

When asthma and rhinitis coexist, could rhinitis reduce asthma control in children?

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ABSTRACT

Background: Bronchial asthma and rhinitis are among the most common diseases in children and frequently coexist in the patient. The primary aim of anti-asthmatic therapy is disease control. Several questionnaires can be used in pediatrics to assess asthma control and the Children Asthma Control Test (C-ACT) is one of the most used.

Objective: To evaluate the percentage of asthma control in our cohort of patients with asthma and correlate C-ACT with bronchial and nasal function tests.

Methods: We enrolled all children ages between 5 and 11 years with persistent bronchial asthma, sensitized to dust mite, and who presented to our center during an 8-month period. All the children had skin-prick tests, spirometry, measurement of fractional exhaled nitric oxide levels, active anterior rhinomanometry, measurement of nasal nitric oxide level, and C-ACT.

Results: Sixty patients were enrolled; 80% of these children had rhinitis. According to C-ACT, 31% of our patients had uncontrolled asthma. Nasal flow values were significantly lower in patients with uncontrolled asthma, who also had higher nasal inflammation.

Conclusion: The disease is not controlled in a significant percentage of children with asthma. In patients with uncontrolled asthma, worse nasal flow was detected. These results supported the relationship between upper and lower airways, and highlighted the importance of performing nasal function tests in all patients with asthma, which could be useful to determine whether better control of asthma symptoms can be reached through an appropriate treatment of rhinitis.

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Asthma is a heterogeneous disease characterized by chronic inflammation of the airways and associated with various risk factors. It is defined by a history of respiratory symptoms, such as wheezing, shortness of breath, chest tightness, and cough, that vary over time and in intensity, with a variable expiratory air-flow limitation.¹ Asthma and rhinitis prevalence are influenced by age and ethnicity. In Europe, 10% and 17.1% of children are affected by these diseases, respectively.^{2,3} Epidemiologic studies show that rhinitis and asthma often coexist in a patient as clinical manifestations of a single allergic disease, and rhinitis plays a key role as a risk factor for asthma onset and control. Accordingly, the prevalence of rhinitis among children with asthma can reach 70–80%.^{4,5} Therefore, it is important to consider the influence of rhinitis on the management of patients with asthma.

The goal of therapy is to achieve asthma control, as shown by the reduction or resolution of the clinical manifestations with an appropriate anti-asthmatic treatment.¹ Control should be assessed through specific tools that provide scores to define different levels of clinical control. Several questionnaires are available^{6,7}: The Children Asthma Control Test (C-ACT) is one of the most commonly used, and it has been validated in different contexts.^{8–10} We used the Italian version of the questionnaire to assess symptoms, limitations on activities, and use of emergency medications. The aim of the study was to investigate the percentage of uncontrolled asthma in our patient cohort, and the relationship between C-ACT scores and objective parameters, such as lung function (fractional exhaled nitric oxide [FeNO]) and nasal function (active anterior rhinomanometry [AAR] and nasal fractional exhaled nitric oxide [nFeNO]).

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METHODS

This was a real-life, prospective, observational study conducted in Rome from June 2017 to February 2018 in the asthma clinic of the Pediatric Department, Policlinico Umberto I. The study was approved by the medical ethics review board of Sapienza University of Rome, Policlinico Umberto I. The patients' parents or guardians signed a written consent form.

Study Participants and Protocol

Among the patients with asthma followed up in our center and who came for routine outpatient control visits, we consecutively enrolled children, ages between 5 and 11 years, with persistent bronchial asthma and sensitized to dust mite. No parent or guardian declined to participate. The diagnosis of asthma had been clinically confirmed by a specialized physician (A.M.Z.) according to the Global Initiative for Asthma (GINA),¹ and by a positive bronchodilator test at spirometry (an increase of at least 12% of forced expiratory volume in the first second [FEV₁] after administration of salbutamol). Children with a body mass index of >25 kg/m², cystic fibrosis, oncologic diseases, chronic heart disease, and lung pathologies other than asthma were excluded. All the patients were on an anti-asthmatic therapy appropriate to their disease severity. In detail, the patients with mild persistent asthma (46.7% of the sample) were on inhaled corticosteroids, whereas patients with moderate (50% of the sample) or severe persistent (3.3% of the sample) asthma were on inhaled corticosteroids and long-acting β_2 -agonists.

