Vérification du critère de réversibilité du VEMS proposé par les recommandations du GINA chez l'enfant asthmatique : VERI-VEMS, une étude rétrospective de cohorte

Anouchka Fillard

UNIVERSITE DE MONTPELLIER

FACULTE DE MEDECINE MONTPELLIER-NÎMES

THESE

Pour obtenir le titre de

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Le 19 octobre 2020

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Papa : Mon modèle, le roc de la famille. Merci de nous supporter au quotidien, je sais que bien des fois ça n'a pas été facile d'être au milieu de filles qui se crêpent parfois (souvent ?) le chignon !! A toutes les fois où j'aurais dû t'écouter, et où tu m'as dit « je te l'avais bien dit », sans me juger pour autant. J'espère que tu seras fier de moi.

Lara : Mon petit Pokémon, ma soeur que j'aime par dessus-tout. Dieu sait qu'on a traversé des moments difficiles et que la santé n'a pas toujours été au rendez-vous, mais je suis tellement fière de la grande fille que tu es devenue.

Wallie : Ma grand-mère, ma deuxième maman. Je t'aime et je chérirai à jamais nos jours heureux.

Papi Gérard : A mon grand-père, dentiste mais surtout artiste et libre penseur. Merci pour toutes ses histoires rocambolesques que tu nous as racontées pour nous faire rire !

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Alex : Finalement ensemble après toutes ces années. On en a mis du temps avant de se trouver ! Mais au moins j'espère que maintenant, on ne se lâchera plus. Tellement heureuse de partager ta vie. Je t'aime.

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Vanille, Hooligan, Titan : Ce n'est pas parce que le temps passe que je vous oublie pour autant… Merci d'avoir partagé notre vie de façon si aimante, ne serait-ce que le temps de quelques (trop courtes) années.

Ibuki : je sais que tu ne sais pas lire, la grosse. Mais je t'aime beaucoup quand même !

Rêveur : On ne se connait que depuis ce matin, demi-patate/demi-peluche. Mais je sens qu'on va bien s'entendre.

Nêo : Oui tu viens en dernier sur la liste, créature maléfique ! Ben écoute, je ne te remercie de rien, en fait… A part de bien faire rire Lara.

À mes chefs :

Du coté pneumo…

Clément : À nos paris foireux et toutes les choses que tu m'as enseigné ! Je t'admire sur beaucoup de plans, s'il te plait reste toujours aussi agréable et compétent, car c'est ce qui fait ta particularité (je veux dire, en plus des blagues en dessous de la ceinture bien sûr…).

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Romain : Notre Roro international, sans qui on s'ennuierait dans la file pour manger à l'internat, s'il ne critiquait pas tout le monde sans arrêt. Pour toutes les fois aussi où tu nous as bien fais rire quand tu disais « ça m'énerve !!! » ! Non mais tu fais d'autres trucs cools aussi, je te rassure.

Paul : Même si tu as beaucoup trop squatté la chambre de garde, je ne t'en tiens pas rigueur. Plus sérieusement, vraiment sympa de travailler avec toi !

Margot : Un grand merci pour ta bonne humeur, ton enthousiasme et nos petites sessions « bitchage » qui m'ont bien souvent remontées le moral !!! Même si tu préfères être une moule plutôt qu'une huître (« les vrais le sachent »), tu es vraiment cool comme fille. Et un gros bisou à Bruce, en passant !

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VERIFICATION OF FEV_1 REVERSIBILITY CRITERIA ACCORDING TO GINA RECOMMANDATIONS IN ASTHMATIC CHILDREN: THE VERI-VEMS RETROSPECTIVE COHORT STUDY

Glossary:

AIT = Allergen Immunotherapy

BMI = body mass index

FEV_1 = forced expiration volume in 1 second

FVC = forced vital capacity

FEF_{25-75} = forced expiratory flow 25-75%

GINA = Global Initiative for Asthma

IgE = Immunoglobulin E

PFT = pulmonary function test

SD = standard deviation

Se = sensitivity

SPT = skin prick test

INTRODUCTION

Asthma is a chronic inflammatory disorder of the bronchi, associated to airflow hyper-reactivity, and possibly leading to acute symptoms, that are reversible either spontaneously or after appropriate bronchodilator treatment[1,2]. With both prevalence and incidence increasing over the last decades, asthma is a major public health problem[3-5]. Almost 300 million people in the world suffer from this disease, and such an evaluation may underestimate the actual prevalence, given the fact that asthma is often underdiagnosed[4]. Many studies have tried to explain the recent increase in prevalence for both asthma and atopic diseases[1], and possible causes may include the « hygiene hypothesis », the use of endocrine disruptor and chemical treatments in agriculture or industry, and the increased pollution of air and waters. Recent studies consider that the strongest risk for developing asthma include an association of both genetic factors and environmental exposures (such as indoor and outdoor allergens, tobacco smoke, air pollution, chemical irritants…)[3]. The actual consensus consists of a mix of all listed risk factors, making of asthma a multi-factorial disease[6].

Asthma is a very heterogeneous disorder with multiple clinical phenotypes[3]. Considering the pediatric population, asthma is the most frequent chronic non-communicable disease, and the leading cause of childhood morbidity, mainly caused by acute exacerbations characterized by breathlessness, wheezing, chest tightness, and/or cough[7]. It is also associated to a high rate of ER visits, hospitalizations, absenteism from school and presenteism, and still contributes to many deaths amongst young people even in developed countries[2,8]. This condition often begins in early childhood, with an earlier onset in males, and initially with intermittent symptoms, especially occurring during viral respiratory tract infections. Other possible triggers include allergies, physical exercise, cold air, extreme emotional arousal, and even some drugs (aspirin, non-steroid anti-inflammatory drugs, or beta-blockers)[3,9,10]. In pediatrics, known predisposition factors include a family history of asthma, atopy, allergic rhinitis, low birth weight or a history of multiple wheezing episodes during the first two years of life[11-15]. In children, the disease may express itself through different pathways: while

some patients will have lifelong asthma with active symptoms and progressive lung function loss over time, other children will undergo asthma remission during adolescence[16-18]. In this latter group, symptoms may remain quiescent or may relapse in mid-adult life leading clinicians to speculate that the absence of symptoms does not correlate with a full recovery from the disease.

