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GUIDELINES

GINA 2020: what's new and why?

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ABSTRACT

The Global initiative against asthma (GINA) 2020 strategy has been released with some changes and updates. GINA recommends the continuation of medications, avoidance of nebulization and spirometry, and ensuring a written asthma action plan in COVID-19 times. GINA 2020 specifies which step of management is to be followed according to the patient's symptoms in an easy flowchart. Clinicians need to be aware of the changes and the evidence behind them.

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The Global initiative against asthma (GINA) 2020 strategy has been released with some changes and updates (1). Even though the significant advancements and landmark changes were made between 2018 and 2019 (2), a few critical changes and evidence-based updates are especially noteworthy in the 2020 version. Probably the most significant change, considering the times, is the one regarding COVID-19. GINA recommends the continuation of medications, avoidance of nebulization and spirometry, and ensuring a written asthma action plan. In another practical and useful change, GINA 2020 now specifies which step of management is to be followed according to the patient's symptoms in a flowchart. Other changes include new evidence for using an inhaled steroid (controller medication) for each patient, the safety of mepolizumab in ages 6–12 years, and a FDA box warning for montelukast (1).

Bronchial asthma and COVID-19

The SARS-CoV2 infection causing COVID-19 has spread rapidly and emerged as a global pandemic with impactful losses in terms of both life and economy. Initial data has revealed that COVID-19 is more severe and lethal in patients with comorbidities, including chronic respiratory illnesses (3). There should be no interruption of controller medications for asthma. Inhaled corticosteroids alone or with long-acting beta-agonist (LABA) should be continued, and additional oral corticosteroids prescribed if required. Given the risk of an acute exacerbation, a written asthma action plan should be meticulously complied and followed. Aerosol generating procedures including nebulization, spirometry, and peak expiratory flow rate measurement, have a risk of spreading COVID-19. To prevent infection transmission to health care professionals and other patients, these procedures should be avoided all together or, in the case of spirometry, postponed. Further, even though some manufacturers claim FeNO to be a safe and aerosol-free investigation (4), it must be remembered that GINA 2020 does not address FeNO with regards to its safety vis-à-vis COVID-19.

New evidence for "no SABA monotherapy"

There is new evidence (Novel START and PRACTICAL clinical trials) that further supports the recommendation of no SABA monotherapy. Table 1 highlights the significant findings of the original SYGMA and other new trials. Taking a cue from these, GINA 2020 advises against the use of SABA monotherapy, independent of the blood eosinophil count and exhaled nitric oxide levels. The current evidence recommends as-needed low dose inhaled steroid-formoterol combination as the preferred therapy in step1, with low dose inhaled steroid (ICS) whenever SABA is taken as the alternative (1). For step 2, either daily low dose ICS or as-needed low dose ICS-formoterol combination can be used as the preferred controller therapy (1).

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Table 1. Clinical trials favoring the 'no SABA monotherapy' recommendation of GINA 2020 guidelines.

Trial name/ Year	Patient	Intervention	Comparison	Outcome	Conclusion/implication
SYGMA I 2018 (5)	AGE >12 Year, Mild Asthma 3836 patients	Placebo twice daily and terbutaline prn Vs Placebo twice daily and budesonide/formoterol prn Vs Budesonide twice daily and terbutaline prn.	Primary objective was to compare budesonide/ formoterol prn to terbutaline for asthma symptom control	Budesonide/formoterol prn provided superior asthma-symptom control VS terbutaline prn, but was inferior to budesonide maintenance therapy. Exacerbation rates in two budesonide-containing regimens were similar and were lower than the rate with terbutaline. Budesonide/ formoterol SOS resulted in substantially lower glucocorticoid exposure than budesonide maintenance therapy	No SABA monotherapy for Step 1 asthma
SYGMA 2 2018 (6)	AGE >12 years, Mild asthma at GINA STEP 2 4215 patients	Placebo twice daily and budesonide/formoterol prn Vs Budesonide twice daily and terbutaline prn.	Annual rate of severe asthma exacerbations	Budesonide/formoterol prn was noninferior for severe exacerbations; dose of inhaled glucocorticoid was lower in the budesonide/ formoterol group. The time to first exacerbation was similar. Change in ACQ-5 score showed a difference in favor of budesonide maintenance therapy.	In patients with mild asthma, budesonide/formoterol prn is non-inferior for exacerbations but inferior for symptom control. Hence, it is preferred therapy for step 1 and one of the preferred therapies for step 2 GINA 2020.
Novel START 2019 (7)	Adults with mild asthma 668 patients	Albuterol prn VS budesonide twice daily and Albuterol prn VS Budesonide/ formoterol prn.	Primary outcome was the annualized rate of asthma exacerbations	The annualized exacerbation rate in the budesonide/formoterol group was lower than that in the albuterol prn alone group, and did not differ significantly from budesonide maintenance and albuterol prn group. The number of severe exacerbations was lowest in the budesonide/formoterol group. The mean dose of inhaled budesonide was lower in the budesonide-formoterol group vs budesonide maintenance group	Patient groups similar to SYGMA 1 and primary outcome and results similar to SYGMA 2
PRACTICAL 2019 (8)	18–75 years with asthma who were using SABA for symptom relief with or without maintenance ICS in the previous 12 weeks	Reliever therapy with budesonide/formoterol prn Vs maintenance budesonide twice daily and terbutaline prn.	Primary outcome was the number of severe exacerbations per patient per year	Adults with mild to moderate asthma, budesonide/formoterol used as needed for symptom relief was more effective at preventing severe exacerbations than maintenance budesonide and terbutaline prn	Findings support the 2020 Global Initiative for Asthma recommendation that inhaled corticosteroid–formoterol reliever therapy is an alternative regimen to daily low-dose inhaled corticosteroid for patients with mild asthma

SABA: short acting beta-2 agonist, ICS: inhaled corticosteroid, ACQ: asthma control questionnaire, BD: twice daily, SOS: as required.

