

R E V I E W

Intermittent and mild persistent asthma: how therapy has changed

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Abstract. In the last few years much attention has been focused on research on severe asthma and the role of biologicals in its treatment, also in children. However, mild asthma is way more common in childhood and still causes as many as 30-40% of asthma exacerbations requiring emergency consultation. The management of “intermittent” and “mild persistent” asthma phenotypes is still a matter of debate, even if the role of inhaled corticosteroids, both continuous and intermittent, is a cornerstone in this field. Nevertheless, updates on the strategies to manage these patients are coming, since evidence emerged on the role of inflammation also in these asthma phenotypes as well as on the potential side effect and risks of short-acting beta 2 agonists overuse, which is common in patients for which they have been prescribed as the only as-needed treatment. Unsurprisingly, international guidelines, including GINA, are starting to recommend associating a corticosteroid when using a reliever. In this paper we overview the (r)evolution regarding the management of intermittent and mild persistent asthma. We also focus on the importance of knowing the chemical and physical characteristics of drugs and inhaler devices in order to optimize the treatment and reach the distal airways, as well as of trying to achieve a good compliance to treatments, especially in adolescents, for which it is currently possible to rely also on new digital health technologies. (www.actabiomedica.it)

Key words: Allergy, asthma control, asthma exacerbations, asthma severity, children, inhaled corticosteroids, GINA, pediatric asthma, type 2 inflammation

Introduction

The advent of specific and effective biological drugs prompted research to focus on severe asthma, which is a rare condition in childhood. Intermittent and mild persistent asthma are way more common in children and are characterized by asthma control with-

out the need for high doses of inhaled corticosteroids (ICS) in combination with long-acting β_2 -agonists (LABA) or other treatments included in steps 4 and 5 of Global Initiative for Asthma (GINA) guidelines.

It should be noted that severe exacerbations in mild asthma represent as many as 30-40% of asthma exacerbations requiring emergency consultation (1), so

that paediatricians and specialists taking care of these patients need to be updated on current evidence regarding new therapeutic approaches.

The management of “intermittent” and “mild persistent” asthma phenotypes remains debated: the old question about the need for continuous treatment with a low dose of ICS in children with episodic exacerbations still lacks definitive answers. For these children all international guidelines, until some years ago, recommended the use of as needed short-acting β_2 -agonists (SABA). However, SABA are associated, in the long term, with a significant number of adverse events due to β -receptor downregulation, decreased bronchodilation, rebound hyperresponsiveness and decreased bronchodilator response (2). SABA overuse is associated with an increased risk of hospitalization and adverse clinical outcomes (3). Moreover, even if SABA use provides quick relief from asthma symptoms, it doesn't exert anti-inflammatory effects and therefore does not reduce airway inflammation causing and maintaining bronchoconstriction. Therefore, it is not surprising that since the 2019 update of GINA guidelines treatment with only as-needed SABA in step 1 is no longer recommended, while associating a ICS to SABA is now recommended (or budesonide/formoterol as a rescue medication in adults and adolescents). The possibility of maintenance therapy with low-dose ICS as an alternative to SABA alone in step 1 had already been included in the guidelines for some years now. Continuous ICS therapy may also be considered during periods of respiratory viral pandemic “at-risk” for exacerbations (for example, in fall or winter), or of high exposure to aeroallergens. Leukotriene receptor antagonists (LTRA) are, on the other hand, an available effective pharmacological treatment in preschool children or children with concomitant allergic rhinitis. In children with episodic asthma, triggered exclusively by viral infections, intermittent administration of ICS has proved less effective than the daily one, but comparable to the continuous use of LTRA in terms of symptoms improvement and reduction of exacerbations, even if recent data and warnings suggest more cautions in long term use of LTRA due to possible neuro-psychiatric adverse effects.