In general, asthma is known to be a chronic disease, tending to present as a life-time condition[19,20]. For such reason, an appropriate management with a correct and prompt diagnosis is crucial to control symptoms and therefore reduce asthma burden and increase patients' quality of life. GINA international guidelines advise to perform pulmonary function tests (PFTs) to diagnose asthma, both in children and adults. Diagnostic criteria in children require a FEV_1/FVC ratio lower than 90% and an increase of 12% of their FEV_1 after bronchodilation test, based on what was observed in adults[4,21-23]. Nevertheless, the bronchodilation test following GINA recommendations, cannot be performed in children younger than 5 years, due to age-related difficulties in achieving test-satisfying controlled expirations[4,12,24,25]. The increase of the FEF_{25-75} after bronchodilation has also been proposed in children to corroborate the diagnosis, but studies seem not to be conclusive[26,27]. Also, the accuracy of these criteria is debated in children and other possible diagnostic methods have been investigated[28,29]. Indeed, in clinical practice, clinical signs and response to inhaled therapy are currently considered by pediatricians as the most useful tools to suspect and then diagnose asthma in children[30,31].

The aim of the present study was to verify the sensitivity of the reversibility criterion proposed by GINA recommendations (the increase of 12% of the FEV_1), and to look for other variables possibly able to show a satisfying sensitivity for a diagnosis of asthma in children.

MATERIALS AND METHODS

A. Study Design

We conducted a multicenter retrospective cohort study that included data from January 2008 to January 2019. Data were collected at the Pediatric and at the Allergy Unit of the University Hospital of Montpellier, France, and at the Immunology and Allergy Pediatric Unit of the University Hospital of Pavia, Italy.

The study was approved by a local ethical committee, in Montpellier (2019_IRB-MTP_01-06), and validated by the Ethical Committee of the University Hospital of Pavia. The study was registered on ClinicalTrials.gov (ID: NCT03814018).

B. Population and collected data

We included all consecutive children, followed by each center, with a diagnosis of asthma, made by a specialist of pediatric asthma, and who performed a PFT at the time of the diagnosis. Diagnosis of asthma had to be reached between their 5^{th} and their 18^{th} anniversary.

Patients with any documented diagnosis of other obstructive disease (such as cystic fibrosis, or ciliary dyskinesia), cancer, and bronchopulmonary dysplasia were excluded from the study. All those children with a diagnosis of asthma, but who did not perform, for any reason, a PFT at the time of the diagnosis were excluded as well.

In each patient, we collected demographic information (height, weight, age at diagnosis, sex), country of provenance (either France or Italy), PFT results at the time of the diagnosis, asthma severity (based on prescribed treatment and GINA guidelines), clinical information (presented symptoms, treatment efficacy after the first consultation, personal history of bronchiolitis/recurrent wheezing during the first two years of life, qualitative improvement – yes or no – of symptoms due to treatment, judged

by the physician during a follow-up consultation). Presence of atopic comorbidities was evaluated as well, including atopy, defined as sensitization to at least one common respiratory allergen (including *Dermatophagoides pteronissinus*, *Dermatophagoides farinae*, grass, cypress, birch, cat, dog, *Alternaria alternata*); allergic rhinitis, defined as the presence of typical disease symptoms due to exposure to an airborne allergen to which the patients are sensitized; food allergy, defined as the appearance of hypersensitivity symptoms related to consumption of a food allergen to which the patients are sensitized, or a positive food challenge to the culprit food; atopic dermatitis.

C. Outcomes of the study

The primary outcome of this study was to assess the reversibility criterion proposed by GINA guidelines of an increase of 12% of FEV_1 after bronchodilation test.

The secondary end points were: (i) to verify if the definition of obstructive syndrome in children, as proposed by GINA guidelines ($FEV_1/FVC < 90\%$) could be applied in clinical settings; (ii) to evaluate if the reversibility of small airways (FEF_{25-75}) defined as an increase greater than 30% after bronchodilation test from basal values, is sensible in discriminating asthmatic children; (iii) to assess which spirometric and clinical variables could correlate to the best sensitivity for the diagnosis of asthma; and (iv) to evaluate, in a subgroups analysis, possible correlations between asthma severity and comorbidities.

D. Statistical analysis

Continuous variables were summarized with descriptive statistics (number, mean, SD), while frequency counts and percentages were provided for categorical data. Statistics were computed for patients with available (i.e. non-missing) data. Comparison of patient characteristics was assessed after grouping patients as for asthma severity (persistent severe, persistent moderate, persistent mild,

and intermittent asthma). We used the Student's *t*-test for data in case of continuous variables and the chi-square test for categorical variables. Differences between groups were considered statistically significant if *p*-values were <0.05.

All analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA).

RESULTS

A. *Included population*

We included a total of 888 children with a diagnosis of asthma reached between January 2008 and January 2019. 17 of them were excluded from the analysis because of missing data (Figure 1).

342 patients were included from the Montpellier University Hospital: 219 of them (64.0%) were males; their mean age at diagnosis was 9.2 years (SD 3.4). 529 patients were included from the Pavia University Hospital: 329 of them (62.2%) were males; their mean age at diagnosis was 9.3 years (SD 3.2). The two populations were not statistically different, when considering their sex and their age (*p-value*: 0.5825 and 0.6605, respectively). Moreover, basal FEV_1 values did not differ between the French and Italian population (1800 mL and 1900 mL, respectively; *p-value*: 0.0728). For all the above reasons, statistical analysis was performed considering the two groups as a single cohort.

An interesting difference between the two populations concerned the prescription of anti-IgE therapy and of Allergen Immunotherapy (AIT): patients were significantly more treated with the monoclonal antibody in the Italian group (5.3% vs. 3.2%; *p-value* < 0.0001), and more AIT treatments were prescribed in the French population (17.0% vs. 8.1%; *p-value* < 0.0001). Another difference concerned sensitization to cypress and birch pollen: in fact, cypress pollen allergy is very common in the Montpellier area, but not in the Pavia area. The opposite consideration is true for birch pollen allergy. We considered these differences very unlikely to influence our objectives.

Characteristics of the children included in the study are shown in Table 1.

