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# Asthma: specific clinical and functional characteristics in childhood. Results of a national program in Romanian asthmatic children

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**Key words**

*Asthma, child, prospective study, severity, control, lung function, Romania*

**Summary**

*Childhood asthma presents with specific clinical and functional characteristics. The aim of our study was the description of a large cohort of asthmatic children. It was also to assess their outcome with maintenance therapy according to guidelines, and to analyze the relationship with baseline's characteristics. We focused particularly on clinical and functional pediatric specificities.* ***Methods:*** *Prospective study driven on asthmatic children, without treatment, recruited during a hospitalization for exacerbation or a visit for uncontrolled asthma, treated according to GINA guidelines and followed for one year.* ***Results:*** *412 children (mean age: 11.6 years +/- 2.7), were included. The level of severity was: intermittent asthma for 30% and persistent asthma for 70% (40.5% mild, 28% moderate, 1.5% severe). Mean preβ2-$FEV_1$ was 88.5% +/- 10.5 (PV) with mean β2-reversibility of 10.8% +/- 7.8 (>12% for 42% patients). 374 patients ended the study. After one year, we observed an improvement of clinical symptoms ($p<0.0001$), rate of hospitalization ($p<0.0001$), and lung function (mean preβ2-$FEV_1$: 91.2% +/- 7.9, $p<0.001$). Asthma control was obtained for only 24.6%. Multivariate analysis show that decrease of symptoms was significantly related to younger age, higher level of initial severity and number of days of hospitalization.* ***Conclusion:*** *This study confirms pediatric specificities of asthma, as a normal $FEV_1$ level and a limited β2-reversibility of $FEV_1$, and the large part of uncontrolled asthma after one year of treatment. It emphasizes the risk of undertreatment in a strategy based on severity. It argues for the regular assessment of control as now recommended, taking into account the pediatric asthma specificities.*

## Introduction

Asthma is a worldwide disease, with a large prevalence, as described by the last report of ISAAC study (1). There are few data on asthmatic children in Eastern Europe countries, especially in Romania (2). Starting from 1997, a National Program of Prevention and Education in the Bronchial Asthma, financed by the Minister of Health, was conducted in the pediatrics department of the Sfanta Maria Hospital in Iasi, Moldavia (Eastern-North of Romania). This program provided medical care, follow-up and free delivery of the treatment to a large population of asthmatic children. It was the opportunity to assess a cohort of asthmatic children, followed prospectively in "real life".

The aim of our study was the description of a large cohort of asthmatic children. It was also to assess their outcome

with maintenance therapy according to guidelines, and to analyze the relationship with baseline's characteristics. We focused particularly on clinical and functional pediatric specificities.

## Methods

All children 7 to 16 years old, with a diagnosis of asthma according to GINA guidelines 1995 (3) referred to the Sfanta Maria Hospital in Iasi between January 1, 1997 and December 31, 2002 were recruited for this study. All patients with another respiratory disease were excluded. General data collected included demographic characteristics (age, sex), past medical history and familial history of atopy and environmental data (current smoking habits, home heating). A detailed anamnesis was done collecting specific asthma information such as age of onset, frequency of daytime and nighttime symptoms, exercise-induced symptoms, and exacerbations (outpatient visits or hospitalizations) during the last 3 months. Severe exacerbation was defined as requirement of systemic corticosteroid therapy and/or oxygen therapy.
Skin prick tests were performed for all patients. *Dermatophagoïdes pteronyssinus, D. farinae*, grass pollen, cat, dog, horse, tree mix, mould mix, and feather were tested. A mean weal diameter of at least 3 mm after 15 min was considered as a positive test. At first visit, patient's serum was analized to determine the total IgE level using the ELISA method. Atopy was defined by at least one positive skin test response or elevated IgE level according to age.

*Lung function measurements*

A baseline spirometry was performed using the SpirolyzerX5 (Medical FIM) according to the American Thoracic Society guidelines (4) during the first medical visit or at the end of hospitalization. Lung function variables ($FEV_1$, FVC, $MEF_{50}$, and $MEF_{25-75}$) were obtained from the flow volume curves. All flow indices reported ($MEF_{50}$, $MEF_{25-75}$) were selected from the best maneuver defined as the curve with the largest sum of $FEV_1$ and FVC. All children were submitted to bronchodilator testing (salbutamol 200 μg) irrespective of their baseline lung function, and spirometric measurements were repeated 15 minutes later. Reversibility was defined by improvement of $FEV_1$ greater than 12%. $FEV_1$, $MEF_{50}$ and $MEF_{25-75}$ values were expressed in percentage of the predicted values (PV) for age, sex and height, using Morris-Polgar predicted values (5).

