UPDATE

Global Initiative for Asthma Guidelines 2024: An Update

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ABSTRACT

Asthma poses significant challenges in pediatric care, particularly in resource-limited settings. The Global Initiative for Asthma (GINA) 2024 guidelines represents a crucial step forward in addressing these challenges. This review critically evaluates the guidelines, focusing on their implementation and impact in developing countries like India. There have been certain key updates including a revised diagnostic flow chart and emphasis on alternative tools like peak flow meters. Challenges related to bronchodilator reversibility and interpreting FEV1/FVC are also explored. The article further addresses the implications of bronchial provocation testing in pediatric asthma. Detailed insights into cough-variant asthma highlight its rising recognition and management strategies. The GINA 2024 guidelines reflect updated criteria for commencing a particular step of therapy, aiming to optimize management and outcomes in pediatric asthma care. The guidelines have updated the role of allergen immunotherapy in pediatric asthma based on emerging evidence of efficacy and safety. Overall, the GINA 2024 guidelines offer a realistic approach to pediatric asthma care, with potential for broader applications pending further research and adaptation.

Keywords: *GINA, Asthma, Children, Diagnosis, Management*

The Global Initiative for Asthma (GINA) recently published updated guidelines for managing asthma in children and adolescents [1]. These new guidelines consolidate previous recommendations and introduce significant updates based on recent research. This article critically appraises these guidelines, focusing on diagnosing asthma and their implementation in developing countries like India.

DIAGNOSIS OF ASTHMA

Updated Diagnostic Flow Chart and Practical Challenges

GINA 2024 has introduced a revised diagnostic flow chart for assessing children aged 6 to 11 years and adolescents who present with recurrent or chronic respiratory symptoms [1]. While documenting bronchodilator reversibility remains the gold standard for diagnosing asthma, it may be impractical in real-world clinical settings due to inconsistency in the availability of spirometry devices and a lack of adequate training among healthcare personnel regarding the correct technique and interpretation of spirometry results.

A survey conducted among healthcare practitioners in India revealed a wide variation in the use of spirometry in clinical practice, ranging from 72% among chest physicians to 12% among general practitioners [2]. Pediatricians, in particular, reported even lower utilization rates, with only 16% incorporating spirometry into their diagnostic approach. Difficulty in interpreting the results of spirometry was considered as a significant barrier by 8% of pediatricians, likely indicative of broader challenges faced in clinical practice, and 19% reported difficulties in performing the procedure. In such resource-constrained settings, peak flow meters emerge as a viable alternative for assessing bronchodilator reversibility through peak expiratory flow (PEF) measurements. While not as precise as spirometry, peak flow meters offer an advantage over relying solely on symptomatic assessments, providing valuable objective evidence to guide

clinical decision-making [1]. Additionally, PEF measurements fill diagnostic gaps, particularly where spirometry is not easily accessible or practical. However, due to a wide variability in PEF readings, results should be interpreted with caution.

Challenges with Bronchodilator Reversibility

One significant challenge in documenting bronchodilator reversibility (BDR) to confirm asthma lies in the inability to perform these maneuvers during severe symptoms, particularly at the initial presentation. This is particularly applicable to children presenting at 7-11 years, who may experience only occasional day-to-day symptoms but may suffer severe attacks upon exposure to various allergens [3]. GINA 2024 offers a pragmatic approach for such children and recommends initiating them on inhaled corticosteroids (ICS) after ruling out alternative diagnoses and conducting lung function analysis during follow-up. Hence, every attempt should be made to document BDR in these children once they are clinically stable and perform spirometry or PEF, as asthma is often misdiagnosed in this age group.