B. *Primary outcome*

The reversibility criterion of an increase of at least 12% of the FEV_1 after bronchodilation test was confirmed in only 266 out of 871 children (Figure 2), with a sensitivity (Se) of 30.4% (Table 2). When

considering children with a $FEV_1/FVC < 90\%$, the reversibility criterion showed a 23.5% sensitivity, being recorded in 205 children only.

Considering this outcome, there was no significant difference between the two centers (31.0% and 30.1% sensitivity in the French and Italian population, respectively). Moreover, the mean change in FEV_1 after bronchodilation was similar in the two centers as well (8.1% with 13.1% of SD, and 8.3% with 8.8% of SD, respectively; *p-value*: 0.7876).

C. Obstruction criterion and small airways criterion

The obstruction criterion proposed by GINA guidelines for children ($FEV_1/FVC < 90\%$) was valid for 595 children at diagnosis, with a sensitivity of 67.5% overall (Table 2). The mean value of the FEV_1/FVC ratio in the entire cohort was 85% (SD 10%).

The increase of more than 30% in FEF_{25-75} after bronchodilation test was only found in 198 children in our cohort (Se 21.9%), with a mean value of 22.1% (SD 30.0%) (Table 2). Furthermore, older children (>11 years group) were also less likely to achieve this reversibility criterion, compared with patients with less than 7 years of age, or between 7 and 11 years (15.1%, 24.9%, and 23.8%, respectively).

D. Best criteria to predict asthma diagnosis

To assess the variables providing the best sensitivity to predict asthma diagnosis, we included in the analysis both the spirometric criteria ($FEV_1/FVC < 90\%$, change in $FEV_1 > 12\%$, change in $FEF_{25-75} > 30\%$), and the clinical ones (dry cough, tight chest, wheezing, pre-school wheezing, exercise-induced dyspnea, atopy, presence of allergic comorbidities). The best single criterion was the presence of "dry cough" (Se 90.9%). Sensitivity of each criterion is shown in Table 3.

The best two combined criteria were "dry cough and atopy" (Se 98.5%), followed by both "dry cough

and wheezing" or "dry cough and allergic comorbidities" (Se of 97.7%).

Furthermore, the best three criteria to predict asthma were "dry cough, wheezing and atopy", and "dry cough, wheezing and exercise-induced dyspnea", with both a sensitivity of 99.5%. The combination of the previously mentioned four criteria (dry cough, wheezing, atopy and exercise-induced dyspnea) was associated to a sensitivity of 100% (Figure 3). In no case, adding spirometric parameters improved the cumulative sensitivity for the diagnosis of asthma. Moreover, when comparing the sensitivity of the different clinical parameters between the subgroup of 383 children with $FEV_1/FVC < 90\%$, but without FEV_1 reversibility and the 205 patients with reversibility criteria, we found no significant difference neither between the groups, nor between each group and the whole cohort of patients (Table 3).

If we consider the follow-up of patients with a diagnosis of asthma, and include the response to the prescribed treatment after the first visit, such criterion was verified in 819 children, and showed therefore the best sensitivity (Se 94.0%), but it cannot be used when first assessing a patient.

E. Subgroup analysis based on asthma severity

The number of included patients significantly differed in each asthma severity subgroup (respectively for severe, moderate, mild persistent and intermittent asthma: 55, 581, 203, 32; all *p-values <0,005*) (Table 4). The small number of patients included in the « intermittent » group could mainly be explained by the fact they are not representative of the average patient consulting at a tertiary University Hospital, and are therefore under-represented, if compared with the general population. Sex and BMI were not statistically different between those four groups (*p-values <0,05*).

The mean improvement in FEV_1 after bronchodilation was higher when the severity was greater: the severe asthma group showed a significantly higher increase in FEV_1 than the moderate asthma group (13.2% (SD 18.2) and 8.9% (SD 10.7), respectively; *p-value*: 0.0084) and the mild group (5.0% (SD 6.9), *p-value* < 0.0001). The same significant difference was also highlighted between the moderate

and the mild group as well (*p-value* < 0.0001). There was no significant difference when we compared the intermittent group with any other severity group. When we assessed patients presenting an increase of at least 12% in their FEV_1, there was a significant difference (*p-value* <0.05) in sensitivity between patients suffering from mild persistent asthma (16.3% of increase in FEV_1, in 33 children) and both moderate persistent asthma (34.3%, n=199, *p-value* < 0.0001) and severe persistent asthma (41.8%, n=23, *p-value* < 0.0001), meaning that, as persistent asthma becomes more severe, the increase in FEV_1 criterion showed a higher sensitivity.

When considering the mean basal obstruction criterion, we found lower values as asthma was more severe. The mean basal FEV_1/FVC was 79.5% (SD 10.5%) in the severe asthma group, 84.1% (SD 9.7%) in the moderate group (*p-value*: 0,0009), and 87.7% (SD 8.5%) in the mild one (*p-value* < 0.0001). When we assessed the FEV_1/FVC < 90% criterion per asthma severity, there was a significant difference (*p-value* <0.005) between each subgroup, showing that when asthma is more severe, patients present increasing obstructive spirometric values (87.5%, 72.1%, 53.2%, in the mild, moderate, and severe persistent asthma subgroups, respectively).

On the other hand, the mean change in FEF_{25-75}, was not statistically different between the four severity groups.

Atopy had a significant impact on asthma severity: we found more atopic patients in the severe group (51 patients, 92.7%), compared with the moderate and mild groups (78.3% (*p-value*: 0.0113) and 73.4% (*p-value*: 0.0023), respectively). Considering specific respiratory allergens and food allergy, there was no significant difference between the groups.

When analyzing the French vs. the Italian cohort separately, we did not find any difference regarding our outcome results (data not shown).

DISCUSSION

Asthma is a common disease in children and it is probably underdiagnosed. International GINA criteria propose that, in pediatric patients with obstructive signs at PFTs, an increase in FEV_1 of 12% after bronchodilation test is suggestive of a proper diagnosis[4,28]. Through the present multicenter study, we wanted to assess the applicability of this criterion and its sensitivity in a real-life setting. No study strongly affirms that the 12% threshold is an adequate cut-off value to diagnose asthma in children. Even in the GINA guidelines, this threshold is not justified by clinical trials, but only based on a specialists' agreement. In our study, this reversibility criterion showed a very low sensitivity (30.4%), as a diagnostic tool for asthma in pediatrics. Thus, such a criterion does not seem to be applicable to children, if compared to adults, as previously highlighted in other studies[32].