After signing informed consent forms, clinical information (age of onset of asthma and related treatments; concomitant diseases, *e.g.*, allergic rhinitis (AR); and a family history of allergic diseases) were collected from participants' parents or guardians. All the patients had skin-prick testing with a standardized panel of common allergens (dust mite, grasses, trees, molds, animals), spirometry with a bronchodilator test, AAR, and measurement of eFeNO and nFeNO. For all the patients enrolled, C-ACT was used to evaluate asthma control.

C-ACT

Children and their parents or guardians completed the C-ACT. The questionnaire consists of four each items addressed to the child (with a score for each item from 0 to 3) and three items addressed to the parents (with a score for each item from 0 to 5). The sum of the scores provides a total index, which indicated the level of asthma control in the 4 weeks preceding the visit. Patients with controlled asthma had an overall score of ≥ 20 , and those with uncontrolled asthma had an overall score of <20.

Spirometry and eFeNO

Spirometry was performed according to ATS (American Thoracic Society)/European Respiratory Society (ERS) standards.¹¹ Flow volume curves were measured with a Cosmed spirometer (Cosmed The Metabolic Company, Rome, Italy). Values were expressed as the percentage of predicted normal values for height and sex.¹² The eFeNO levels were measured with a Cosmed

Quark NO breath device according to the procedures published for eFeNO measurement.¹³

AAR and nFeNO

The AAR studies the nasal function through the measurement of the nasal airflow and the resistance to air passage. The test is easy to perform and takes ~10 minutes. A rhinomanometer measures the flow (cm³/s) in both the right and left nostril at a pressure of 150 Pa in inspiration and expiration. The values obtained are compared with the pediatric values, height dependent, reported in the literature. Nasal obstruction is classified as very severe if airflow values are <29% of predicted, severe if values are between 29% and 42%, moderate if values are between 43% and 56%, mild for values between 57% and 70%, and absent for values >70%.^{14–16} The nFeNO is a marker of eosinophilic inflammation synthesized by the epithelial cells of the nasal mucosa and increased levels are found in AR; it has been described that is useful for monitoring the disease.¹⁷ This marker can be easily measured by a recent noninvasive method, equipped with nNO software (Medisoftware FeNO, Medisoftware s.r.l., Naples, Italy) according to the American Thoracic Society/European Respiratory Society recommendations.¹³

Statistical Analysis

A descriptive analysis was performed by using the number and frequency (*n* [%]) for categorical variables, whereas mean $\pm$ standard deviation and median (interquartile range) for numeric variables were used. The differences between continuous variables of two groups were compared by using a bilateral Mann-Whitney *U* test, whereas the presence of the significant differences among three or more groups were determined by the Kruskal Wallis test, followed by the Dunn *post hoc* test. Correlations between continuous variables were assessed by computing the Pearson rank correlation test. In all cases, $p \leq 0.05$ was considered statistically significant.

RESULTS

The primary objectives of our study were to evaluate the level of uncontrolled asthma in our patients and to investigate the relationship between C-ACT scores and objective parameters, such as lung function (spirometry and eFeNO) and nasal function (AAR and nFeNO).

Descriptive Findings

We enrolled 60 children (44 boys), with a mean age of 10.6 ± 2.75 years and a mean body mass index of 19.66 ± 3.68 kg/m². In our population, 80% of children had persistent rhinitis not treated by an appropriate therapy. According to the GINA classification of