*Follow-up*

Patients were followed during one year and had medical visits at 3, 6, 9, and 12 months. Each examination included detailed assessment of respiratory symptoms, clinical evaluation and a measurement of lung function (spirometry) at one year. At baseline and during follow-up, the severity of asthma was evaluated at each visits by the same practitioner and classified as intermittent asthma, mild persistent asthma, moderate persistent asthma, severe persistent asthma derived from patient and parents-reported questionnaires and respiratory function parameters, according to GINA guidelines (3). Patients having persistent asthma were all advised to adopt a maintenance therapy according to GINA recommendations (3): inhaled corticosteroids (ICS), alone or in association with long-acting inhaled β2-agonists (LABA), or leukotriene receptor antagonist (LTRA). Adherence to treatment was not evaluated except by asking parents. Maintenance treatment was given free to all patients at each medical visit for the following three months thanks to the National Program of Prevention and Education in the Bronchial Asthma.

*Statistical analysis*

Data were collected in a database and analyzed using a descriptive and inferential statistical method. The software used for statistical analysis was SAS version 9.1 (SAS institute, Inc, Cary, NC). The same analysis model was used for all patients (overall) and separately for age (7-11 years old versus 12-16 years old).
Children who withdrew from the study were included in the analysis until the last contact, without imputation of values for missing data. At baseline, patients lost of follow-up were compared to the others by student test. Regression models were used to assess for differences at baseline and one-year of follow-up for all outcomes. Linear regression was performed to assess the moment (3, 6, 9 or 12 months) of significant variation with regard to baseline. Univariate regression models including each parameter of the baseline and end of study (student test and Wilcoxon test) were first used to narrow the list of covariates to be incorporated into the final multivariate model to determine data related to evolution at one year.
P values of less than 0.05 were considered to indicate statistical significance.

## Results

412 children were enrolled (age: 11.6 years +/-2.7). Patient demographics and characteristics at baseline are shown in Table 1. Thirty-eight patients were lost of follow-up during the study. Patient demographics at baseline were similar in patients who completed study and patients lost of follow-up. Family atopy was recorded in 204 cases (49.5%) and personal atopy in 267 cases (65%). 165 patients (40%) had passive smoking history. At baseline, the great majority of patients (80%) had preβ2-$FEV_1$ greater than 80%, and only 3 patients had $FEV_1$ less than 60%. After β2-agonist, mean $FEV_1$ raised 10.8% +/-7.8 and 176 patients (42%) had improvement greater than 12%. One third of patients had intermittent asthma. Mild and moderate persistent asthma were the most frequent diagnoses (68.5%) independently of age. Severe persistent asthma was infrequent (1.5%).

Maintenance therapy was prescribed after the enrollment. 86% of patients with mild persistent asthma were advised to take low dose of ICS. ICS were prescribed for all patients with moderate or severe persistent asthma, with ICS as monotherapy in 19%, association of two drugs in 61%, and association of three drugs in 20%. 64% of patients with intermittent asthma were also treated by LTRA because of rhinitis.

*Follow-up:* 374 patients completed the study. At one-year of follow-up, daytime and nocturnal asthma symptoms decreased significantly, independently of level of severity. Days of hospitalization decreased also significantly for the global population but not significantly for the intermittent asthma group (Table 2). A significant improvement of symptoms and number of days of hospitalization was observed from the first follow-up visit (at 3 months). This improvement was even greater at the second follow-up visit (at 6 months) and severe exacerbation decreased significantly after the 6$^{th}$ month of the study.

Changes in lung function test are shown in Table 3. At one year follow-up, there was a significant increase in all lung function parameters: $FEV_1$, post β2- $FEV_1$ reversibility, $MEF_{50}$ and $MEF_{25-75}$. According to the level of asthma severity, an increase of preβ2-$FEV_1$ at one-year follow-up was significant for intermittent asthma, moderate and severe persistent asthma, but not for mild persistent asthma in comparison to baseline spirometry (Table 4). Postβ2-$FEV_1$, pre and postβ2-$MEF_{50}$ and $MEF_{25-75}$ increased significantly for all levels of severity.