In 2016, Hopp et al. proposed a literature review to search for the evidence that the 12% threshold was appropriate to diagnose asthma in children[29]. The authors found that most studies reported that a smaller improvement in FEV_1 should be applicable in children, and then suggested an alternative interpretative strategy, which our results support. Several authors indeed searched for a different cut-off to assess reversibility response in pediatrics. Martinez et al. proposed a 9% threshold in children aged 7-14 years as the best option to define the bronchodilation test as positive[33]. Using such a threshold (data not shown), in our population including 571 children belonging to this age group, we would find a sensitivity of 41.7% (with 238 children with a reversibility of at least 9%). Kang et al. found that an increase of at least 7.5% in FEV_1 was a better option to diagnose asthma in a cohort of Chinese children (Se 50.7%), while the increase of 12% correlated to a 28.7% sensitivity[34], which is even lower than the value found in our study. On the other hand, the cut-off of an increase in FEV_1 of 7.5% proposed by the Authors still shows a low sensitivity, and does not seem appropriate to diagnose asthma in children. Jat et al. affirmed that spirometry is a very useful investigation tool to diagnose asthma in children, if the test is well-performed and patients received adequate training;

nevertheless, they also admitted that the diagnosis should also be based on clinical symptoms and personal history, to be more reliable[24].

As for the obstruction threshold FEV_1/CVF of 90%, proposed by several authors, including Quanjer et al., such value should not be used in children to assess airways obstruction, considering the unsatisfying sensitivity of this criterion in our study[23]. On the other hand, we showed that, as asthma severity increases, patients tend to present lower FEV_1/FVC ratio, therefore more important bronchial obstruction, and greater increases in FEV_1 after bronchodilation test.

Several authors proposed to evaluate the change in FEF_{25-75} after bronchodilation test to diagnose asthma in children, assuming that FEV_1 may be a poor criterion in this age group[26,27,35,36]. These authors claim that FEF_{25-75} could be considered as a more sensitive measure of the small airways obstruction, but, in our study, such criterion showed an even lower sensitivity than FEV_1, to reach a diagnosis.

In a study by Dufetelle et al., the authors proposed two thresholds suggestive of bronchodilator response in asthmatic children[37]. Based on spirometry z-scores, their preliminary results showed that a 0.42 z-score for FEV_1 and a −0.16 z-score for FEV_1/FVC could indicate bronchoreversibility even in children with normal baseline spirometry. In our cohort, when considering patients presenting with these z-score values (n=279), we found a sensitivity of 32.0% (data not shown). Therefore, these thresholds might be useful to suggest a bronchodilator response in asthmatic children, but their usefulness in diagnosing pediatric asthma seems limited.

As for patients presenting with intermittent asthma, our data showed that this group of patients reported results which were not consistent with those from the other groups. These patients are not representative of the typical patient referring to a tertiary University Hospital. Indeed, they are most likely to be seen outside the hospital, by a general practitioner or a pediatrician, since they do not require a specialized expertise. Further studies in this severity group might be of interest.

A quite surprising observation from our study was that the proportion of patients treated with AIT was not significantly different between severity groups (Table 4), while we were expecting the more

severe group to be the one with patients treated the most with AIT, also considering that children with severe asthma were more atopic. Such aspect could be explained by the fact that AIT is usually prescribed in children not only as a treatment for allergies, but also to prevent the development of further allergen sensitizations and to reduce the burden and the possible aggravation of allergic respiratory diseases (allergic rhinitis, allergic rhino-conjunctivitis, and asthma).

In our study, the best criteria for asthma diagnosis was the response to the prescribed treatment (Se 94.0%): therefore, even in those patients for whom the diagnosis is not sure at the first visit, the follow-up allows to strengthen the doctor's hypothesis. Nevertheless, when focusing on the possibility of diagnosing asthma when evaluating a patient for the first time, the best single clinical predicting criterion was dry cough. When adding three clinical criteria together, such as dry cough, wheezing and atopy or dry cough, wheezing and exercise-induced dyspnea, we reached a very satisfying sensitivity (> 99%), while PFTs values were not providing sufficient support to increase the diagnostic sensitivity. These simple clinical features could therefore be easily and practically used in everyday clinical practice to diagnose asthma in children. These findings are strongly supported by other studies that affirm that a combination of different symptoms seems to be more discriminative than just one or two separate symptoms to reach a diagnosis of pediatric asthma[12,34,38]. These criteria are simple to assess during a medical consultation and require no specific tool. Therefore, this attitude could simplify the diagnostic process, while showing at the same time a better sensitivity.

The primary strength of this study was the great number of included patients: we present the largest pediatric cohort focusing on this subject, and including both spirometric and clinical parameters. 871 children were indeed included in our analysis, which also enabled us to perform subgroup analysis, based on asthma severity, with satisfying group sizes. Also, our multi-centric approach, including patients from two centers from different countries, France and Italy, allowed us to gather a cohort with data coming from physicians with different backgrounds, and could bring us to speculate that our results could also be extended and applied to other countries and/or settings.

Our study presents some limitations as well. We present a retrospective cohort study, based on information found in patients' files: for such reason, we had a few missing data for 17 patients, which nevertheless represented less than 2% of our entire cohort. Also, we included asthmatic children only, and a prospective study including any patients consulting for possible asthma could help strengthen our results and provide further insights. Finally, we did not have data assessing F_ENO in our population. However, in a study by Murray et al., the authors showed that F_ENO is the most sensitive objective test to diagnose asthma in children, with a low 44% sensitivity[38]. Nevertheless, we should consider two different aspects: firstly, our data come from real-life settings, and F_ENO measurements are not routinely evaluated by pediatricians, and therefore such data are not systematically included in patients' chart; secondly, this parameter still shows a lower sensitivity if compared with those found by our study.

We believe that our results bring an important contribution to current knowledge on asthma diagnosis in children. The results strongly suggest that spirometric reversibility values, along with other data such as obstruction criterion, even though essentials for the follow-up of pediatric asthmatic patients, have a very unsatisfying sensitivity for the diagnosis of asthma in children.