The regular treatment with ICS requires a careful risk/benefit evaluation, particularly in children with infrequent symptoms, considering the long-term ef-

fects of these drugs on the growth curve and the hypothalamic-pituitary-adrenal axis. However, the safety of intermittent or continuous low-dose treatments is well defined, while a lower potency inhaled steroid should be preferred when higher doses are required. In children with mild persistent asthma, regular therapy with ICS is crucial for their anti-inflammatory properties, and the available data demonstrates a greater efficacy of ICS compared to oral administration of LTRA in terms of efficacy in preventing symptoms and exacerbations as well as in improving the quality of life. Low-dose ICS is the first choice in school-age children with reduced respiratory function, positive type 2 inflammation markers (e.g., IgE, FeNO, eosinophilia), and a better response to ICS administered daily has been demonstrated in children with allergic sensitization and peripheral eosinophil counts $> 300 \mu\text{L}$.

In the TREXA study Martinez et al. demonstrated that in children with mild persistent asthma, the most effective therapy to prevent exacerbations is regular, low dose ICS. However, ICS as a rescue medication along with SABA could be an effective strategy for the prevention of exacerbations in children with well-controlled mild asthma. This regimen allows children to avoid daily ICS and relative side effects but could be considered only in mild asthma and in stepping down approach (4). In subjects in which low doses of ICS are not effective in keeping asthma under control, a “step-up” therapy must be considered: a medium ICS dose or adding a LABA to a low dose of ICS or adding an LTRA, as an alternative option. In particular, fluticasone/salmeterol combination was demonstrated to be the most effective approach (in children six years or older). In adults and adolescents another possibility of “stepping up”, is the so-called SMART strategy (Single Maintenance And Reliever Therapy), which includes a very low dose of ICS/Formoterol combination, as maintenance, but also as a “reliever” therapy, instead of SABA, or the addition of a long-acting antimuscarinic (LAMA), such as Tiotropium.

However, some recent studies demonstrate that, despite significant updates in GINA recommendations, asthma is still frequently not well controlled, and approximately 50% of children and adolescents have a non-controlled or partially controlled asthma (5-6). Uncontrolled asthma is common also in adults

and correlates with poor asthma-related quality of life, a higher risk of exacerbations, and a significant consumption of healthcare resources (7).

How much frequent is mild asthma?

Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation and defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough, which vary in time and intensity, together with variable expiratory airflow limitation (8). Asthma affects 5-16% of people worldwide (9) and about 30 million children and adults under 45 years of age in Europe, with a percentage ranging from 3% to more than 9% in northern and western countries (10). In Italy, asthma rate is about 8% among general population, 8.9% among young adults, 9.5% among children and 10.4% among adolescents (11).

Most guidelines propose a stepwise approach to treat asthma, reflecting an increasing intensity of treatments required to achieve and maintain asthma control. For this purpose, asthma is usually classified on the basis of its severity, even though different methods are recommended by different guidelines to evaluate asthma severity. According to GINA asthma severity should be considered retrospectively from the level of the treatment required to control symptoms and exacerbations. GINA does not distinguish between “intermittent” and “mild persistent asthma”, considering that this distinction was based on an untested assumption that patients with symptoms twice a month or less would not benefit from ICS. GINA stepwise approach has been recently significantly updated and will be discussed in the next part of this paper (8); briefly, frequency of symptoms has been better clarified and stressed to define GINA steps and related treatment: in patients aged ≥ 6 years, GINA step 1 currently includes patients with symptoms less than twice a month, while patients with symptoms twice a month or more, but less than daily, should be included in step 2. As a whole, mild asthma is the most common phenotype of asthma, representing up to 75% of all patients with asthma, with a worldwide prevalence estimated at 3.3% (1). Although several studies have estimated asthma