***Table 1*** - Baseline characteristics of children

| Characteristic | global | 7-11 years old | 12-16 years old |
|---|---|---|---|
| Number | 412 | 179 | 233 |
| Sex ratio (F/M) % | 44/56 | 35/65 | 50/50 |
| Residence Urban/rural | 284 / 128 (69%/31%) | 123 / 56 (69%/31%) | 161 / 72 (69%/31%) |
| Duration of asthma - mean (year +/- SD) | 3.4 ± 2.9 | 2.92 ± 1.94 | 3.97 ± 3.63 |
| Family atopy | 204 (49.5%) | 84 (47%) | 120 (52%) |
| Allergic rhinitis | 239 (58%) | 100 (56%) | 139 (60%) |
| Active smokers or tabacco exposure | 194 (47%) | 71 (40%) | 123 (53%) |
| Heating wood or coal | 120 (29%) | 51 (28.5%) | 69 (30%) |
| Skin Prick Tests, any positive | 239 (59%) | 121 (67%) | 118 (51%) |
| Exercice induced asthma | 158 (38,3%) | 76 (42.5%) | 82 (35.2%) |
| Preβ2-$FEV_1$ (%PV) (mean ± SD) | 88.5 ± 10.5 | 87 ± 10 | 90 ± 10.6 |
| Postβ2-$FEV_1$ (%PV) (mean ± SD) | 97.5 ± 10.4 | 97 ± 10.6 | 99 ± 10 |
| Intermittent asthma | 125 (30%) | 56 (31%) | 69 (30%) |
| Mild persistent asthma | 167 (40.5%) | 68 (38%) | 99 (42.5%) |
| Moderate persistent asthma | 114 (28%) | 53 (30%) | 61 (26%) |
| Severe persistent asthma | 6 (1.5%) | 2 (1.1%) | 4 (1.7%) |

SD: standard deviation - Preβ2-$FEV_1$: $FEV_1$ measurement before β2-mimetics

Postβ2-$FEV_1$: $FEV_1$ after β2-mimetics – PV: predicted values

***Table 2*** - Evolution of asthma symptoms between baseline and one-year follow-up

| Parameters | Intermittent asthma | | | Mild persistent asthma | | | Moderate persistent asthma | | | Severe persistent asthma | | | All patients | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | One year | P | Baseline | One year | P | Baseline | One year | P | Baseline | One year | P | Baseline | One year | P |
| Daytime and nighttime symptoms-mean (days/3 months) | 8 ± 2.5 | 5 ± 3.9 | 0,0001 | 16 ± 5 | 9 ± 3.9 | 0.0001 | 36 ± 9.8 | 10 ± 4.1 | 0.,0001 | 55 ± 13.6 | 20 ± 7 | 0. 0029 | 19,4 ± 13.4 | 8.2 ± 4.7 | 0.0001 |
| hospitalization-mean (days/3 months) | 0 ± 0.4 | 0 ± 0.4 | 0.227 | 1 ± 1.9 | 0 ± 0.5 | 0.0001 | 10 ± 6 | 0 ± 0.5 | 0.0001 | 29 ± 6.3 | 0 ± 0.5 | 0.,0001 | 3.8 ± 6.2 | 0.2 ± 0.5 | 0.0001 |

***Table 3*** - Evolution of lung function test between baseline and one-year of follow-up

| | Baseline (N=412) | One-year (N=374) | P |
|---|---|---|---|
| | Mean +/- SD | Mean +/- SD | |
| Preβ2-$FEV_1$ (%PV) | 88.5 ± 10.5 | 91.2 ± 7.9 | <0.0001 |
| Postβ2-$FEV_1$ (%PV) | 97.5 ± 10.4 | 102.2 ± 9.2 | <0.0001 |
| β2-reversibility (%PV) | 10.8 ± 7.8 | 12.3 ± 6.4 | <0.0025 |
| Preβ2- MEF50 (%PV) | 82.4 ± 10.8 | 86.7 ± 8.9 | <0.0001 |
| Postβ2-MEF 50 (%PV) | 93.4 ± 11.4 | 99.7 ± 8.9 | <0.0001 |
| Preβ2 MEF 25-75 (%PV) | 82.4 ± 10.8 | 86.7 ± 8.9 | <0.0001 |
| Postβ2- MEF 25-75 (%PV) | 93.8 ± 10.4 | 98 ± 7.8 | <0.0001 |

SD: standard deviation - Preβ2-$FEV_1$: $FEV_1$ measurement before beta2-mimetics

