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Clinical and bronchial parameters associated with the exacerbation frequency of severe preschool wheezers



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Clinical Implications

To limit the risk of exacerbations in preschool wheezers, clinicians must aim to prevent and delay early-life wheezing episodes and target bronchial smooth muscle remodeling, as these are independent risk factors associated with the frequency of exacerbations.

Recurrent preschool wheezers represent approximately 10% of children under 5 years of age.¹ Among them, those who report frequent exacerbations (ie, 3 or more per year), mainly due to viral and/or bacterial infections, have an increased risk of persistent asthma and poor lung function throughout life.^{1,2} The risk of exacerbation has been previously associated with several clinical and/or biological parameters, including those of bronchial remodeling. The latter corresponds to a poorly reversible structural abnormality of the bronchial tissue (ie, altered epithelial integrity, increased mass of mucus gland and/or bronchial smooth muscle [BSM], increased density of blood vessels, and an increased collagen deposition leading to reticular basement membrane [RBM] thickening and increased submucosal fibrosis).^{2,3} However, it remains unclear whether these factors are independently associated with exacerbation frequency (no exacerbation), infrequent (1 or 2) exacerbations, or frequent (≥ 3) exacerbations. We aimed to identify the parameters independently associated with short-term subsequent exacerbation frequency (ie, within a year) in 80 severe preschool children (1-5 years old). These children have been pooled from 2 independent cohorts with the same inclusion criteria (NCT02806466 and NCT04558671), as described previously.³ All children had uncontrolled severe recurrent preschool wheeze despite receiving high doses of inhaled corticosteroids (ICS) and a second controller.⁴ Fiberoptic bronchoscopy with bronchial biopsies was performed during the stable period at least 4 weeks after an exacerbation. A detailed description of methods has been previously published elsewhere.³

Patients were divided into 3 groups according to the number of exacerbations in the year after the fiberoptic bronchoscopy: “No-Ex” (no exacerbation, 20/80 [25.0%]), “Low-Ex” (1 or 2 exacerbations, 27/80 [33.7%]), and “High-Ex” (3 exacerbations

or more, 33/80 [41.3%]). Clinical, biological, and histological parameters were compared between the groups using χ^2 tests or the Kruskal-Wallis test with Dunn's *post hoc* test using the SPSS software (version 29.0; IBM Corp, Armonk, NY). A *P* value of $<.05$ was considered significant.

Patients in the “High-Ex” group were younger at the first episode of wheezing, had a lower RBM-BSM distance and greater BSM area and RBM thickness, and required more frequently an increase in ICS in the follow-up year than the other 2 groups, and had a higher prevalence of atopy than the “Low-Ex” group. The “Low-Ex” group had the highest prevalence of *Haemophilus* genus and *Streptococcus* genus bacteria in the bronchoalveolar lavage fluid (BALF) and an increased BSM mass compared with the “No-Ex” group (Table I). There were no other significant differences between the 3 groups according to clinical, biological, or histological parameters.

All clinical, biological, and bronchial remodeling parameters were included in an ordinal regression analysis adjusted for the patients' initial cohort membership to identify the parameters associated with the exacerbation frequency. Only the BSM area and the age at first episode of wheezing appeared as factors independently associated with the exacerbation frequency in severe preschool wheezers (Table II). The greater the BSM area and the earlier the first episode of wheezing, the higher the frequency of exacerbations in the year after the bronchoscopy (Table II).

In the present study, no association between exacerbation frequency and blood or bronchial inflammation has been identified. However, these results may have been impacted by a high dose of ICS treatment of the patient. By contrast, we highlighted an increased prevalence of bacteria in the BALF in both low and high subsequent exacerbation frequency groups, even though the bronchoscopies were performed in patients in a stable condition. However, the presence of bacteria in the BALF did not appear as an independent factor associated with the exacerbation frequency, which could suggest a beneficial effect of antibiotic treatment after bacterial identification of BALF.

These results also confirm an association between a high exacerbation frequency and both very early-life first episode of wheezing and increased BSM area. These 2 parameters have been previously associated with exacerbation frequency, asthma persistence, and/or low lung function later in life.^{2,3} Our results can thus suggest an interplay between early-life infection and BSM remodeling in the disease pathophysiology. Indeed, on one hand, the first months of life appeared as a critical period in the history of respiratory diseases^{2,3} characterized by a high susceptibility to BSM growth and remodeling supported by a mitochondria-dependent BSM cell proliferation^{4,5} in severe preschool wheezers,⁶ and, on the other hand, viral infection can promote BSM remodeling by inducing BSM cell migration⁷ and the release of mediators that stimulate BSM cell proliferation.⁸ In addition, BSM can increase the susceptibility to viral infection, as demonstrated in asthmatic adults.⁹ However, the effect of early viral infection on the BSM growth and remodeling remained totally unknown.