Another limitation of relying solely on BDR for diagnosing asthma in children is the low sensitivity to a specific cutoff value of 12%. Revised GINA guidelines (2024) have not adopted the recommendation of the American Thoracic Society and European Respiratory Society to modify the BDR cutoff to ≥ 10% from ≥ 12%. Given the variability of spirometry in children, using any specific cutoff for BDR may be inappropriate. A randomized controlled trial by Tse et al addressed this issue and demonstrated a very poor sensitivity of 35.6% when using a cutoff of 12% for BDR in asthmatic children [4]. Similarly, the Childhood Asthma Management Program (CAMP) study could document BDR in only 36% of asthmatic children using a threshold of ≥ 12% [5]. Further studies are needed to determine the optimal cutoff for documenting BDR in children before any definitive conclusions can be drawn.

Interpretation of FEV1/FVC Ratios

The 2024 revision has omitted the necessity for documenting expiratory airway limitation as a diagnostic criterion for asthma (Box 1-2 in GINA 2024 guidelines). Typical symptoms alongside the documentation of variable expiratory airflow limitation, are now recommended for ease of diagnosis. While measuring FEV1/FVC (ratio of the forced expiratory volume in the first one second to the forced vital capacity of the lungs) indeed indicates expiratory airflow limitation and aids in ruling out other causes of FEV1 reduction, factors such as poor technique or inducible laryngeal obstruction due to the procedure itself, can lead false positives. Additionally, there may be a subset of patients who exhibit typical symptoms and BDR on spirometry but have a normal baseline FEV1/FVC. Dufetelle et al documented significant BDR in 4.9% of asthmatic children with normal baseline spirometry [6]. Therefore, the absence of a reduced baseline FEV1 or FEV1/FVC ratio in a child with clinical suspicion of asthma should not discourage clinicians from conducting testing for BDR, a notion strongly emphasized in the GINA 2024 guidelines.

Additionally, when interpreting FEV1/FVC, it's advisable to compare it with either the baseline values or the lower limit of normal (LLN) values, rather than relying on a specific value or % predicted. The LLN is defined as the fifth percentile of the distribution, corresponding to a -1.64 z-score [7]. Unlike the previous guidelines (GINA 2023) which suggested a cutoff of 0.90, no specific value for FEV1/FVC has been mentioned in the revised version. It is crucial to utilize age-specific cutoffs for LLN when interpreting

FEV1/FVC, as it may not correspond to predicted values if the coefficient of variance is higher than 10% [7]. There is a need to collect data to develop LLN reference values of FEV1/FVC from Africa, the Arab world, South America, and the Indian subcontinent [8]. Furthermore, defining LLN as a fixed FEV1/FVC ratio can introduce biases related to height, sex, age, and ethnicity, and such practice is strongly discouraged [8].

Bronchial Provocation Testing

GINA 2024 maintains its stand on the exclusion of bronchial challenge tests involving hypertonic saline, hyperventilation, or mannitol, opting instead for standardized exercise challenges as the only acceptable method for documenting bronchial hyper-responsiveness in asthmatic children. These tests serve a crucial role in confirming a diagnosis in cases of variable clinical symptoms without evident airflow limitation, diagnosing cough-variant asthma where spirometry often yields normal results, and establishing diagnoses in specific populations such as athletes. However, their major limitation lies in their limited specificity. While GINA has not provided specific reasons for excluding methods other than exercise challenges in children, it is likely due to concerns regarding their safety in children. Few studies have demonstrated the efficacy and safety of these tests in diagnosing and monitoring asthmatic children as young as 4-years-old [9,10]. Nevertheless, data on the safety of these tests remain scarce, and these trials may not fully represent the pediatric population. Therefore, it is currently not recommended to perform these tests due to potential adverse effects such as shortness of breath, chest tightness, and, in rare cases, life-threatening acute bronchospasm requiring resuscitation. With more safety data, there is potential for broader application of these modalities in diagnosing asthma in children.

Cough-variant Asthma

Cough-variant asthma receives expanded attention in GINA 2024; children typically present solely with persistent cough as the primary symptom (cough-variant asthma), or as the most prominent feature (cough-predominant asthma). These individuals often lack other symptoms, such as breathlessness or chest tightness, and may not exhibit typical signs on examination. The results of spirometry may be normal. In the majority of instances, the only abnormality that can be demonstrated is through bronchial provocation testing, which is not widely available. Consequently, effective management hinges on a robust clinical suspicion and a trial of inhaled corticosteroids (ICS) to assess clinical response.