Postβ2-$FEV_1$: $FEV_1$ after beta2-mimetics – PV: predicted values

***Table 4*** - Evolution of $FEV_1$% according to level of asthma severity at baseline

| | | | | |
|---|---|---|---|---|
| Intermittent asthma N=118 | Preβ2-$FEV_1$ (mean values ±SD) | Baseline<br>One-year | 99.9 ± 6.6<br>97.5 ± 6.6 | p 0.0004 |
| | Postβ2-$FEV_1$ (mean values ±SD) | Baseline<br>One-year | 109 ± 7.5<br>109 ± 8 | p 0.3084 |
| Mild persistent asthma N=144 | Preβ2-$FEV_1$ (mean values ±SD) | Baseline<br>One-year | 87 ± 4.9<br>89 ± 6.7 | p 0.3084 |
| | Postβ2-$FEV_1$ (mean values ±SD) | Baseline<br>One-year | 96 ± 5.6<br>101 ± 8.8 | p <0.0001 |
| Moderate persistent asthma N=106 | Preβ2-$FEV_1$ (mean values ±SD) | Baseline<br>One-year | 80 ± 6.6<br>88 ± 4.5 | p <0.0001 |
| | Postβ2-$FEV_1$ (mean values ±SD) | Baseline<br>One-year | 90 ± 5.5<br>97 ± 3.7 | p <0.0001 |
| Severe persistent asthma N=6 | Preβ2-$FEV_1$ (mean values ±SD) | Baseline<br>One-year | 59 ± 5.3<br>68.5 ± 3.5 | p 0.0009 |
| | Postβ2-$FEV_1$ (mean values ±SD) | Baseline<br>One-year | 66 ± 4.9<br>82.5 ± 6.6 | p 0.0013 |

All values are expressed in percentage of predicted values.

SD: standard deviation - Preβ2-$FEV_1$: $FEV_1$ measurement before beta2-mimetics - Postβ2-$FEV_1$: $FEV_1$ after beta2-mimetics

The level of asthma severity was reevaluated at one-year follow-up according to residual symptoms, lung function, regardless maintenance therapy. 262 patients (70.5%) had intermittent or mild persistent asthma at baseline versus 301 (80.5%) at the end of study (Table 5). No significant change was found. On residual symptoms and lung function, 24. 6% had the criteria of well controlled asthma.
Finally, we evaluated by a multivariate analysis if some parameters were related to the evolution of the disease between baseline and end of the study. Decrease of daytime and nocturnal symptoms was significantly related to younger age, heating with wood or coal, higher level of asthma severity and number of days of hospitalization at baseline, higher post$\beta$2-$FEV_1$ at baseline, lower pre$\beta$2-$MEF_{25-75}$ but higher post$\beta$2-$MEF_{25-75}$ at baseline. Reduction of hospitalization was significantly related to more frequent exacerbations and asthma symptoms, more asthma severity at baseline, and absence of atopy. Increase of pre$\beta$2-$FEV_1$ was significantly related to more severe asthma at baseline, lower post$\beta$2-$FEV_1$, higher $FEV_1$ $\beta$2-reversibility, pre$\beta$2-$MEF_{50}$ and pre and post$\beta$2-$MEF_{25-75}$ at baseline. Increase of post$\beta$2-$FEV_1$ was significantly related to more severe asthma, lower pre$\beta$2-$FEV_1$ and $FEV_1$ $\beta$2-reversibility at baseline.

*Discussion*

The aim of our study was to describe a population of Romanian asthmatic children, and to evaluate their evolution after one year of treatment, according to GINA guidelines (3). It was the opportunity to focus on some specificities of pediatric asthma, especially functional aspect, the limits of severity concept and classification in children, and the benefits of a strategy focused on the patient with a regular control assessment.
To our knowledge, this is the first large prospective, observational study providing information on Romanian asthmatic children, aged 7 to 16 years. The strength of this study is the observation of a large population (412 patients) in "real life", without asthma-maintenance therapy at enrollment, treated and followed during one year. Few patients were lost of follow-up (9%). We did not have objective evaluation of adherence to maintenance therapy. However, the treatment was freely delivered every three months, financed by the National Program of Prevention and Education in the Bronchial Asthma. Children were enrolled during a hospitalization for an exacerbation or during a medical visit for uncontrolled asthma. Asthma may consequently be more severe than in a general asthmatic population.

