 194)	RW (n = 262)	OW (n = 227)	RW (n = 252)	OW (n = 197)	RW (n = 270)	OW (n = 686)	RW (n = 678)	OW (n = 2616)	RW (n = 2568)
Emergency department visits	401 (54.8)	483 (72.7)*	360 (62.1)	346 (77.9)*	141 (72.7)	228 (87.0)*	124 (54.6)	166 (65.9)*	105 (53.3)	193 (71.5)*	312 (45.5)	470 (69.3)*	1443 (55.2)	2079 (80.9)*
Severe episodes	264 (36.1)	379 (57.1)*	274 (47.2)	278 (62.6)*	89 (45.9)	173 (66.0)*	105 (46.2)	150 (59.5)*	83 (42.1)	144 (53.3)*	226 (32.9)	402 (69.3)*	1041 (39.8)	1526 (59.4)*
Hospitalization due to wheezing	96 (13.1)	149 (22.4)*	75 (12.9)	117 (26.4)*	33 (17.0)	60 (22.9)	16 (7.0)	27 (10.7)	30 (15.2)	62 (23.0)*	56 (8.2)	116 (17.1)*	306 (11.7)	531 (20.7)*
Nocturnal symptoms	109 (14.9)	200 (30.1)*	93 (16.0)	185 (41.7)*	63 (32.5)	186 (71.0)*	70 (30.8)*	49 (19.4)	88 (44.7)	202 (74.8)*	303 (44.1)	495 (73.0)*	726 (27.8)	1317 (51.3)*
Asthma	104 (14.2)	201 (30.3)*	59 (10.2)	91 (20.5)*	21 (10.8)	76 (29.0)*	10 (4.4)	25 (9.9)*	7 (3.5)	28 (10.4)*	38 (5.5)	110 (16.2)*	239 (9.1)	534 (20.8)*
Pneumonia	135 (18.4)	189 (28.5)*	149 (25.7)	161 (36.3)*	48 (24.7)	91 (34.7)*	43 (18.9)	69 (27.4)*	40 (20.3)	104 (38.5)*	107 (15.6)	176 (25.9)*	522 (20.0)	790 (30.8)*
Inhaled β_2 agonist	635 (86.7)	604 (91.0)	461 (82.6)	371 (85.3)	156 (80.4)	247 (94.3)*	147 (64.7)	206 (81.7)*	162 (82.2)	240 (88.9)*	539 (79.0)	608 (89.6)*	2100 (80.3)	2276 (88.6)*
Inhaled steroids	138 (18.9)	168 (25.3)*	120 (23.7)	89 (22.9)	37 (19.0)	71 (27.1)*	19 (8.4)	34 (13.5)	13 (6.6)	42 (15.5)*	90 (13.2)	160 (23.6)*	417 (15.9)	564 (22.0)*
Leukotriene modifier	6 (0.8)	10 (1.5)	23 (4.9)	10 (2.9)	4 (2.0)	8 (3.0)	1 (0.4)	3 (1.3)	4 (2.0)	8 (2.9)	26 (3.8)	47 (6.9)*	64 (2.4)	86 (3.3)
Oral corticosteroids	317 (13.4)	190 (28.7)*	73 (12.5)	162 (36.7)*	50 (25.8)	104 (39.7)*	10 (4.4)	24 (9.5)*	61 (30.9)	124 (45.9)*	109 (16.0)	126 (18.6)	620 (23.7)	730 (28.4)*
Physician-diagnosed asthma	74 (10.1)	145 (21.9)*	29 (5.5)	65 (14.6)*	18 (9.1)	56 (21.3)*	7 (3.0)	18 (7.3)*	7 (3.5)	20 (7.5)*	34 (4.9)	74 (10.9)*	167 (6.4)	383 (14.9)*

OW, occasional wheezing; RW, recurrent wheezing.

*p < 0.05

prescribed for the treatment of less severe wheezing or for the treatment of other diseases, such as viral wheeze. The banalization of prescription of oral corticosteroids causes concern regarding their possible side effects, which are often overlooked.

The European Task Force has described two different phenotypes of preschool wheeze: episodic viral wheeze and multiple-trigger wheeze (6). A recent review of corticosteroid use in children reinforced that a short burst of oral corticosteroids must not be given in all cases of attacks of viral wheeze. They should be considered only in young children admitted to hospital with symptoms strongly suggestive of atopic asthma (combination of multiple-trigger wheeze, severe eczema, and a family history of atopic asthma) or with severe bronchodilator-unresponsive wheeze that needs high dependency or intensive care (7). Given the established associations between atopic features and the likelihood of early childhood wheezing persisting to become school-age asthma (8), it is possible that children with these atopic features might respond better to OCS than those without atopic tendencies.

There is concern about the side effects, especially in growth, induced by corticosteroids use in children. These effects have been reduced but not eliminated with the use of ICS. Physicians must weigh the benefits against the potential detrimental effects. It is recommended that standard protocols for the use of corticosteroids should be followed, and physicians should be alert to the potential hazards in prolonged use.

We observed a stronger association between pneumonia, and having been hospitalized for pneumonia and being an RW infant. In general, risk factors for respiratory infections, asthma, and wheezing in infants and children in developing

countries are similar, so it is estimated that high rates of acute respiratory infection in the lower airways are expected in children with asthma and wheezing in early life. Furthermore, a recent study identified that bacterial infection of the bronchial tree is common in persistent preschool wheezers and provides a possible explanation for the non-response to ICS therapy. Non-typeable *H. influenzae* seems to be the predominant pathogen involved, followed by *S. pneumoniae* and *M. catarrhalis* (9).

A limitation of this study is that the frequency of drug use has been estimated by the account of parents or guardians and not through medical records, which would be more reliable. However, using written questionnaires, parents are able to remember diseases, such as asthma and perception of symptoms with high levels of accuracy (10).

It is encouraging that there continues to be active research to improve our approach to the early diagnostic of asthma and clinical management of wheezing in the preschool years.

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References

- Mallol J, García-Marcos L, Solé D, Brand P, the EISL Study Group. International prevalence of recurrent wheezing during the first year of life: variability, treatment patterns and use of health resources. *Thorax* 2010; **65**(11): 1004–9.
- Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995; **332**: 133–8.
- Bush A. Practice imperfect-treatment for wheezing in preschoolers. *N Engl J Med* 2009; **360**: 409–10.
- Dela Bianca AC, Wandalsen GF, Miyagi K, et al. International Study of Wheezing in Infants (EISL): validation of written questionnaire for children aged below 3 years. *J Investig Allergol Clin Immunol* 2009; **19**: 35–42.
- Bacharier LB, Boner A, Carlsen KH, et al. Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. *Allergy* 2008; **63**: 5–34.
- Bradn PLP, Baraldi E, Bisgaard H, et al. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. *Eur Respir J* 2008; **32**: 1096–110.
- De Benedictis FM, Bush A. Corticosteroids in respiratory diseases in children. *Am J Respir Crit Care Med* 2012; **185**: 12–23.
- Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000; **162**: 1403–6.
- De Schutter I, Dreesman A, Soetens O, et al. In young children, persistent wheezing is associated with bronchial bacterial infection: a retrospective analysis. *BMC Pediatr* 2012; **12**: 83.
- Samet JM, Cushing AH, Lambert WE, et al. Comparability of parent reports of respiratory illnesses with clinical diagnoses in infants. *Am Rev Respir Dis* 1993; **148**: 441–6.