Original Article

# Neutrophilic Steroid-Refractory Recurrent Wheeze and Eosinophilic Steroid-Refractory Asthma in Children

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***What is already known about this topic?*** In preschool children, recurrent wheezes have a good prognosis but severe phenotypes exist. At school age, severe asthma is often associated with multiple allergies. In these 2 cases, the physiopathological pathways are not well known.

***What does this article add to our knowledge?*** Inflammatory cells and different triggers are associated with 2 phenotypes of severe obstructive diseases during childhood: neutrophils and bacterial infection in preschool children and eosinophils and multiple allergies at school age.

***How does this study impact current management guidelines?*** These 2 severe childhood obstructive diseases—neutrophilic steroid-refractory recurrent wheeze and eosinophilic steroid-refractory asthma—could be treated by targeted therapies such as antibiotic and T helper lymphocyte type 2 biotherapy directed towards neutrophil and eosinophil inflammation, respectively.

**BACKGROUND: Little is known about inflammatory pathways of severe recurrent wheeze in preschool children and severe asthma in children.**

**OBJECTIVES: The aim of the Severe Asthma Molecular Phenotype cohort was to characterize phenotypes of severe recurrent wheeze and severe asthma during childhood in terms of triggers (allergic or not), involved cells (eosinophil or neutrophil), and corticoid responsiveness.**

**METHODS: Children with moderate-to-severe asthma and preschool children with moderate-to-severe recurrent wheeze were enrolled prospectively. They underwent standardized clinical and blood workup, and bronchoalveolar lavage (BAL) evaluation. Cluster analysis was applied to 350 children with 34 variables.**

**RESULTS: Three clusters were identified: cluster 1, *Neutrophilic steroid-refractory recurrent wheeze phenotype*, with 138 children uncontrolled despite high-dose inhaled corticosteroids (ICS) (92%, $P < .001$), with more history of pneumonia (31%, $P < .001$), more gastroesophageal reflux disease (37%, $P < .001$), and the highest blood neutrophil count (mean 4.524 cells/mm$^3$, $P = .05$); cluster 2, *Severe recurrent wheeze with sensitization to a single aeroallergen* (12%, $P = .002$), with 104 children controlled with high-dose ICS (63%, $P < .001$); cluster 3, *Eosinophilic steroid-refractory asthma phenotype*, with 108 children uncontrolled despite high-dose ICS (76%, $P < .001$) with more allergic rhinitis, atopic dermatitis, and food allergies (82%, 40%, 31%, $P < .001$, respectively). They also had a higher blood eosinophil count and a higher percentage of BAL eosinophil (506/mm$^3$, 2.6%, $P < .001$ respectively).**

**CONCLUSIONS: Inflammation pathway of asthma and recurrent wheeze are related to eosinophil cells in older children and neutrophil cells in younger children. These results could improve personalized treatments.** © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

***Key words:*** *Severe asthma; Severe recurrent wheeze phenotypes; Children; Bacterial infection; Gastroesophageal reflux; Multiple allergies*

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*Abbreviations used*
*BMI- Body mass index*
*FP- Fluticasone propionate*
*GERD- Gastroesophageal reflux*
*ICS- Inhaled corticosteroid*
*LTRA- Leukotriene receptor antagonist*
*MTW- Multiple-trigger wheeze*
*SAMP- Severe Asthma Molecular Phenotype*
*SARP- Severe Asthma Research Program*
*SPT- Skin prick test*
*TAP- Trousseau Asthma Program*

Asthma is a heterogeneous disease related to various phenotypes. Severe asthma is rare but represents a high burden of the disease. Two pathophysiological pathways of asthma can be described in terms of the principal triggers: allergic and nonallergic.[1] However, in 1999, Humbert et al[2] found IgE in bronchial biopsies of patients tested negative for allergy. These results contest the dichotomous feature of *extrinsic* and *intrinsic* asthma. Moreover, it seems that in birth cohorts, allergic asthma conveys the highest risk of persistence during childhood.[3] Nevertheless, nonallergic asthma (with predominance in girls) seems to be more common and more severe than allergic asthma in cohorts of children with asthma[4] than in adult patients.[5,6] This difference could be due to the fact that the nonallergic asthma phenotype is not considered as a phenotype of asthma in the general population but related to viral-induced wheeze carrying with it the notion of a favorable disease course or remission during childhood.