The recognition of cough-variant asthma is on the rise among children and plays a significant role as a cause of chronic cough without specific cough pointers, also known as non-specific cough [11]. In a previous study, authors reported an asthma-like illness characterized by persistent dry cough without specific pointers in 10.3% of children with chronic cough, who responded favorably to inhaled corticosteroids and were treated as asthma cases [12]. Hence, it's imperative to consider and address this entity in children with chronic non-specific cough.

TREATMENT OF ASTHMA

Children (6-11 years)

For children aged 6-11 years, step 1 suggests low-dose ICS to be added with as-needed short-acting beta-2 agonists (SABA) as controller therapy. Step 2 recommends daily low-dose ICS. Step 3 offers options like increasing daily ICS to a medium dose, or adding a long-acting beta-agonist (LABA) to low-dose ICS, or

very low-dose ICS-formoterol (Maintenance and Reliever Therapy; MART) as the preferred controller. As-needed SABA (or ICS-formoterol, MART) is recommended as the reliever (step 3 or 4). Referral to experts is now prioritized for children not controlled on step 3 before increasing the dose to medium-dose ICS, ensuring early management of asthma-mimicking conditions or other co-morbidities. Previously, GINA 2023 recommended referral only after trying medium-dose ICS. Other alternatives in step 4 include medium-dose ICS-LABA or low-dose MART. Step 5 recommends phenotypic assessment and considering biological treatments. Significant algorithm changes include recommending as-needed ICS with SABA for those with symptoms twice a month or more but less than 2 days a week, instead of daily low-dose ICS. This addresses compliance issues and concerns about daily ICS impacting growth [13].

The recommendation for MART in children is based on a single study showing a significant reduction in exacerbations compared to maintenance with the same dose of ICS-formoterol or higher-dose ICS and SABA as a reliever [14]. This highlights the limited literature and the need for further studies in this age group.

GINA suggests biologic therapy only for severe asthma cases where optimized treatment fails to control symptoms. Various clinical features and biomarkers help assess eligibility for different biologicals and predict responses. Increasing options for biologicals, especially for children under 12, are emerging as safety data becomes available. Currently, omalizumab (anti-IgE), mepolizumab (anti-IL-5/5Rα), and dupilumab (anti-IL-4Rα) are available for children aged 6-11 years. There is an urgent need for studies comparing different biologicals in eligible patients.

Adolescents (12-18 years)

For adolescents, GINA continues to recommend two tracks for ongoing asthma treatment. Track 1 uses low-dose ICS-formoterol (anti-inflammatory reliever, AIR) as needed,while MART (Track 1) remains preferred due to its reduction in severe exacerbations compared to SABA-only regimens, and its simplicity as a single medication for both maintenance and reliever therapy. In Track 1, Step 1-2 involves as-needed low-dose ICS-formoterol. In Step 3, low-dose ICS-formoterol MART can be escalated to medium-dose ICS-formoterol MART in Step 4. Step 5 includes add-on long-acting muscarinic agonists (LAMA), phenotypic assessment, and consideration of biologicals. In Track 2, patients use SABA and low-dose ICS together, as needed in Step 1. Step 2 provides continuous low-dose ICS maintenance. Step 3 adds LABA to the low-dose ICS maintenance therapy. Step 4 includes medium/high-dose ICS-LABA. Step 5 remains the same as Track 1. Deciding between Steps 2 and 3 can be challenging based on symptom frequency alone. GINA 2024 offers clinical points for Step 3 initiation, considering recent severe exacerbations, past life-threatening episodes, or severe airway hyper-responsiveness despite less frequent symptoms. Another significant parameter for considering daily therapy (Step 3) is low lung function despite few symptoms. This can result from impaired perception of bronchoconstriction, leading to less frequent symptoms, which is a significant risk factor for severe exacerbations or higher odds of emergency department visits. This issue is increasingly recognized in children [15]. Previous GINA guidelines considered low lung function only in the context of daily symptoms for starting step 4 treatment.

