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Controversies in the treatment of mild asthma. What novelties and practical implications?

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Abstract

Mild asthma is prevalent in childhood and causes as many as 30%–40% asthma exacerbations requiring emergency visits. 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. Recent updates of the guidelines on the strategies to manage these patients are coming, since the role of inflammation in these asthma phenotypes is crucial, as well as the potential side effect and risks of short-acting beta 2 agonists overuse, prescribed as the only "as-needed" treatments. In this paper, we overview the new (r)evolution regarding intermittent and mild persistent asthma management.

KEYWORDS
asthma control, asthma severity, children, GINA, inhaled corticosteroids

1 | INTRODUCTION

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.[1]

Intermittent asthma and mild persistent asthma are the most frequent forms of the disease in children and adolescents, so that pediatricians need to be updated on current evidence regarding some new therapeutic approaches. The management of "intermittent" and "mild persistent" asthma remains still debated: in particular, the need for maintenance with low-dose ICS in children with episodic exacerbations.[2] For many years, all international guidelines recommended using short-acting β2-agonists (SABA) during exacerbations, prescribed as the only as-needed treatment. However, SABA overuse is associated with an increased risk of hospitalization and adverse clinical outcomes, and even if SABA treatment provides quick relief from asthma symptoms, it does not reduce airway inflammation.[3]

Therefore, SABA as the only rescue medication in step 1 has been no longer recommended in GINA 2019 update. Low-dose inhaled corticosteroids (ICS) treatment combined with SABA or budesonide/formoterol as rescue medication is recommended in adults and adolescents. A regular ICS treatment significantly reduces the risk of exacerbations, also as “a rescue medication” (along with SABA) in children with well-controlled mild asthma. Continuous ICS treatment requires a careful risk/benefit evaluation, particularly in children with infrequent symptoms, but efficacy and safety of a low-dose ICS are well demonstrated in children or adolescents with symptoms twice a month or more like maintenance, even if some authors believe that a "symptom-driven" approach in asthma therapy could be easier to apply.

In subjects in which low doses of ICS are not effective in maintaining asthma control, a "step-up" therapy must be considered. A medium ICS dose or adding a long-acting β2-agonist (LABA) to a low dose of ICS (or a leukotriene receptor antagonist—LTRA) represents an alternative option. In particular, the fluticasone/salmeterol association is the most effective combination in children ≥ 6 years. The so-called SMART strategy (single maintenance and reliever therapy), which includes a very low dose of ICS/formoterol as a reliever and maintenance, is also suggested in adolescents or adults.[1] However, some recent studies demonstrate that asthma is still not well or only partially controlled in approximately 50% of children and adolescents despite these significant updates in GINA recommendations.[4]

Key Message

New strategies to manage mild asthma are emerging since evidence has demonstrated the critical role of inflammation in these asthma phenotypes and the potential side effect and risks of short-acting beta 2 agonists overuse. Unsurprisingly, international guidelines recommend associating corticosteroids when using a reliever in mild asthma as "as needed" or low-dose regular treatment.

2 | HOW MUCH IS FREQUENT MILD ASTHMA?

Asthma affects 5%-16% of people worldwide. In Italy, the asthma rate is about 8% among the general population, 9.5% among children, and 10.4% among adolescents.[5]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 week or less would not benefit from ICS.[1] Only a few studies have been focused on the epidemiology of mild asthma, showing that it is the most common phenotype of asthma, representing up to 75% of all patients with asthma, with a worldwide prevalence estimated at 3.3%.[3] Among 10.939 asthmatic patients included in the Asthma Insights and Reality surveys conducted in 29 countries, the percentage of intermittent asthma was 22%–54% and that of mild persistent asthma was 12%–20%.[6] In a large international study, Zureik et al. have evaluated 1,132 asthmatic patients. 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 showing that 50% of the patients had mild asthma, 29% had moderate asthma, and 21% had severe asthma. The proportion of mild asthma varied according to the geographical area, ranging from 63% in Europe to 42% in Australia and New Zealand.[7] 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, showing that 63%, 23%, and 14%, respectively, had mild, moderate, and severe asthma.[8] Lastly, Liard et al. classified 4,362 asthmatic patients with a combination of two independent GINA classifications, the first one based on symptoms and FEV1 and the second one based on current medication. 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. In comparison, 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, demonstrating that adding treatments to a symptoms-FEV1 classification can change asthma severity classification.[9]

3 | A REVOLUTION IN THE TREATMENT OF INTERMITTENT/MILD PERSISTENT ASTHMA

Validated epidemiological studies showed that "intermittent" and "mild persistent" asthma are the most frequent phenotypes in children with asthma. However, it was estimated that the frequency of severe exacerbations in these groups is about 0.12–0.77 per patient/year requiring 30%–40% of cases of emergency care.[2] The low frequency and/or non-troublesome nature of symptoms in mild asthma are associated with an unsatisfactory patient's adherence toward controller medications and may contribute to SABA overuse with an increased risk of adverse events and fatal asthma.