CONCLUSION

Our data strongly affirm that PFTs, even though essentials for the follow-up of pediatric asthmatic patients, have a low sensitivity for the diagnosis of asthma. Clinical symptoms, on the other hand, show a very high sensitivity. For such reason, any physicians could diagnose asthma in children, without needing to perform PFTs to confirm their diagnosis. Therefore, we would like to stress that general practitioners and pediatricians could diagnose asthma in children, through carefully evaluating the clinical history and the symptoms presented by patients, while asthmatic patients presenting with severe forms or needing a follow-up require a more complete assessment in specialized centers.

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FIGURES

Figure 1 – Patients included in the study.

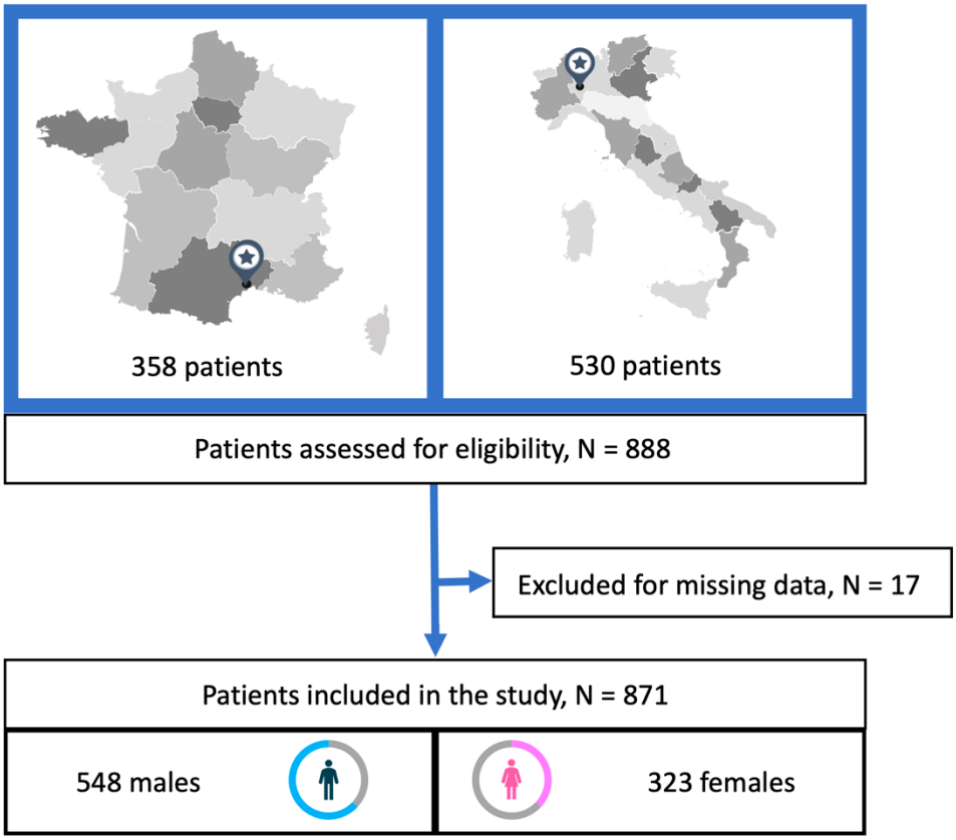
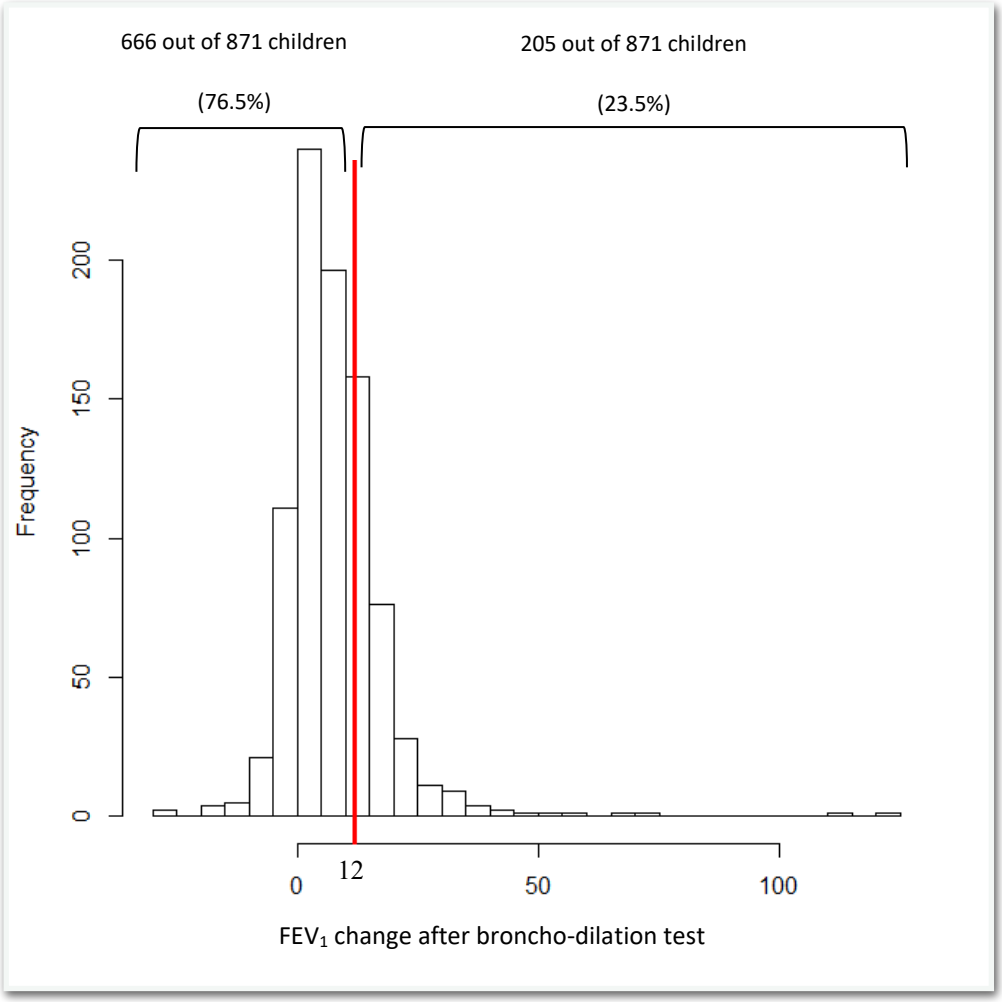
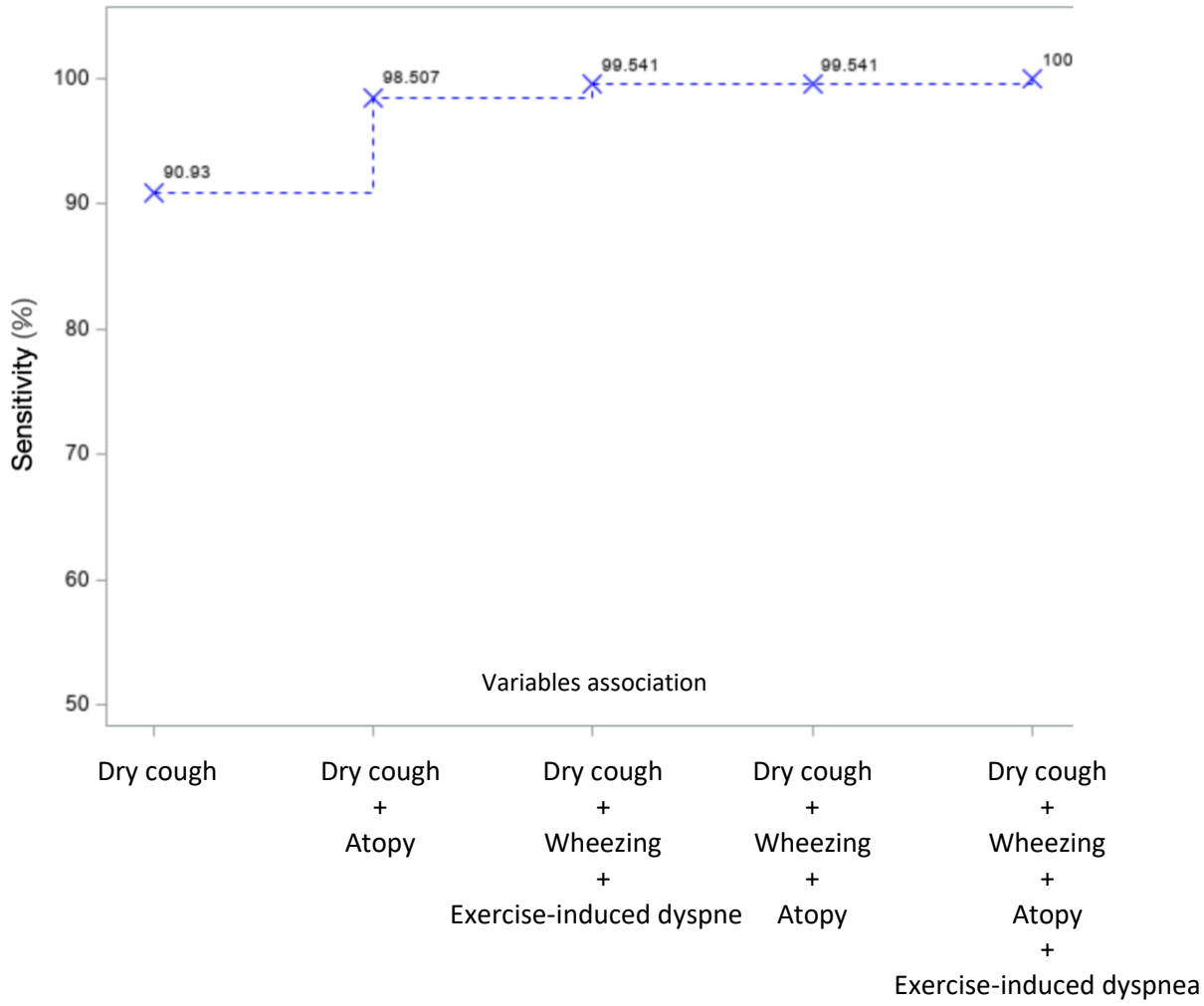