spread in the general population, only few studies have been focused on the diffusion of asthma in relation to its severity and/or on mild asthma. Among those studies, that by Rabe et al. included 10,939 asthmatic patients in the Asthma Insights and Reality (AIR) surveys, conducted in 29 countries: the percentage of intermittent asthma was 22-54% and that of mild persistent asthma was 12-20%; furthermore, the authors showed that the distribution of asthma symptoms severity varied by region, with Central and Eastern European countries reporting more severe asthma symptoms compared to Japanese and Asian Pacific asthmatic patients. In this study the classification of asthma severity was made according to GINA guidelines (12). Zureik et al. have evaluated 1132 asthmatic patients in an international study in which asthma was classified as mild, moderate or severe according to forced expiratory volume in one second (FEV₁), number of asthma attacks in the past 12 months, number of hospital admissions for asthma in the past 12 months and use of reliever inhalers. Of the 1132 asthmatic patients, 50% had mild asthma, 29% had moderate asthma and 21% had severe asthma. The proportion of mild asthma varied according to geographical area, ranging from 63% in Europe to 42% in Australia and New Zealand (13). In an epidemiological study, Firoozi et al. used a database index of asthma severity and control, derived from definitions included in the Canadian Asthma Consensus Guidelines, in a cohort of 139,283 patients with asthma: the distribution of severity levels was 63% for mild, 23% for moderate and 14% for severe asthma (14). Moreover, the CREDES study determined a percentage of 49% for intermittent asthma and 29% for mild asthma with a different severity distribution according to age: 69% and 15% of children under 5 years had intermittent or mild persistent asthma, while 24% and 38% of subjects over 70 had intermittent or mild asthma respectively (15). Lastly, Liard et al. classified 4362 asthmatic patients with a combination of two independent GINA classification: the first one based on symptoms and FEV₁ (Intermittent – step 1: asthma symptoms < 1/week; night-time asthma < 2/month; FEV₁ >80%; Mild persistent – step 2: asthma symptoms > 1/week but <1/day, night-time asthma > 2/month but <1/week, FEV₁ >80%) and the second one based on current medication (Intermittent – step 1: no controller

medication; Mild persistent – step 2: daily low dose ICS <800 µg/day). The authors showed that between the 953 patients classified as Step 1 in the symptom-FEV1 classification, only 60.3% were in step 1 of the final classification, while 30.3% of the 1.368 patients classified as step 2 in the symptom-FEV1 classification were assigned to categories of higher severity in the final classification, showing how, adding treatments to a symptoms-FEV1 classification, can change asthma severity classification (16).

The (r)evolution of the treatment of intermittent / mild asthma

Asthma severity is assessed retrospectively from the level of treatment required to control symptoms and exacerbation. Therefore, this parameter is not a static feature but may change over time, and can be assessed when the patient has been on controller treatment for several months allowing to distinguish mild, moderate and severe asthma. The asthma severity model was the foundation for the stepwise approach to asthma management, which goal is to achieve good symptom control and to minimize future risk of asthma-related mortality, exacerbation, persistent airflow limitation and side-effects of treatment. In order to achieve these goals, appropriate pharmacological treatment should be accompanied by optimal non-pharmacological strategies which include education of patients for self-management and correct use of devices, environmental control for airway irritants and specific allergens and identification and treatment of comorbidities (17).

Recently, new evidence has emerged in the pharmacological treatment of asthma but mostly on severe asthma, and especially in adult patients, while the evidence for the long-term management of intermittent and mild persistent asthma is still limited. However, it should be emphasized that severe asthma is quite rare in children and probably accounts for no more than 5% of global cases observed in paediatric population while most of children aged 6 to 12 years have mild asthma, (19-20). Based on validated epidemiological studies, the “intermittent” and “mild persistent” asthma phenotypes represent the great majority in the paediatric age group (21). Nevertheless, it was estimated that

the frequency of severe exacerbations in mild asthma ranged between 0.12 to 0.77 per patient/year and that between 30-40% of exacerbations in this group of patients required emergency care (1). The low frequency and/or non-bothersome nature of symptoms in mild asthma are associated with an unsatisfactory patient’s adherence towards their controller medications, especially to ICS, and may contribute to SABA overuse. The over-reliance on SABA is also facilitated by the perception of a quick-relief when these drugs are used (22-25).

Even if it is well known that asthma is characterized by chronic airway inflammation, for many years, only symptomatic treatment has been recommended in intermittent and mild asthma. Specifically, different guidelines suggested a SABA in step 1 treatment, despite the lack of anti-inflammatory pharmacological properties (26). In fact, inflammation was initially considered to occur in only moderate or severe asthma while intermittent and mild asthma were considered as diseases characterized only by bronchoconstriction, although first in 1988 and then in 1990 some authors demonstrated the occurrence of marked inflammation in bronchoalveolar lavage in a group of symptomatic and asymptomatic mild asthmatic patients (27-28). Notably, despite this evidence, SABA monotherapy played a strong role as first-line rescue medication from GINA first publication in 1995 until 2019. The only changes in the first step of treatment over the years concerned the recommended maximum number of SABA inhalations.