Several limitations must be pointed out: (1) The 2 initial cohorts of patients were pooled despite several differences between them.³ However, inclusion criteria were the same in the 2 cohorts,

TABLE I. Baseline patients' characteristics according to the number of exacerbations during 1 year of follow-up

Variables	No-Ex	Low-Ex	High-Ex	P value
N	20	27	33	
At inclusion				
Male sex	12/20 (60.0)	18/27 (66.7)	24/33 (72.7)	.627
Age (y)	3.4 [2.0; 4.1]	2.4 [1.6; 3.6]	2.6 [2.0; 3.7]	.227
History or current atopic dermatitis	8/20 (40.0)	4/27 (14.8)	19/33 (57.6)	.003*
Aeroallergen allergy/sensitization	5/20 (25.0)	6/27 (22.2)	12/33 (36.4)	.442
Food allergy/sensitization	6/20 (30.0)	5/27 (18.5)	6/33 (18.2)	.543
Age at first wheezing episode (mo)	5.0 [4.0; 9.0]	4.0 [3.0; 9.5]	3.0 [1.0; 5.0]	.007*,†
Postnatal cigarette smoke exposure	10/20 (50.0)	16/27 (59.3)	19/33 (57.6)	.602
Gastroesophageal reflux	6/20 (30.0)	9/27 (33.3)	15/33 (45.5)	.456
Within a year before inclusion				
No. of OCS bursts	5.0 [2.0; 7.0]	4.0 [3.0; 5.5]	5.0 [3.0; 8.0]	.475
No. of hospitalizations	1 [0; 1]	2 [0.5; 2.5]	2 [1; 3]	.163
Total IgE (kIU/L)	63.0 [10.0; 132.0]	22.0 [8.0; 106.5]	24.5 [9.0; 85.5]	.797
Blood eosinophils (/mm ³)	200.0 [100.0; 300.0]	330.0 [170.0; 460.0]	220.0 [110.0; 470.0]	.374
Daily dose (µg, eq. beclomethasone)	1000 [500; 1700]	1600 [900; 2000]	1600 [500; 2000]	.279
Montelukast	16/20 (80.0)	23/27 (85.2)	29/33 (87.9)	.738
Long-acting β-agonists	11/20 (55.0)	6/27 (22.2)	14/33 (42.4)	.063
Cytology of BALF	17/20 (85.0)	23/27 (85.2)	28/33 (84.8)	1.000
Cells (× 10 ⁴) /mL	16.5 [10.8; 30.0]	24.0 [19.0; 45.0]	16.0 [11.5; 28.3]	.051
Macrophages (%)	79.0 [66.5; 90.0]	69.0 [24.5; 82.0]	71.0 [66.5; 83.0]	.156
Neutrophils (%)	2.0 [1.5; 9.5]	9.0 [2.5; 69.0]	6.0 [2.5; 17.0]	.132
Lymphocytes (%)	20.0 [8.0; 23.0]	10.0 [6.5; 17.5]	14.0 [4.0; 18.5]	.225
Eosinophils (%)	0.0 [0.0; 0.0]	0.0 [0.0; 0.0]	0.0 [0.0; 1.0]	.128
Microbiology of BALF				
Haemophilus genus	7/20 (35.0)	25/27 (92.6)	22/32 (68.8)	<.001*,†,‡
Streptococcus genus	9/20 (45.0)	22/27 (81.4)	23/32 (71.9)	.025‡
Staphylococcus genus	0/20 (0.0)	2/27 (7.4)	1/32 (3.1)	.408
Neisseria genus	4/20 (20.0)	13/27 (48.1)	13/32 (40.6)	.134
Other bacteria genus				
Viruses present	10/20 (50.0)	13/27 (48.1)	23/33 (69.7)	.178
Bronchial remodeling				
Epithelial integrity (%)	18.4 [9.9; 30.9]	18.1 [6.0; 32.6]	14.1 [5.2; 26.2]	.488
RBM thickness (µm)	3.2 [3.1; 3.5]	3.3 [3.0; 3.5]	3.8 [3.4; 4.1]	<.001**†
RBM-BSM distance (µm)	64.5 [43.0; 84.3]	64.5 [41.6; 99.2]	36.8 [31.5; 50.0]	.001**†
Normalized BSM area (%)	13.6 [11.1; 15.4]	19.6 [12.0; 24.0]	31.0 [24.3; 36.9]	<.001*,†,‡
Normalized submucosal fibrosis area (%)	31.9 [25.3; 50.3]	39.5 [34.3; 52.7]	31.4 [23.7; 40.2]	.065
Normalized mucus gland area (%)	14.7 [6.4; 20.0]	7.0 [2.0; 20.1]	8.0 [2.3; 12.8]	.154
Density of blood vessels (/µm ²)	124.0 [79.1; 156.8]	161.0 [116.5; 212.5]	156.0 [117.0; 247.0]	.271
Within days after fiberoptic bronchoscopy				
Pathogenic bacteria treated by ATB	9/11 (81.8)	21/26 (80.8)	23/26 (88.4)	.730
After 12 months of follow-up				
Increased daily dose of ICS	0/20 (0.0)	2/27 (7.4)	16/33 (48.5)	
Unchanged daily dose of ICS	9/20 (45.0)	15/27 (55.6)	14/33 (42.4)	<.001**†
Decreased daily dose of ICS	11/20 (55.0)	10/27 (37.0)	3/33 (9.0)	