Figure 2 – Reversibility criteria (FEV_1/FCV < 90% and increase in FEV_1 > 12%) after bronchodilation test in all 871 included children.



The line shows the 12% cut-off proposed by GINA guidelines. All children on the left of the line would be considered as non-asthmatics following current recommendations.

Figure 3 – Best option for cumulative sensitivity of different variables to predict a diagnosis of asthma in children.



TABLES

Table 1 – Characteristics of the population included in the study.

	Overall	France	Italy
General information			
Number of patients, n (%)	871 (100%)	342 (39.3)	529 (60.7)
Males, n (%)	548 (62.9%)	219 (64.0)	329 (62.2)
Age, mean (SD)	9.2 (3.3)	9.2 (3.4)	9.3 (3.2)
BMI, mean (SD)	18.1 (3.7)	17.6 (3.3)	18.5 (3.8)
Results of PFTs			
Basal FEV_1, in liters, mean (SD)	1.9 (0.80)	1.8 (0.79)	1.9 (0.81)
Mean Change in FEV_1 after bronchodilation, % (SD)	8.2 (10.7)	8.1 (13.1)	8.3 (8.8)
Mean basal FEV_1/FVC, % (SD)	84.9 (9.7)	86.1 (11.3)	84.0 (8.5)
Mean Change in FEF_{25-75} after bronchodilation, % (SD)	22.1 (30.0)	20.0 (38.9)	23.4 (22.3)
Prescription of biotherapies			
Patients treated with Anti-IgE, n (%)	39 (4.5)	11 (3.2)	28 (5.3)
Patients treated with AIT, n (%)	101 (11.6)	58 (17.0)	43 (8.1)
Clinical symptoms			
Any of the below evocative symptom, n (%)	868 (99.7)	339 (99.1)	528 (100)
Patients presenting with dry cough, n (%)	791 (90.8)	322 (94.1)	469 (88.7)
Patients presenting with wheezing n (%)	553 (63.5)	138 (40.3)	415 (78.5)
Patients presenting with exercise-induced dyspnea, n (%)	410 (47.1)	193 (56.4)	217 (41.0)
Patients presenting with tight chest, n (%)	149 (17.1)	40 (11.7)	109 (20.6)
Patients with a history of pre-school wheezing, n (%)	315 (36.2)	119 (34.8)	196 (37.1)
Patients with symptoms improvement after treatment, n (%)	819 (94.0)	295 (86.3)	524 (99.1)
Atopic comorbidities			
Patients presenting with any atopic comorbidity, n (%)	713 (81.9)	289 (84.5)	424 (80.2)
Patients suffering from Allergic Rhinitis, n (%)	605 (69.5)	210 (61.4)	395 (74.7)
Patients suffering from food allergy, n (%)	108 (12.4)	28 (8.2)	80 (15.1)
Patients suffering from atopic dermatitis, n (%)	193 (22.2)	65 (19.0)	128 (24.2)
Atopic patients, n (%)	678 (77.8)	244 (71.4)	434 (82.0)
Atopic sensitization			
Patients sensitized to house dust mites, n (%)	471 (54.1)	151 (44.2)	320 (60.5)
Patients sensitized to grass, n (%)	407 (46.7)	111 (32.5)	296 (56.0)
Patients sensitized to cypress, n (%)	109 (12.5)	103 (30.1)	6 (1.1)
Patients sensitized to birch, n (%)	135 (15.5)	37 (10.8)	98 (18.5)
Patients sensitized to animal dander, n (%)	314 (36.1)	108 (31.6)	206 (38.9)
Patients sensitized to molds, n (%)	175 (20.1)	54 (15.8)	121 (22.9)

Legend – BMI: Body Mass Index; SD: Standard Deviation; FEV_1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; FEF_{25-75}: mean Forced Expiratory Flow between the 25% and 75% of the FVC; AIT: Allergen Immunotherapy.

Table 2 – Sensitivity of the reversibility criteria in children proposed by GINA guidelines for FEV_1, of bronchial obstruction in children, of the reversibility criteria for FEF_{25-75}, and of the association or either the reversibility of the FEV_1 criterion or the FEF_{25-75}, in the overall population and in the subgroups based on asthma severity and patient's age.

	Overall	Based on severity				Based on patient's age		
		Persistent severe asthma	Persistent moderate asthma	Persistent mild asthma	Intermittent asthma	< 7 years	7-11 years	> 11 years
Number of patients	871	55	581	203	32	221	432	218
Sensitivity of reversibility criteria: increase of FEV_1 > 12% in patients with FEV_1/FVC < 90%	23.5%	38.2%	27.4%	10.8%	9.4%	18.6%	27.5%	20.6%
Sensitivity of reversibility criteria: increase of FEV_1 > 12%	30.4%	41.8%	34.3%	16.3%	31.3%	32.1%	32.4%	24.8%
Sensitivity of obstruction criteria: FEV_1/FVC < 90%	67.5%	87.3%	72.1%	53.2%	43.8%	48.0%	26.5%	76.6%
Sensitivity of reversibility criteria: increase of FEF_{25-75} > 30%	21.9%	25.5%	23.8%	16.7%	15.6%	24.9%	23.8%	15.1%
Sensitivity of reversibility of either FEV_1 or FEF_{25-75}	36.7%	50.9%	40.1%	23.2%	37.5%	43.0%	37.5%	28.9%

Legend: FEV_1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; FEF_{25-75}: mean Forced Expiratory Flow between the 25% and 75% of the FVC.

The *p-value* was statistically significant (<0.05):

- for the reversibility criterion (increase of 12% in FEV_1 in patients with FEV_1/FVC < 90%): between the severe group and the mild and intermittent ones; between the moderate group and the mild and intermittent ones; between the <7 years group and the 7-11 years one;
- for the FEV_1 criterion: between mild asthma and any other severity group;
- for the obstruction criterion: between severe and any other severity group; between moderate and any other severity group; between the <7 years group and any other group;
- for the FEF_{25-75} criterion: between severe and mild; between moderate and mild; between the >11 years group and any other group;
- for either the FEV_1 criterion or the FEF_{25-75} criterion: between severe and mild; between moderate and mild; between the >11 years group and any other group.

Table 3 – Sensitivity of the different clinical criteria in the whole cohort of 871 children, in the subgroup of patients in which normal FEV_1/FVC, in those with $FEV_1/FVC < 90\%$ and an increase in $FEV_1 < 12\%$ after bronchodilation, and in those presenting with reversibility criteria.

	In the whole cohort (N = 871)		Patients with $FEV_1/FVC \geq 90\%$ (N = 283)		Patients with $FEV_1/FVC < 90\%$ and increase in $FEV_1 < 12\%$ after bronchodilation (N = 383)		Patients with $FEV_1/FVC < 90\%$ and increase in $FEV_1 \geq 12\%$ after bronchodilation (N = 205)	
	Number of patients (n)	Sensitivity (%)	Number of patients (n)	Sensitivity (%)	Number of patients (n)	Sensitivity (%)	Number of patients (n)	Sensitivity (%)
Clinical criteria								
Dry cough	792	90.9%	250	88.3%	350	91.4%	192	93.7%
Wheezing	553	63.5%	162	57.2%	251	65.5%	140	68.3%
Exercise-induced dyspnea	410	47.1%	122	43.1%	187	48.8%	102	49.8%
Tight chest	149	17.1%	32	11.3%	73	19.1%	44	21.5%
Pre-school wheezing	315	36.2%	108	38.2%	134	35.0%	73	35.6%
Atopy	678	77.8%	202	71.4%	306	79.9%	170	82.9%
Allergic comorbidities	713	81.9%	219	77.4%	320	83.6%	174	84.9%

We found a significant difference between the whole cohort and the subgroup of patients with normal FEV1/FVC for the tight chest (*p-value* 0.0198) and atopy (*p-value* 0.0264) criteria.

Table 4 – Characteristics of the population, per asthma severity.