*I Initial evaluation*

Clinical characteristics of the patients were conformed to the literature, with a majority of atopic children (65%), male (56%), and a large prevalence of allergic rhinitis (58%) (2, 6). Induced exercise asthma, a main feature of pediatric asthma was also frequent (38%) (7). At enrollment, asthma severity assessment was facilitated by the absence of asthma maintenance therapy. Patients were classified as having persistent asthma in 70%, with a majority of mild persistent asthma (28%). Only 6 patients (1.5%) presented severe persistent asthma. The level of severity was not related to the age groups. As already presumed, the high severity level probably reflects recruitment during a severe exacerbation. Indeed, the AIRE study assessed the level of severity and control in a general asthmatic population in Europe. For children, it showed that 72% were considered to have a mild form of asthma (55.4% of intermittent and 18% of mild persistent) (8).
Our study illustrates the limits and difficulties of using the severity classification. Specific symptoms like exercise induced asthma, frequency and intensity of exacerbations, health care utilization are usual pediatric features, not

***Table 5*** - Evolution of level of asthma severity

| N | Level of severity at one-year follow-up | | | | Total at baseline |
|---|---|---|---|---|---|
| Level of severity at baseline | Intermittent asthma | Mild persistent asthma | Moderate persistent asthma | Severe persistent asthma | |
| Intermittent asthma | 70 | 48 | 0 | 0 | 118 |
| Mild persistent asthma | 22 | 94 | 28 | 0 | 144 |
| Moderate persistent asthma | 0 | 67 | 38 | 1 | 106 |
| Severe persistent asthma | 0 | 0 | 6 | 0 | 6 |
| Total at end of study | 92 | 209 | 72 | 1 | 374 |

clearly included in GINA severity assessment. Furthermore, asthma is a dynamic disease and growth may influence its severity. From pediatric data of the TENOR cohort, Miller et al reported that classification of severity on the basis of current asthma symptoms may not completely reflect the real asthma condition (9). They showed a lack of agreement among asthma severity assessment modalities (GINA, NAEPP, practitioner evaluation, treatment pressure). They emphasized that assessment of severity should also consider patient's medication use and consumption of health care resources for exacerbations (9). In our study, exacerbations were observed in all levels of severity, even in mild asthma, as previously reported (10). Phenotype of patients with asthma prone to exacerbations is now described, corrisponding to the phenotype of severe intermittent asthma in young children (11).

In our study, the mean baseline preβ2-$FEV_1$ value was 88.5% PV. $FEV_1$ values beyond 100% PV were found in 15.3% patients and greater than 80% in 80.3% of all cases. Only 3 patients recorded values of $FEV_1$ lower than 60%. The results showed that the majority of the asthmatic children, even when they are markedly symptomatic, have near normal $FEV_1$ values. The GINA $FEV_1$ values reported to distinguish between mild, moderate, and severe asthma, based on experts' opinions are inadequate for children. Bacharier et al. in a population of 219 patients aged 5 to 19 years (intermittent asthma: 7%; mild moderate and severe persistent asthma: 28%, 22%, and 43%, respectively), followed in subspecialty asthma clinics, showed that only 6.5% of moderate group and 16% of severe group had $FEV_1$ values less than 80% (11). Only 3.5% children had a $FEV_1$ less than 60%. $FEV_1$, usually considered as the gold standard parameter to evaluate bronchial obstruction, is clearly insufficient in pediatric asthma. $FEV_1$/FVC seems to be a better parameter in discriminating severity groups (12). Asthma in children is characterized by a distal bronchial obstruction, evaluated by mid expiratory flows such as $MEF_{50}$ and $MEF_{25-75}$ values. In our patients, the baseline pre $\beta_2$ $MEF_{50}$ and $MEF_{25-75}$ values, lower than 80%, were noted among 43% and 39% of patients respectively. Paull et al. showed on 2728 asthmatic children aged 3 to 18 years old, that $MEF_{25-75}$ is more adapted to evaluate lung function (13). In this study, 24% of children had a normal $FEV_1$ but an abnormal $MEF_{25-75}$ (lower than the fifth percentile). Despite individual variation in the measurement of $MEF_{50}$ and $MEF_{25-75}$, these parameters might be more appropriate to assess and monitor lung function impairment in children with asthma.

Post β2-$FEV_1$ improvement greater than 12% was recorded in only 176 patients (42%). Baatenburg de Jonge et al reported lung function measurements of 301 children (5 to 17 years old) with mild to moderate persistent asthma (14). They confirmed the frequency of distal obstruction, with $MEF_{50}$ values less than 80% PV observed in 42.3% of children with stable asthma and normal $FEV_1$. They also showed that children with uncontrolled asthma, had a better response to β2-mimetic compared with patients with a stable asthma (17.3% versus 5.7% respectively). $FEV_1$ β2-reversibility was present in only 10% of children with stable asthma, compared to 48 % in the uncontrolled asthma group (14). These results are comparables with our results on children with uncontrolled asthma.