Patients were divided according to their number of exacerbations in the year after bronchoscopy into No-Ex (0 exacerbation), Low-Ex (1-2 exacerbations), and High-Ex (≥3 exacerbations).

Results are presented as absolute values and percentage: n/N (%); or as median with interquartile ranges: median [IQR₂₅; IQR₇₅].

Comparisons between the groups were performed using Kruskal-Wallis tests, with Dunn's post hoc tests for quantitative variables and χ^2 tests for categorical variables.

Bold P values indicate statistical significance: $P < .05$.

ATB, Antibiotics; BALF, bronchoalveolar lavage fluid; BSM, bronchial smooth muscle; ICS, inhaled corticosteroids; OCS, oral corticosteroids; RBM, reticular basement membrane.

* $P < .05$ for Low-Ex vs High-Ex.

† $P < .05$ for No-Ex vs High-Ex.

‡ $P < .05$ for No-Ex vs Low-Ex.

TABLE II. Factors associated with increased exacerbation frequency in severe preschool wheezers

Parameters	OR (95% CI)	P value
Normalized BSM area (%)	0.199 (0.112; 0.286)	<.001
Age at first wheeze (mo)	-0.980 (-0.119; -0.004)	.046
Atopic dermatitis (yes vs no)	-0.839 (-2.021; 0.342)	.164
<i>Haemophilus</i> genus in the BALF (yes vs no)	-3.999 (-1.896; 1.098)	.602
<i>Streptococcus</i> genus in the BALF (yes vs no)	-0.319 (-1.777; 1.131)	.666
RBM-BSM distance (µm)	0.003 (-0.012; 0.018)	.699
RBM thickness (µm)	0.516 (-0.330; 1.362)	.232

Patients were divided according to the number of exacerbations in the year after the fiberoptic bronchoscopy into the No-Ex (0 exacerbation, n = 20), Low-Ex (1 or 2 exacerbations, n = 27), and High-Ex (≥3 exacerbations, n = 33) groups. Independent associations between factors and exacerbation frequency were determined using stepwise multiple multinomial regression with No-Ex as the reference group and using ordinal regression analysis. Bold P values indicate statistical significance: P < .05.

and analyses were performed by using cohort membership as a covariable. (2) The number of patients remained limited, which has decreased the size of each group. Thus, the risk of type 2 error in the group comparisons and the 95% confidence intervals in the logistic regression analysis may have been increased. However, this pooled analysis represents the largest cohort describing both clinical and fiberoptic bronchoscopy parameters in severe preschool wheezers. (3) Our data did not include long-term follow-up (ie, more than 1 year), allowing the assessment of the stability of exacerbation frequency over time and its consequences on lung function and asthma persistence at school age.

Taken together, our results underline the interplay between early-life wheeze/viral infection and BSM remodeling in the pathogenesis of severe preschool wheezing and reinforce the need of further studies to better understand the underlying mechanisms leading to BSM remodeling and its role in exacerbation frequency, lung function, and asthma persistence.

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bank, and conducting immunohistochemistry. V. Siao-Him-Fa, V. Boisserie-Lacroix, S. Blanchon, S. Debelleix, G. Labouret, A. M. Blondel, M. Mittaine, and F. Semjen performed bronchoscopy and anesthesia procedures.

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Ingelheim, AstraZeneca, and Sanofi, outside the submitted work. In addition, P. Berger has 3 patents: (1) (EP number: 15152886.6, ie, New compositions and methods of treating and/or preventing chronic obstructive pulmonary disease), pending; (2) (EP number: 3050574, ie, Use of plexixafor for treating and/or preventing acute exacerbations of chronic obstructive pulmonary disease), delivered; and (3) (EP number: 20173595.8, ie, New compositions and methods of treating COVID-19 disease), pending. The rest of the authors declare that they have no relevant conflicts of interest.

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