Table 1 Population features

Characteristic	Subjects, no. (%)	Value, mean $\pm$ standard deviation
Age, y	—	10.6 $\pm$ 2.75
Body mass index, kg/m ²	—	19.66 $\pm$ 3.68
Sex		
Boys	44 (73.3)	—
Girls	16 (26.7)	—
Rhinitis	48 (80.0)	—
Asthma severity*		
Mild persistent	28 (46.7)	—
Moderate persistent	30 (50.0)	—
Severe persistent	2 (3.3)	—
FEV ₁ level %		
$\geq 80\%$	45 (75.0)	70.66 $\pm$ 8.06%
$< 80\%$	15 (25.0)	96.95 $\pm$ 8.55%
Children-Asthma Control Test		
Controlled	41 (69.0)	—
Uncontrolled	19 (31.0)	—
Mean nasal flow %		
Controlled	41 (69.0)	23.09 $\pm$ 1.65
Uncontrolled	19 (31.0)	16.78 $\pm$ 1.98
Nasal fractional nitric oxide level ppb		
Controlled	41 (69.0)	536.62 $\pm$ 295.41
Uncontrolled	19 (31.0)	843.813 $\pm$ 307.82

FEV₁ = Forced expiratory volume in the first second.

* From Ref.

asthma severity,¹ 46.7% of our patients had mild persistent asthma, 50% had moderate persistent asthma, and 3.3% had severe persistent asthma. With regard to lung function, the 75% of children had an FEV₁ level of $\geq 80\%$ of predicted and 25% of them had an FEV₁ level of $< 80\%$ of predicted (Table 1).

Control of Asthma in the Study Population

According to C-ACT results, 31% of our patients had uncontrolled asthma (Table 1).

Nasal Function and Asthma Control

The analysis of our data showed that the subjects who reported rhinitis symptoms had nasal flows at rhinomanometry significantly lower than the subjects who did not have rhinitis symptoms ($48.1 \pm 16.3\%$ versus $76.8 \pm 23.9\%$; $p = 0.00035$) (Table 1; Fig. 1A). When comparing mean nasal flow values between the groups of patients with uncontrolled asthma and patients with controlled asthma, we found that nasal flow values were significantly lower in the first group ($45.6 \pm 16.74\%$ versus $57.7 \pm 22.3\%$; $p = 0.022$) (Fig. 1B). The Pearson rank correlation coefficients revealed an inverse correlation between the values of nFeNO and C-ACT scores ($r = -0.311$; $p = 0.026$) (Table 1; Fig.

2), which showed that the greater the nasal inflammation, the worse the asthma control.

Lung Function and Asthma Control

The C-ACT mean score was significantly lower in the group of patients with an FEV₁ level of $< 80\%$ compared with the group with an FEV₁ level of $\geq 80\%$ ($19.3 \pm 4.1\%$ versus $21.7 \pm 3.2\%$; $p = 0.039$) (Table 1; Fig. 1C). Conversely, we did not observe a significant correlation between the eFeNO values and the C-ACT scores ($r = -0.096$; $p = 0.46$).

DISCUSSION

In this study, we found that, in our clinic, only 69% of the children had controlled asthma and that children with uncontrolled asthma had nasal flow values that were significantly lower than the controlled group. In addition, the nFeNO value increased when asthma control decreased. As expected, when the FEV₁ level was lower, asthma was less controlled; conversely, there was not a correlation between the eFeNO level and the C-ACT score. The main objective of the study was to investigate the level of asthma control in a sample of patients followed up in our center. The percentage of the children whose asthma was controlled