The risks of SABA overuse were the focus of extensive research in the 1980s and 1990s which showed an increased risk of death (29-30). Concurrently, randomised controlled trials found no advantage in regular versus as-needed SABA (31-32) so that, by the late 1990s, most guidelines recommended as-needed rather than regular SABA. In parallel, many authors highlighted the protective role of regular use of ICS which resulted associated with a dramatic reduction in the risk of asthma-related hospitalisations and death (33-34).

Multiple studies demonstrated a significant number of adverse effects in association with SABA use. Some effects, such as tachycardia, tremor and headache are due to lack of selectivity with their receptors,

while a mechanism of beta2 adrenoceptors desensitization results in loss of the bronchoprotective effect or exacerbation of airway inflammation (35). More severe side effects include sudden constriction of the bronchial airways, or paradoxical bronchospasm, hypokalemia, myocardial infarction (36). In addition, poor asthma control has strongly been associated with infrequent controller medication use and concomitant SABA overuse (26).

In 2006, the GINA update highlighted the importance of controller medications, such as ICS, supporting a stepwise therapeutic approach based on progressive increases in the dose and the number of controller medications in order to minimise the need for rescue medication, especially salbutamol. In those years, only isolated studies such as BEST suggested that ICS could also be used as a rescue medication when associated with SABA (37).

In the same year the SMART study (Salmeterol Multicenter Asthma Research Trial) included salmeterol, a LABA, as an add-therapy to previous asthma treatments, showing an increase in mortality and life-threatening events associated with asthma in the group of patients using this drug. Although the cause of these deaths was likely related to inadequate anti-inflammatory treatment in these patients (38), these results had been connected to the negative experiences with SABA.

However, for many years SABA-only treatment remained unchallenged as the initial therapy for mild asthma while ICS use was recommended only for patients with recurrent symptoms.

SABA are crucial in acute asthma management allowing an immediate relief of symptoms associated with bronchoconstriction. Recent evidence clarified that the association between SABAs and adverse events, such as increased risk of asthma exacerbations, hospital admissions and asthma-related deaths, is not necessarily due to the direct actions of the drugs, but to the fact that these drugs may be used preferentially by patients instead of regular ICS or ICS + LABAs and may mask worsening asthma symptoms (39).

The need for more studies was supported by the findings of the UK National Review of Asthma Deaths in 2014, showing that 9% of asthma deaths were in patients being treated with SABA alone and 39% were