Asthma severity	Persistent severe asthma	Persistent moderate asthma	Persistent mild asthma	Intermittent asthma	Statistical difference between groups, *p-value*					
					Between severe and moderate asthma	Between severe and mild asthma	Between severe and intermittent asthma	Between moderate and mild asthma	Between moderate and intermittent asthma	Between mild and intermittent asthma
General information										
Number of patients, n (%)	55 (6.3)	581 (66.7)	203 (23.3)	32 (3.7)	< 0.0001	< 0.0001	0.0014	< 0.0001	< 0.0001	< 0.0001
Males, n (%)	34 (61.8)	375 (64.5)	122 (60.1)	17 (53.1)	0.6867	0.8170	0.4273	0.2577	0.1903	0.4557
Age, mean (SD)	9.6 (3.3)	9.4 (3.2)	8.6 (3.2)	10.3 (3.6)	0.6588	0.0422	0.3588	0.0022	0.1244	0.0065
BMI, mean (SD)	18.6 (3.8)	18.2 (3.7)	17.9 (3.5)	17.3 (2.8)	0.4448	0.1977	0.0955	0.3136	0.1761	0.3566
Results of PFTs										
Mean Change in FEV_1 after bronchodilation, % (SD)	13.2 (18.2)	8.9 (10.7)	5.0 (6.9)	7.2 (8.9)	0.0084	< 0.0001	0.0847	< 0.0001	0.3782	0.1094
Mean basal FEV_1/FVC, n (SD)	79.5 (10.5)	84.1 (9.7)	87.7 (8.5)	89.4 (10.4)	0.0009	< 0.0001	0.0001	< 0.0001	0.0028	0.3095
Mean Change in FEF_{25-75} after bronchodilation, % (SD)	23.9 (23.8)	23.1 (32.5)	19.6 (24.5)	16.2 (21.1)	0.8588	0.2465	0.1334	0.1615	0.2358	0.4585
Prescription of biotherapies										
Patients treated with Anti-IgE, n (%)	37 (67.3)	2 (0.3)	0	0	< 0.0001	N/A	N/A	N/A	N/A	N/A
Patients treated with AIT, n (%)	5 (9.1)	64 (11.0)	28 (13.8)	4 (12.5)	0.6609	0.3544	0.6146	0.2898	0.7946	0.8429
Atopic comorbidities										
Patients presenting with any atopic comorbidity, n (%)	47 (85.5)	493 (84.9)	149 (73.4)	24 (75.0)	0.9053	0.0634	0.2248	0.0003	0.1354	0.8429
Patients suffering from Allergic Rhinitis, n (%)	42 (76.4)	418 (71.9)	128 (63.1)	17 (53.1)	0.4839	0.0648	0.0253	0.0177	0.0224	0.2829
Patients suffering from food allergy, n (%)	6 (10.9)	75 (12.9)	23 (11.3)	4 (12.5)	0.6707	0.9301	0.8225	0.5582	0.9464	0.8470
Patients suffering from atopic dermatitis, n (%)	14 (25.5)	140 (24.1)	34 (16.8)	5 (15.6)	0.8222	0.1411	0.2846	0.0301	0.2723	0.8738
Atopic patients, n (%)	51 (92.7)	455 (78.3)	149 (73.4)	23 (71.9)	0.0113	0.0023	0.0085	0.1518	0.3922	0.8565
Patients sensitized to house dust mites, n (%)	35 (63.6)	318 (54.7)	104 (51.2)	14 (43.8)	0.2041	0.1016	0.0713	0.3890	0.2248	0.4315

Legend: BMI: Body Mass Index; SD: Standard Deviation; FEV_1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; FEF_{25-75}: mean Forced Expiratory Flow between the 25% and 75% of the FVC; N/A: not applicable; AIT: Allergen Immunotherapy

SERMENT

- En présence des Maîtres de cette école, de mes chers condisciples et devant l'effigie d'Hippocrate, je promets et je jure, au nom de l'Etre suprême, d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la médecine.

- Je donnerai mes soins gratuits à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail.

- Admis (e) dans l'intérieur des maisons, mes yeux ne verront pas ce qui s'y passe, ma langue taira les secrets qui me seront confiés, et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.

- Respectueux (se) et reconnaissant (e) envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

- Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.
  Que je sois couvert (e) d'opprobre et méprisé (e) de mes confrères si j'y manque.

RÉSUMÉ

Introduction : L'asthme est la maladie chronique la plus fréquente chez l'enfant et un diagnostic robuste est crucial afin d'optimiser la prise en charge des patients et d'améliorer « le fardeau de la maladie ». Pour poser le diagnostic d'asthme chez l'enfant, les recommandations du GINA proposent une amélioration de 12% du VEMS après le test de broncho-dilatation, mais en pratique clinique, ce critère est rarement présent chez ces patients. L'objectif de cette étude était d'évaluer la sensibilité de ce critère de réversibilité et de trouver des variables capables de montrer une grande sensibilité pour prédire le diagnostic d'asthme.

Méthodes : VERI-VEMS était une étude multicentrique internationale rétrospective incluant tous les enfants consécutifs (de 5 à 18 ans), avec un diagnostic d'asthme posé par un médecin spécialiste de l'asthme. Les résultats des EFR au moment du diagnostic ont été relevés pour chaque patient. Le critère de jugement principal était de vérifier si le critère de réversibilité proposé par le GINA était corrélé chez les enfants avec le diagnostic d'asthme.

Résultats : 871 ont été inclus au total. Le critère de réversibilité de 12% du VEMS montrait une sensibilité de seulement 30,4%. Par ailleurs, en évaluant tous les critères spirométriques et cliniques, les trois meilleurs critères diagnostiques étaient « toux sèche, sifflements et atopie » et « toux sèche, sifflements et dyspnée à l'effort », avec une sensibilité atteignant 99.5%, alors que les paramètres spirométriques ne présentaient pas d'interêt dans le calcul de la sensibilité cumulée pour le diagnostic.

Conclusion : Les EFR ont une sensibilité insuffisante pour le diagnostic de l'asthme chez l'enfant, bien qu'ils soient essentiels pour le suivi. L'association de symptômes cliniques devrait être considérée comme le gold standard pour effectuer ce diagnostic en pédiatrie.

Mots clés : Asthme, Diagnostic d'Asthme, Enfant, Épreuves Fonctionnelles Respiratoires, Symptômes cliniques, GINA