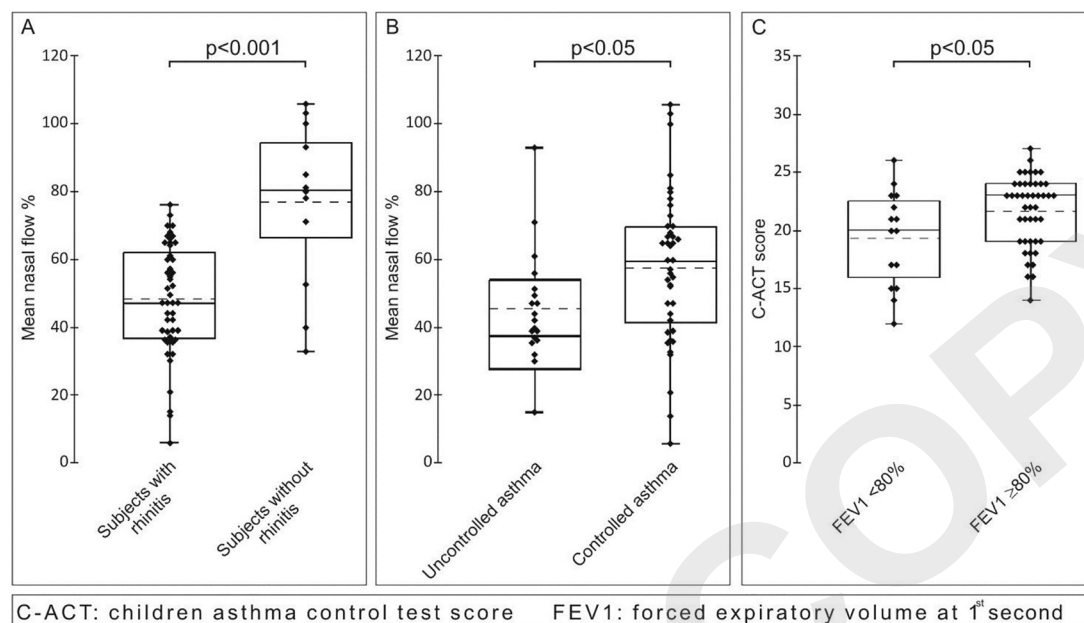


Figure 1. The correlation between symptoms and respiratory function tests. Box and whisker plots, showing the median, interquartile range and mean (dotted line) values for (A) percentage mean nasal flow in subjects with and without rhinitis; (B) percentage mean nasal flow in subjects with uncontrolled and controlled asthma; (C) Children-Asthma Control Test (C-ACT) score for patients with forced expiratory volume in the first second (FEV1) <80% and ≥80%. A *p* value of <0.05 was considered statistically significant.

(C-ACT score of ≥20) was 69%. Despite the spread wide diffusion of guidelines, the current percentage of asthma control is still insufficient. In Europe, only 15% of the patients with asthma achieve control of the disease,¹⁸ and, in Italy, it varies between 14% and 27%.¹⁹ However, the percentage of control rises to 64.4% among patients with asthma followed up in hospital settings, as we found in our study.^{19,20}

The majority of our patients were affected by rhinitis, as measured by nasal flow through AAR and nasal inflammation (nFeNO). We found the association among nasal flow values, the nFeNO value, and the C-ACT score. Specifically, nasal flow values were significantly lower in subjects with uncontrolled asthma than in subjects with controlled asthma. Previous studies assessed rhinitis as a risk factor on asthma con-

trol.^{21,22} Lin *et al.*²³ showed, in adult patients, that AR plays an important role in worsening asthma control and that control is more difficult when the AR symptoms are severe. In our patients, nFeNO values increased when asthma control decreased. Therefore, the nFeNO level seems to be a reliable tool to correlate allergic inflammation and asthma control, despite its use still being controversial.²²

A recent study showed that the nFeNO level is significantly higher in patients with asthma and AR and in those with AR only than in healthy subjects.²⁴ Our results confirmed that allergic inflammation was present both in high and in low airways, and indicated that AR and asthma represent manifestations of one disease in two parts of the respiratory tract.²⁵ Nasal allergic inflammation can reach lower airways for continuity and contigu-

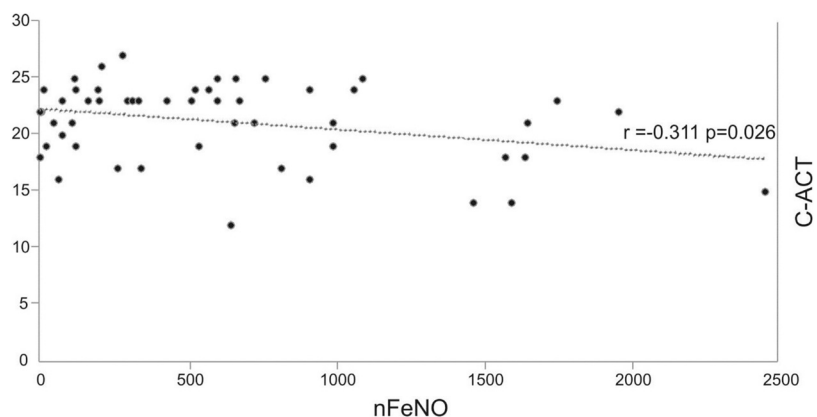


Figure 2. The correlation between nasal fractional exhaled nitric oxide (nFeNO) values and Children-Asthma Control Test (C-ACT) scores. The Pearson rank correlation test value as well as the *p* value are also reported. A *p* value of ≥0.05 was considered statistically significant.