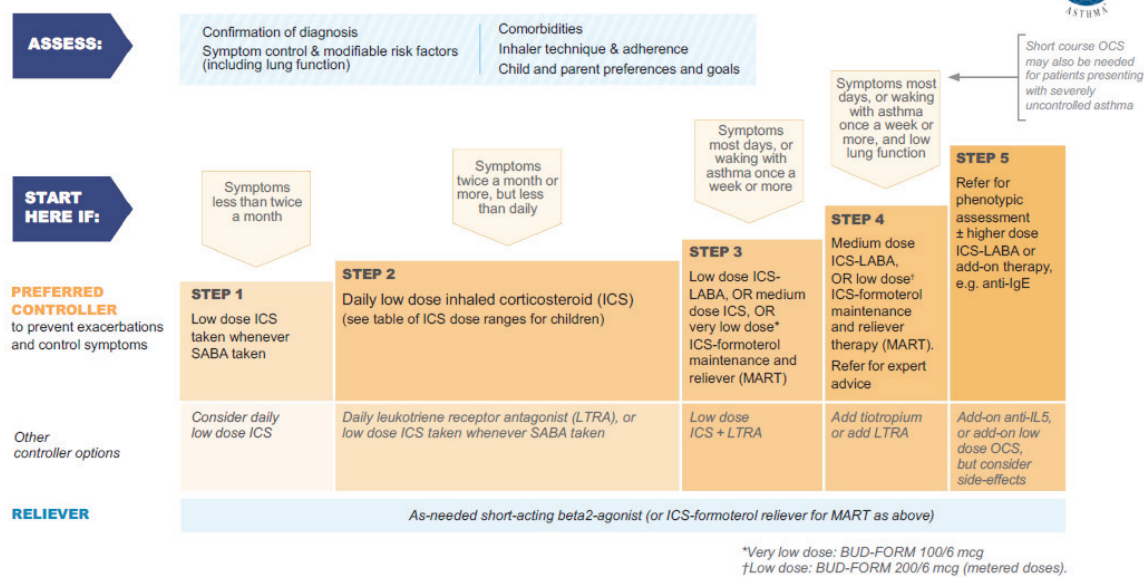
associated with excess prescriptions for SABA (40). Unsurprisingly, in 2014 GINA recommended that SABA-only treatment should be restricted to patients with symptoms twice a month or less and with no risk factors for exacerbations. However, in April 2019, the Global Initiative for Asthma published new recommendations, prompted by concerns about the risks of the long-standing approach of commencing asthma treatment with SABA alone. According to GINA experts, the update to treatment recommendations for mild asthma published in 2019 might be considered the most fundamental change in asthma management in the last 30 years: as a matter of fact, the GINA 2019 strategy report no longer supports SABA-only therapy at Step 1 treatment level but comprises as-needed low dose ICS-formoterol. However, these recommendations were off-label in children in most countries and were made on the basis of the safety concerns about SABA-only treatment, taking into account the fact that ICS and ICS-LABA already had an extensive safety record. Such evolution in GINA strategy was prompted by evidence generated in several trials such as SYGMA (Symbicort Given As Needed in Mild Asthma) 1 and 2 favouring the use of such combination as rescue medication (41) and showing the non-inferiority of the as-needed budesonide-formoterol combination compared to the maintenance ICS plus as-needed SABA regimen in reducing the annual severe exacerbation rate in patients with mild asthma (22).

The rationale behind the SYGMA strategy is based on a pathophysiological explanation. In fact, it was found that LABA may affect glucocorticoid receptor nuclear localisation and may prime the functions of these receptors within the nucleus and, in turn, glucocorticoids may regulate β_2 -agonist receptor function by increasing their expression and inhibiting their down-regulation, thereby preventing desensitisation (42).

The results of the recent Symbicort Turbohaler Asthma Reliever Therapy (START) and Personalised Asthma Combination Therapy with an Inhaled Corticosteroid And fast-onset Long-acting beta agonist (PRACTICAL) trials support these findings and are against the recommendation of SABA monotherapy (43-44).

STARTING TREATMENT

Children 6–11 years with a diagnosis of asthma



GINA 2021, Box 3-4Di

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Figure 1. The recently updated GINA personalized stepwise asthma management in children aged 6 - 11 years (8).

Taking a cue from these, GINA 2020 further advises against the use of SABA monotherapy in step 1 and recommends low dose ICS whenever SABA is taken or low daily dose ICS in children aged 6-11 years and as-needed low dose ICS-formoterol combination as the preferred therapy, with low dose ICS whenever SABA is taken as the alternative in adolescents and adults. In the 2021 update, GINA highlights that ICS administration whenever SABA is taken is preferred over daily ICS in children ages 6-11 years with symptoms less than twice/month, as poor adherence is highly likely in this group of patients (Figure 1). Furthermore, the authors propose a two 'tracks' approach based on evidence about outcomes with the two controller and reliever choices across asthma severity in the group of adolescents and adults (Figure 2). In particular, track 1 combines steps 1 and 2 suggesting as-needed low dose ICS-formoterol as the preferred controller therapy, while track 2 suggests the administration of ICS whenever SABA taken as the alternative in step 1. In the same group, the latest guidelines described low dose ICS-formoterol as preferred reliever approach while SABA as the reliever as an alternative choice. Track 2 is an alternative whenever track 1 option is not possible, or is not preferred by a patient with no exacerbations on their current control-

ler therapy. Before considering a regimen with SABA reliever, it is important to verify whether the patient is likely to be adherent with daily controller (8).