GINA 2024 also provides comprehensive details on ICS-formoterol devices and doses for anti-inflammatory reliever (AIR) therapy across all age groups, serving as a valuable resource for clinicians.

GINA strongly advises against using oral salbutamol, oral theophylline, montelukast, or home nebulization for symptom control and exacerbation management due to lack of efficacy and the potential for serious systemic side effects.

Children 5 years and younger

Distinguishing between viral-induced episodes, seasonal or allergen-triggered asthma, and unrecognized asthma can be challenging in children under 5 years old with intermittent or episodic wheezing. Initial management typically involves using a SABA as needed until symptoms resolve, usually within 1 to 7 days. Uncertainty regarding the nature of these episodes complicates decisions about additional medications. If SABA use exceeds twice weekly on average over a month, a trial of low-dose ICS is recommended. A trial of regular controller treatment, typically low-dose ICS for at least 3 months is recommended if symptoms are suggestive of asthma, such as frequent episodes (three or more in a season), prolonged symptoms (>10 days), interval symptoms, allergic sensitization, atopy, or a family history of asthma. This approach helps assess treatment response while considering potential benefits and risks, including effects on growth velocity, which are typically modest and not cumulative over time.

Allergen Immunotherapy (AIT)

GINA 2024 recommends that AIT may be considered as add-on therapy, both in adults and children with asthma who had clinically significant sensitization to aeroallergens. It may be difficult to define this "clinically significant sensitization". Further, GINA suggests that there is insufficient evidence for recommending house dust mite (HDM) sub-lingual immunotherapy (SLIT) in children with asthma. GINA also mentions concerns about sub-cutaneous immunotherapy (SCIT) e.g. complexity of making SCIT extracts, risk of serious adverse events, and long duration of therapy (3-5 years). To sum up, AIT has a limited specific role and should be judged very carefully by a specialist in AIT.

Role of Azithromycin

GINA 2024 advises considering add-on azithromycin only for adult patients with persistent symptoms despite high-dose ICS-LABA, recommending a trial of at least six months. This is indicated for adults with severe asthma who lack evidence of type-2 inflammation, making them ineligible for type-2 targeted biologicals, or when biologic therapy is unavailable or unaffordable. These recommendations are based on adult studies, with no guidance provided for adolescents or children. However, recent evidence suggests azithromycin efficacy in children. A trial showed improved asthma control and reduced exacerbations in children aged 5-15 years with poorly controlled asthma despite standard ICS $\pm$ LABA treatment [16]. Further studies and incorporation of the new available evidences are needed to draw conclusions.

Table I summarizes the key changes in GINA 2024 compared to GINA 2023. **Box 1** highlights the key messages for pediatricians based on GINA 2024 guidelines.

Scope of Improvement in GINA 2024 Guidelines

There are several areas where the GINA 2024 guidelines could be enhanced to better support asthma management. Firstly, the few recommendations for children have been mostly extrapolated from studies in

adults and there is a need to have robust data from studies in children. The role of Fractional exhaled Nitric Oxide (FeNo), both bronchial and nasal, as well as azithromycin in children and adolescents should also be elaborated, incorporating the latest evidences. Oscillometry may be emphasized as a useful and feasible tool for monitoring lung functions with a need to develop normative data in children. Additionally, the guidelines need to define the role of allergy testing, including the indications and types (in-vitro and in-vivo). More detailed information on AIT, such as SCIT and SLIT, along with clear indications and referral criteria to an allergist for allergy work-up, should be provided. A comprehensive flow chart that includes clinical, structural, functional, inflammatory, and spirometry assessment, followed by pharmacological, non-pharmacological, biologic, preventive, and immunotherapy treatment options, needs to be created. These additions would greatly enhance the utility and clarity of the guidelines further.