The term "recurrent persistent wheeze" is applied to infants and preschool age children who present with recurrent episodes of coughing and/or wheezing. Although these symptoms are common in the preschool years, they are frequently transient.[7] Bacharier et al[8] described a phenotype of severe intermittent wheezing in preschool children where children with oral corticosteroid used in the previous year were likely to have more severe disease, documented by a higher incidence of visits to the emergency department, hospitalizations, and aeroallergen sensitization. Severe recurrent preschool wheeze is also defined by Fleming et al[9] as a history of breathlessness and wheeze and persistent symptoms and/or frequent severe exacerbation despite a combination of high-dose inhaled corticosteroid (ICS) with a leukotriene receptor antagonist (LTRA). Although the underlying mechanisms are not yet known, some of these preschool children have evidence of airway remodeling and inflammation.[10] Some of them, especially those with severe recurrent wheeze, will also develop asthma during childhood.[11] Indeed, a retrospective analysis of a cohort of severe asthma in children aged more than 6 years (Severe Asthma Research Program [SARP] cohort) suggests that many school-age children with severe asthma have symptoms that appeared within the first 24 months of life.[12] At the time of the development of various biotherapies directed against T helper lymphocyte type 2 (Th2) or T helper lymphocyte type 1 pathways for the treatment of severe asthma,[13] it could also be interesting to describe severe asthma in children and severe recurrent wheeze in preschool children (potentially at risk of persistence) as regards the triggers and link to atopy, but also in terms of inflammatory features and corticoid responsiveness.[11,14,15]

We therefore performed a study in a new population of the Trousseau Asthma Program (TAP) called the Severe Asthma Molecular Phenotype (SAMP) cohort, to characterize preschool recurrent wheeze phenotypes and severe asthma in children.

## METHODS

### Design and setting

This was a prospective cross-sectional study performed from 2011 to 2015 from SAMP, a part of the TAP cohort, at Trousseau Hospital, Paris. All the children had been referred to the center by a primary care physician because of persistence of recurrent wheeze despite long-term treatment. Two-thirds of the children were from Paris and the surrounding area, and the remaining third were from all regions of France. The Institutional Review Board of Saint Antoine Hospital, Paris, endorsed the protocol as an observational study. Written informed consent was obtained from the parents of the children included.

### Inclusion criteria

The population included in the present study consisted of children meeting the following inclusion criteria: (i) children with severe asthma or severe recurrent wheeze (as defined below) aged from 1 to 15 years at the time of exploration; (ii) who had undergone exploration at least 6 weeks after an episode of exacerbation, acute respiratory illness or treatment by antibiotics; (iii) had a history of recurrent wheeze (more than 3 episodes of bronchodilator reversible bronchial obstruction documented within the previous 6 months); (iv) had been explored by flexible bronchoscopy for severe asthma, severe recurrent wheeze, moderate recurrent wheeze, or moderate asthma with unusual symptoms (ie, cough with phlegm associated with wheezing, and/or persistent parenchymental shadowing); (v) for whom other diseases known to provoke wheezes had been ruled out by flexible bronchoscopy and bronchoalveolar lavage (BAL) with microbiological analysis consisting of bacterial cultures and viral analysis (PCR for influenza (A and B), parainfluenzae (1, 2, 3), metapneumovirus); available blood-cell count, IgG, IgM, IgA blood levels, post-vaccine tetanus and diphtheria serologies; and a sweat test. In the rare cases of bronchiectasis and/or chronic severe ear or sinus disorders, a bronchial biopsy/brushing was performed to rule out a primary ciliary pathology. Definitions of asthma in children: (i) moderate asthma was defined as controlled asthma or partially controlled asthma with moderate dose ICS ($\geq$200 and $<$500 mcg/day fluticasone propionate [FP]) plus another controller medication (LTRA, long-acting β-agonist); (ii) severe asthma was defined as controlled asthma with high-dose ICS ($\geq$500 mcg/day FP) and 2 other controller medications; and (iii) steroid-refractory asthma was defined as uncontrolled asthma despite high-dose ICS ($\geq$500 mcg/day FP) and 2 other controller medications according to GINA guidelines[16] and dosage for fluticasone available in France.

Definitions of asthma in preschool children: (i) moderate recurrent wheeze was defined as controlled or partially controlled symptoms with moderate-dose ICS ($\leq$200 mcg/day FP) and LTRA[9]; (ii) severe recurrent wheeze was defined as controlled symptoms with high-dose ICS ($>$200 mcg/day) and LTRA; and (iii) steroid-refractory recurrent wheeze was defined as uncontrolled symptoms (persistent and frequent exacerbations) despite high-dose ICS ($>$200 mcg/day) and LTRA.[9] The severity of asthma or recurrent wheeze of the entire population was assessed after at least 6 months of follow-up before inclusion in the study, by an experienced pulmonologist pediatrician after repeated individual or group health education measures to improve adherence to antiasthmatic treatment and after