Finally, ICS were the main controller therapy. A large proportion of children were treated with two or three long-term medications, probably because of asthma severity according to guidelines, and also a large prescription of LTRA. This prescription is questionable, particularly in children with allergic rhinitis, whose most effective and first line treatment is nasal corticosteroids (15).

*II Follow up*

In our study, maintenance therapy was initiated before the implementation of guidelines based on control evaluation. However, we approached the evaluation of asthma control measuring the severity at one year follow-up based on the residual symptoms and lung function regardless maintenance therapy. We observed that 80.5% were classified as intermittent or mild persistent asthma, versus 70.5% at baseline and this improvement did not reach statistical significance. Furthermore, only 24.6% had the criteria of intermittent asthma, which means controlled asthma. The majority remained uncontrolled, and probably undertreated. However, this result must be analyzed according to the limitations of our study, the absence of asthma control assessment to guide treatment decision as it was conducted, and the limits of the severity concept as discussed above. We did not evaluate properly the adherence to treatment and asthma severity symptom components were derived from patient and parents-reported questionnaires at each visits. The perception of symptoms and disease was probably better at 12 months of follow-up, in comparison to the initial evaluation, which may have been underscored as previously reported (8). Furthermore assessment of severity using point-in-time assessments of lung function, short-acting beta-agonist use, or asthma symptoms might lead to an uncompleted estimation of the disease as shown on placebo groups of clinical trials (16, 17). The clinical course of asthma varies substantially among

individuals and is often quite unpredictable. Stempel and al. noted in an asthmatic population (children and adults) followed for 3 years that the proportion of uncontrolled patients remains constant, but the uncontrolled patients vary over time. In fact, significant fluctuations in asthma symptoms exist; 73% of the patients presented at least three months of uncontrolled asthma during that study even in patients with prior controlled asthma (18). Our data confirm the limits of asthma severity concept in childhood, with the risk of under treatment and the need of a treatment strategy based on regular assessment of asthma control. Recent guidelines emphasize this strategy with a patient-focused approach, and the aim of a tailored asthma management plan appropriate to individualized clinical and functional assessment. Furthermore, a better knowledge of the determinants of uncontrolled asthma may improve the choice of the best intervention and criteria for the evaluation of efficacy. New strategies based on the monitoring of inflammation (exhaled nitric oxide) cannot be routinely recommended for clinical practice at this stage (19). Finally, new treatment options, particularly for difficult to treat asthma are now available. Add on Omalizumab is effective and well tolerated in children with moderate to severe asthma whose symptoms are not controlled under medium to high dose of ICS (20).

The $FEV_1$ and distal airflows values (pre and post β2) improved significantly during the study. Compared to baseline, more patients had a significant $FEV_1$ β2-reversibility at the end of the study. This may be explained by an initial obstructive but not or just partially reversible pattern related to inflammation, improved by ICS. Persistent bronchial hyperresponsiveness may also reflect progression of asthma, independently of anti-inflammatory treatment. This was also observed in the CAMP study, and associated with a progression of the obstruction in a subpopulation of children who had more pronounced disease progression (21).

Finally, concerning the parameters related to the evolution during the study, we observed that the efficiency of ICS was present at all levels of severity. A better improvement was indeed observed in patients with more severe asthma at enrolment, as shown by a greater reduction of hospitalizations rate and increase of $FEV_1$. Furthermore the functional improvement ($FEV_1$) was more pronounced in patients with higher initial obstruction and $FEV_1$ β2-reversibility. That may evoke a better response to the treatment by ICS and so, a non fixed bronchial obstruction. It was also more pronounced in the youngest patients that may suggest a better prognosis of asthma which begins early in childhood as previously reported (22).

## Conclusion

In conclusion, this study was not a clinical trial but an observational study of a large Romanian pediatric population in "real life", without maintenance treatment at inclusion. Childhood asthma is a variable disease, with specific characteristics. Our work emphasizes the limits of the concept of asthma severity in daily practice, and the need of a patient focused approach. Regular assessment of asthma control and a tailored management plan appropriate to this individualized evaluation is now recommended by the guidelines (23).

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