ity (there is not an anatomic barrier between the nose and bronchi), and AR contributes to the pathogenesis of asthma-releasing systemic mediators.²⁶

To analyze the association between lung function and asthma control, all our patients performed spirometry: when the FEV₁ level was lower, asthma was less controlled. Previously, Waibel *et al.*²⁷ demonstrated a correlation between spirometry parameters and asthma control. Their findings, in agreement with ours, show that C-ACT and spirometry are complementary and efficient tools to assess asthma control.²⁷ Conversely, we did not observe a significant correlation between the C-ACT score and the eFENO value, which proved a questionable utility of this marker in the management of asthma, as also shown in other studies.^{28–30}

Indeed, the eFeNO value by itself is not useful to confirm or exclude the diagnosis of asthma when also considering that multiple factors can influence the concentration of this marker (use of inhaled corticosteroids, bronchoconstriction, the presence of viral infections, smoking exposure). However, it may be useful to monitor the severity of the disease and the response to the treatment.^{1–17,31} Other markers have been shown to be helpful to evaluate asthma control in children. Caffarelli *et al.*³² showed that the pH of the exhaled breath condensate in children with asthma is decreased, possibly related to airway inflammation and to pharmacologic treatment. The pH measurement may be a useful noninvasive biomarker to guide treatment of asthma exacerbations in childhood. Our study was one of the first to analyze the relationship between objective respiratory parameters and asthma control in children. However, our study had some limitations: our cohort had a relatively small number of participants, and these participants were all recruited in a single specialized outpatient setting. Multicentric studies, with a wider sample are necessary to confirm the results.

CONCLUSION

A total of 31% of the children followed up in a specialized university center had uncontrolled asthma despite appropriate therapy. There was a correlation between the FEV₁ level and asthma control. In addition, AR represented a risk factor that negatively affected asthma control, as assessed by rhinomanometry and nFeNO. This finding supported the existence of a relationship between upper and lower airways. Further studies are needed to confirm that rhinomanometry could be a useful tool in the diagnostic toolbox for a complete assessment of the patient with asthma and to determine whether better control of asthma symptoms can be reached through an appropriate treatment of AR.

REFERENCES

- GINA. Global Initiative for Asthma 2017 [cited 2018 Feb 1]. Available from: <http://ginasthma.org/>.