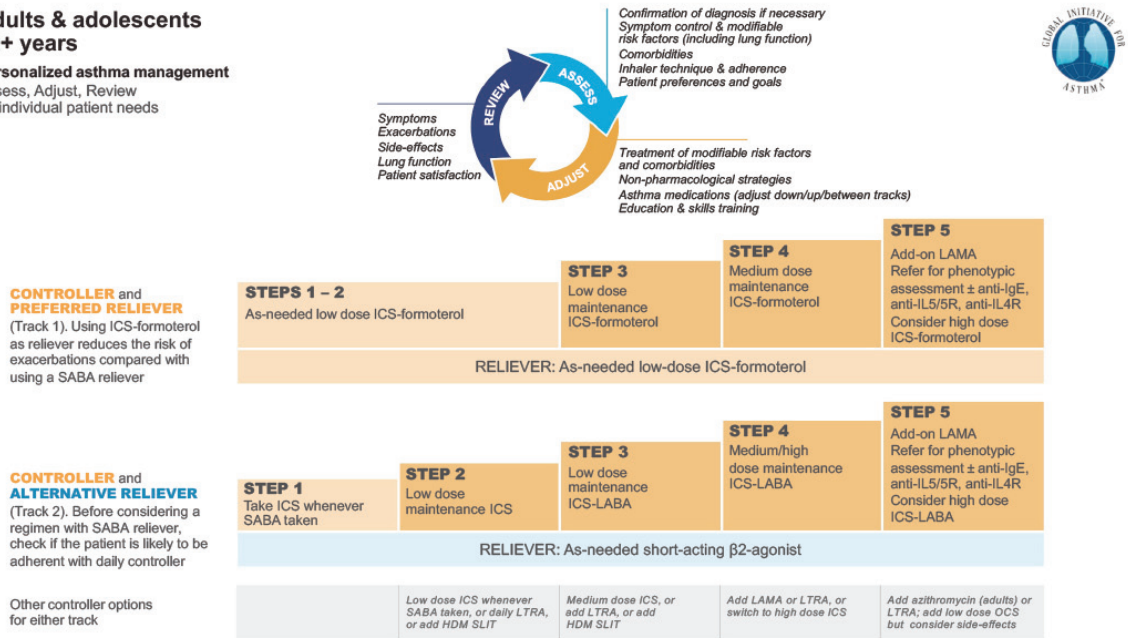
Future perspectives

Asthma is a highly heterogeneous disease, to the point that a recent Lancet Asthma Commission proposed to consider the term "asthma" as no more than an umbrella term, covering many different clinical phenotypes, in similar way as anemia and arthritis are generic terms including different diseases (45,46). Therefore, asthma should be considered as a syndrome comprising multiple clinical phenotypes with different pathophysiological mechanisms (the so-called asthma "endotypes") (47), so that the idea that "one size does not fit all" is particularly proper in asthma treatment, including mild asthma. It is well known that childhood onset-asthma, as opposed to adult onset-asthma, mostly belongs to the allergic phenotype, characterized by a personal and/or family history of atopy and presence of Type 2 inflammation markers such as elevated total and specific immunoglobulin E to various aeroallergens, airway eosinophilia and increased levels of FeNO (48). Such evi-

Adults & adolescents 12+ years

Personalized asthma management

Assess, Adjust, Review
for individual patient needs



GINA 2021, Box 3-5A

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Figure 2. The recently updated GINA personalized stepwise asthma management in adults and adolescents (8).

dence is particularly useful in the management of severe asthma, for which three biologicals agents are currently available for pediatric use: omalizumab, an anti-IgE, and mepolizumab, an anti-IL-5, are approved in children age ≥ 6 years, while dupilumab, an anti-IL4/IL13, is approved starting from 12 years of age (49). In the last 10 years research has been focused on this particular phenotype, occurring in 5% of pediatric asthma, due to its burdensome morbidity and mortality. Regarding the much more common phenotype of mild asthma, research is currently focused on identifying which phenotype will benefit most from daily or as-needed treatment and which drug will work better, as recently underlined also in the 2021 update of GINA guidelines (8): detailed data on the endotypes and related specific treatment is limited in mild asthma, even if a huge amount of evidence supports the effective use of ICS in children with Type 2 inflammation markers (50). Predictors of exacerbations and persistent airflow limitation are still partially known in these children (51), but it should be remembered that “mild” asthma is not always a “mild” diseases, but a condition potentially leading to severe exacerbation (1). It is worth noting the recent introduction of a specific score to identify children at risk for an exacerbation during the autumn season, the Seasonal

Asthma Exacerbation Predictivity Index (saEPI). saEPI includes the evaluation of age, total IgE level, number of allergen skin tests and blood eosinophils at baseline and that of exacerbations, treatment step for ICS, FEV1/FVC and FeNO during the previous season (52-53).