In parallel, many authors highlighted the protective role of regular use of ICS.

In 2006, the GINA update supported a stepwise approach with controller drugs to minimize the need for rescue medication. However, for many years SABA-only treatment remained the only therapy for mild asthma while ICSs were recommended for patients with recurrent symptoms. 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.[3] However, GINA 2019 new recommendations, considered the most fundamental change in asthma management in the last 30 years. This new strategy report no longer supports SABA alone at step 1 of asthma treatment but supports a low-dose ICS with SABA or ICS-formoterol as needed. These findings were supported by the recent START and PRACTICAL trials.[10,11]

Taking a cue from these studies, GINA 2020 recommended 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, 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 intermittent symptoms and proposed a two "tracks" approach with the two controller and reliever choices according to asthma severity in adolescents and adults.[1]

4 | OPTIMIZING ASTHMA TREATMENT

Asthma is a highly heterogeneous disease that should be considered as a syndrome encompassing multiple clinical phenotypes with different pathophysiological mechanisms (asthma "*endotypes*").[12] It is well known that childhood onset-asthma mostly belongs to the allergic phenotype, characterized by a personal and/or family history of atopy and the presence of type 2 inflammation markers. Such evidence is beneficial in the management of severe asthma, occurring in 5% of pediatric asthma.

Data on the endotypes and related specific predictors of exacerbations, persistent airflow limitation, and response to treatments are still limited in mild asthma, even if a considerable amount of evidence supports the effective use of ICS in children with type 2 inflammation markers.[13] To optimize asthma treatment, aerosols with a mass median aerodynamic diameter (MMAD) ≥ of 1 μm but less than 5 μm should be preferred to reach the distal airways and reduce oropharyngeal deposition. The most used inhalers in children are pressurized metered-dose inhalers (pMDI) delivering "fine" particles (MMAD ≥2 μm and <5 μm), but newer pMDI delivering "extra-fine" particles (MMAD 1–2 μm) have lower oropharyngeal deposition and more significant lung deposition. These devices are licensed for use internationally, but with variable approval for pediatric use since data on potential side effects in this age group due to ICS systemic bioavailability are still lacking.

Finally, it is essential to obtain good compliance to treatments, which is particularly difficult in adolescents and mild asthma rather than in moderate or severe asthma. Hopefully, shortly, digital health technologies will help physicians in improving asthma management. Many different digital health interventions are already available for childhood asthma, ranging from electronic monitoring of drug use and asthma symptoms, with the ability to set acoustic reminders, to educational materials such as video or interactive games on inhalers technique, even if few studies have evaluated their efficacy.[14] Smart inhalers and specific mobile apps are also available for smartphones and tablets, including those providing data on daily weather, pollen concentration, and air pollution. However, there is still no standard measure to assess their technical and scientific quality nor data sharing security.[14]

5 | CONCLUSIONS

The treatment of asthma in children, especially those with mild or moderate intermittent asthma, still represents an important challenge in clinical practice, hampered by poor compliance. Many treatments are currently available, and low doses of ICS allow to keep most asthmatic children in a condition of good control, particularly those with type 2 inflammation (atopy, eosinophilia, increased FeNO). International guidelines are changing the approach to treat milder forms of asthma, underlining the importance of anti-inflammatory drugs together with bronchodilators, but probably this revolution will take time to be well known and applied. Future studies on clinical, genetic, laboratory biomarkers will shed more light on milder phenotypes to define the best strategy for these patients.

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CONFLICT OF INTERESTS

Authors declared they have no conflict of interests.

AUTHOR CONTRIBUTIONS

Maria Angela Tosca: Conceptualization (equal); Writing—review and editing (equal). **Maria Elisa Di Cicco**: Conceptualization (equal); Writing—review and editing (equal). **Maddalena Leone**: Conceptualization (equal); Writing—review and editing (equal). **Maria Scavone**: Conceptualization (equal); Writing—original draft (equal). **Amelia Licari**: Supervision (lead); Writing—review and editing (equal).

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