- Lai CK, Beasley R, Crane J, et al. Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax*. 2009; 64:476–483.
- Pearce N, Ait-Khaled N, Beasley R, et al. Worldwide trends in the prevalence of asthma symptoms: phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax*. 2007; 62:758–766.
- Lin J, Gao J, Lai K, et al. The characteristic of asthma control among nasal diseases population: results from a cross-sectional study. *PLoS One*. 2018; 13:e0191543.
- Hojó M, Ohta K, Iikura M, Hirashima J, Sugiyama H, Takahashi K. The impact of co-existing seasonal allergic rhinitis caused by Japanese Cedar Pollinosis (SAR-JCP) upon asthma control status. *Allergol Int*. 2015; 64:150–155.
- Nathan RA, Sorkness CA, Kosinski M, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol*. 2004; 113:59–65.
- Juniper EF, Svensson K, Mörk AC, Ståhl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med*. 2005; 99:553–558.
- Schatz M, Sorkness CA, Li JT, et al. Asthma Control Test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. *J Allergy Clin Immunol*. 2006; 117:549–556.
- Schatz M, Mosen DM, Kosinski M, et al. Validity of the Asthma Control Test completed at home. *Am J Manag Care*. 2007; 13:661–667.
- Schatz M, Zeiger RS, Drane A, et al. Reliability and predictive validity of the Asthma Control Test administered by telephone calls using speech recognition technology. *J Allergy Clin Immunol*. 2007; 119:336–343.
- Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005; 26:319–338.
- Zapletal A, Motoyama EK, Van De Woestijne KP, Hunt VR, Bouhuys A. Maximum expiratory flow volume curves and airway conductance in children and adolescents. *J Appl Physiol*. 1969; 26:308–316.
- American Thoracic Society, European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med*. 2005; 171:912–930.
- Zapletal A, Chalupová J. Nasal airflow and resistance measured by active anterior rhinomanometry in healthy children and adolescents. *Pediatr Pulmonol*. 2002; 33:174–180.
- Ottaviano G, Fokkens WJ. Measurements of nasal airflow and patency: a critical review with emphasis on the use of peak nasal inspiratory flow in day practice. *Allergy*. 2016; 71:162–174.
- Clement PA, Gordts F. Consensus report on acoustic rhinometry and rhinomanometry. *Rhinology*. 2005; 43:169–179.
- Suojalehto H, Vehmas T, Lindström I, et al. Nasal nitric oxide is dependent on sinus obstruction in allergic rhinitis. *Laryngoscope*. 2014; 124:E213–E218.
- Cazzoletti L, Marcon A, Janson C, et al. Asthma control in Europe: a real-world evaluation based on an international population-based study. *J Allergy Clin Immunol*. 2007; 120:1360–1367.
- Caminati M, Bettoncelli G, Magnoni MS, et al. The level of control of mild asthma in general practice: an observational community-based study. *J Asthma*. 2014; 51:91–96.
- Allegra L, Cremonesi G, Girbino G, et al. Real-life prospective study on asthma control in Italy: cross-sectional phase results. *Respir Med*. 2012; 106(2):205–214.
- Togias A, Gergen PJ, Hu JW, et al. Rhinitis in children and adolescents with asthma: ubiquitous, difficult to control, and associated with asthma outcomes. *J Allergy Clin Immunol*. 2019; 143(3):1003–1011.e10.

22. Bonner K, Roberts G. Does allergy explain why some children have severe asthma? *Clin Exp Allergy*. 2018; 48:1594–1605.
23. Lin J, Gao J, Lai K, et al. The characteristic of asthma control among nasal diseases population: results from a cross-sectional study. *PLoS One*. 2018; 13:e0191543.
24. Takeno S, Okabayashi Y, Kohno T, Yumii K, Hirakawa K. The role of nasal fractional exhaled nitric oxide as an objective parameter independent of nasal airflow resistance in the diagnosis of allergic rhinitis. *Auris Nasus Larynx*. 2017; 44:435–441.
25. Duong-Quy S, Vu-Minh T, Hua-Juy T, et al. Study of nasal exhaled nitric oxide levels in diagnosis of allergic rhinitis in subjects with and without asthma. *J Asthma Allergy*. 2017; 10:75–82.
26. Chen IC, Lin YT, Hsu JH, Liu YC, Wu JR, Dai ZK. Nasal airflow measured by rhinomanometry correlates with FeNO in children with asthma. *PLoS One*. 2016; 11:e0165440.
27. Waibel V, Ulmer H, Horak E. Assessing asthma control: symptom scores, GINA levels of asthma control, lung function, and exhaled nitric oxide. *Pediatr Pulmonol*. 2012; 47:113–118.
28. Ciprandi G, Tosca MA, Cirillo I, Capasso M. Impact of allergic rhinitis on asthma in children: effects on bronchial hyperreactivity. *Allergy*. 2010; 65:1199–1201.
29. Khalili B, Boggs PB, Shi R, Bahna SL. Discrepancy between clinical asthma control assessment tools and fractional exhaled nitric oxide. *Ann Allergy Asthma Immunol*. 2008; 101: 124–129.
30. Leung TF, Ko FW, Sy HY, et al. Identifying uncontrolled asthma in young children: clinical scores or objective variables? *J Asthma*. 2009; 46:130–135.
31. British Thoracic Society and Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. 2014 [cited 2017 Jun 5]. Available from: www.brit-thoracic.org.uk/document-library/clinical-information/asthma/btssign-asthma-guideline-2014/.
32. Caffarelli C, Dascola CP, Peroni D, et al. Airway acidification in childhood asthma exacerbations. *Allergy Asthma Proc*. 2014; 35:51–56. □

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