As far as the available inhaled treatments, it should be noted that asthma is a chronic inflammatory disease affecting both the proximal airways and the peripheral airways (54): consequently, in the choice of treatment, it is essential to know the size of the particles delivered by the different available devices, in order to reach the distal smaller airways, with internal diameter less than 2 mm, representing the eighth airway generation and beyond (55). To properly treat asthma as well as reduce oropharyngeal deposition, clinicians should prefer aerosols with mass median aerodynamic diameter (MMAD) $\geq 1 \mu\text{m}$ but less than $5 \mu\text{m}$ (56-57). The most used inhalers in children are pressurized metered dose inhalers (pMDI) delivering “fine” particles (MMAD ≥ 2 microns and < 5 microns) (58). However, pMDI delivering “extra-fine” particles (with MMAD 1-2 μm), have lower oropharyngeal deposition and more significant lung deposition: such devices have been developed and are licensed for use internationally, but with variable approval for pediatric use (as an example,

they cannot be prescribed in children in Italy) (59). Some clinical trials and real-life studies using ICS or ICS/LABA in asthmatic patients comparing fine and extrafine aerosols suggest that smaller particles have similar or higher efficacy compared to larger particles and that they achieve a reduction in the daily ICS dose and a greater asthma control and quality of life (60). Moreover, in adults, a step up with an extra-fine ICS rather than a standard-sized particles drug seems to be an effective strategy, with similar results to adding a LABA. Nevertheless, it should be noted that some systematic reviews and meta-analyses of randomized controlled trials comparing fine and extra-fine particles ICS have led to conflicting results, and studies in children and potential side effects in this age group due to ICS systemic bioavailability are lacking.

As far as the use of spacers and the practice of shaking the inhaler, they should be always advised in children, respectively to increase lung deposition of the inhaled drug and to correctly distribute the suspension in the propellant (61). Shaking will not be needed when using inhalers produced with Modulite[®] technology which contain a solution rather than a suspension (62). Soft mist inhalers based on the RespiMat[®] technology, delivering a slow-moving fine mist, are available for tiotropium administration and are promising tools with even higher lung deposition, but are still off-label in childhood (63).

Last but not least, a pivotal point in asthma treatment is obtaining a good compliance to treatments, especially to controllers. Unsurprisingly, compliance is worse in adolescents and in mild asthma than in moderate or severe asthma (64). Non-compliance is associated with poor symptom control and reduced quality of life but is quite common in pediatric patients, even though healthcare providers offer continuous education, information and interventions to them and their caregivers. In such context, digital health technologies have a great potential to improve asthma management (65): many different digital health interventions are available for pediatric asthma, ranging from electronic drug use and clinical manifestations monitoring with the ability to set daily acoustic reminders to educational materials such as video or interactive games on inhaler technique (66). However, few studies have evaluated their efficacy. Smart inhalers are also available. Many

different mobile apps are also freely available for smartphones, including those providing data on weather, air pollution and pollen concentration, but there is no standard measure to assess their technical and scientific quality nor data sharing security. Scientific societies are starting to face these issues as well as the related opportunities and hopefully in the near future clinicians and patients will have indications on what digital strategy and how should it be used (67).

Conclusion

The treatment of mild or moderate intermittent and persistent asthma remains an important challenge in clinical practice complicated by poor compliance with long-term therapies.

As emerges from the literature data, available therapies are numerous, and low doses of ICS allow to keep most asthmatic children in a condition of good control, particularly those with type 2 inflammation phenotype (atopy, eosinophilia, increased FeNO). Guidelines suggest different approach at asthma management and changes from the past are numerous and significant, but probably this evolution or re-evolution requires time to be well-known and applied. In the future, new clinical, genetic, and laboratory and clinical bio-markers will further help define the best strategy for the initial treatment of asthma and the better “stepping up” in patients with non-severe asthma.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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