Box 1. Key Messages from GINA 2024 Guidelines on Pediatric Asthma

1. Early and accessible diagnosis: Use of peak flow meters as an accessible tool for early diagnosis in resource-limited settings is emphasized. However, most of the experts in India have concern regarding wide variability in PEF reading.
2. Tailored treatment initiatives: Deciding to start treatment based on how often symptoms occur rather than using low-dose ICS daily for all helps manage symptoms while considering growth concerns in children under 5 years.
3. Simplified treatment algorithms for adolescents focus on effective symptom management and reducing exacerbation risks using MART and ICS-formoterol.
4. SABA is not recommended as monotherapy.
5. GINA does not recommend the use of oral salbutamol. While inhalation is the method of choice, however, in our country where inhaled salbutamol is not feasible, oral salbutamol may be justified in children whose symptoms are mild and infrequent.
6. Leukotriene receptor agonists (LTRA) alone are inferior to ICS. These can be used as an add on therapy in Step 4 of asthma. FDA has issued warnings about serious behaviour and mood-related changes with montelukast.
7. Oral steroid is recommended in moderate to severe exacerbation of asthma for short duration (3-5 days).
8. The diagnosis of cough-variant asthma should be made in older children who typically present with chronic cough, with a clear-cut response to a therapeutic trial of asthma medication, where alternative diagnosis has been ruled out.
9. Application of allergen immunotherapy should be carefully considered and monitored by specialists in allergen immunotherapy due to its currently limited specific role.
10. Continued research is essential to refine diagnostic tools and therapeutic strategies, ensuring optimal asthma management in diverse clinical settings.

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Table I Comparison of GINA 2024 and GINA 2023 Guidelines for Pediatric Asthma

	GINA 2024	*GINA 2023*
1. Diagnostic flowchart		
• Severely uncontrolled respiratory symptoms/ signs	• Focuses on starting empirical treatment after ruling out alternative diagnosis	• Less detailed; not well-highlighted
• Spirometry/PEF availability and feasibility	• Addressed	• Not addressed
2. Diagnostic criteria		
Bronchodilator reversibility	Includes PEF ≥ 15%	PEF ≥ 20%
Documented expiratory flow limitation	Removed from diagnostic criteria table	Included in the diagnostic criteria table
Cough variant asthma	Detailed discussion; emphasizes bronchial provocation testing; management similar to asthma in general	Less detail on diagnosis and management
3. *Asthma treatment*		
3.1. Adolescents (Track 1)		
Step 1 & Step 2	Combined evidence	Evidence discussed separately
Criteria to start Step 1	Same as Step 2 (combined in the algorithm)	Symptoms < twice a month
Criteria to start Step 2	Symptoms < 3-5 days a week with normal/mildly reduced lung function	No specific cutoff; Symptoms ≥ twice a month but not most days; no mention of lung function
Criteria to start Step 3	Additional clinical points like exacerbation and airway hyper-responsiveness	Symptoms most days (frequency unspecified); waking at night ≥ once a week
Low lung function without frequent symptoms	Criteria to start Step 3 (additional point)	Not addressed in this context Considered only for starting Step 4 treatment if present along with daily symptoms or night awakening
3.2. Children 6-11 years		
Criteria for Step 1 (as needed ICS with SABA)	Symptoms < 2 days a week	Symptoms < twice a month
Criteria for Step 2	Specific frequency (2-5 days a week)	Symptoms > twice a month but less than most days
If symptoms are not controlled in Step 3	Consider early referral for expert advice	Increase the dose to medium-dose ICS; Expert opinion if not controlled on medium-dose ICS
4. MART		
Details on ICS-formoterol devices and doses for AIR	Provided in a separate table	Not elaborated comprehensively
5. Allergen immunotherapy (AIT)		
Indication	May be considered as add-on therapy in a selected group of asthmatic children with clinically significant sensitization to aeroallergen after taking account all pros and cons of AIT.	Recommended only for adults with allergic rhinitis and house dust mite sensitization