Table 2. Preferred controller therapy in the 'Step wise' approach to asthma (1).

ADULTS AND ADOLESCENTS-STEP WISE APPROACH TO ASTHMA		
STEP	SYMPTOMS	PREFERED CONTROLLER
1	<2/MONTH	AS-NEEDED LOW DOSE ICS + FORMETEROL
2	>2/MONTH	DAILY LOW DOSE ICS OR SAME AS STEP 1
3	MOST DAYS SYMPTOMS + WAKING UP ≥ 1/WEEK	LOW DOSE ICS + LABA
4	STEP 3+ LOW LUNG FUNCTION	MEDIUM DOSE ICS + LABA
5		HIGH DOSE ICS + LABA PHENOTYPIC ASSESSMENT +/- ADD ON THERAPY
CHILDREN 6–11 YEARS-STEP WISE APPROACH TO ASTHMA		
STEP	SYMPTOMS	PREFERED CONTROLLER
1	<2/MONTH	NO CONTROLLER
2	>2/MONTH TO LESS THAN DAILY	DAILY LOW DOSE ICS
3	MOST DAYS SYMPTOMS + WAKING UP ≥ 1/WEEK	DAILY LOW DOSE ICS + LABA OR DAILY MEDIUM DOSE ICS
4	STEP 3+ LOW LUNG FUNCTION	DAILY MEDIUM DOSE ICS + LABA OBTAIN EXPERT ADVICE
5		PHENOTYPIC ASSESSMENT +/- ADD ON THERAPY

ICS- inhaled corticosteroid, LABA- long acting beta agonist.

Step-wise management

The diagrammatic representation of the 'Steps' of asthma management are presented in GINA 2020 in a single flowchart each for ages 6–11, and 12 years and beyond, in Boxes '3-4D' and '3-4B' of the document, respectively. The reworked flowcharts now include clear pointers toward 'when to start each step of treatment'. These are beneficial for both clinicians and trainees, and are self-sufficient to be applied in daily practice (1). The stepwise controller treatment with each clinical presentation is mentioned in Table 2. In a patient with symptoms less than twice a month, step 1 therapy is advised. If symptoms occur twice a month to daily, then step 2 treatment should be followed. Patients waking up due to asthma symptoms at least once a week are initiated on step 3, and if associated with poor lung function, step 4 therapy is used. The up-gradation of steps is according to symptom control.

FDA box warning for montelukast

The 2020 update in GINA highlights the recent addition of a boxed warning to Montelukast by the Food and Drug Administration (FDA, USA). The reason for the safety warning is the small albeit worrisome risk of mood change and suicidal tendencies following exposure to the drug. Even though studies did not show increased side effects (only one suicidal ideation with no completed suicide) (9), due to the availability of safer alternatives, the FDA advises against using montelukast as first-line therapy in allergic rhinitis (10). As a corollary to the FDA advisory for allergic rhinitis (10), even asthma care physicians should practice caution while prescribing montelukast based on a risk-benefit ratio. Despite the current warnings, many health care professionals may not be aware of the risk of mental health effects. Wherever prescribed, risk should be explained to patients and caregivers, and they should be advised to look for behavioral changes and suicidal thoughts, and get medical attention promptly if these occur.

Asthma plus COPD phenotype (ACO)

The terminology and definition of ACO is an ever-evolving subject in and of itself. The 2020 update has a reworked chapter on ACO. The previous 'Box' on the syndromic approach to the asthma-ACO-COPD axis has been completely reformulated. The new version provides a simplification on the identification and initial management of the axis. Two of the previously used terms, 'could be ACO' and 'possibly COPD', have been removed and the definitive term 'ACO' has been used, which increases confidence in the diagnosis. Previously, some ACO patients would invariably be labeled as 'possibly COPD'. The removal of this term decreases confusion, and brings management of ACO closer to asthma than before. The new 'Box' makes a clear statement of using inhaled steroids as initial treatment, while recognizing the fact that bronchodilator supplementation is usually required. Asthma patients must be advised that inhaled corticosteroids should be used as the initial controller therapy and supplemented with bronchodilators according to a stepwise approach. Short-acting beta-agonists should never be used alone as controller therapy in asthma. COPD, on the other hand, should be treated primarily using bronchodilators (muscarinic antagonists and/or beta-2 agonists) with supplementation using corticosteroids according to specific indications.

Update for pediatric populations

The current strategy recommends using mepolizumab in the age group 6 years and above compared to the

age cutoff of 12 years in the previous version. The change in the age group cites a single study that enrolled 30 children with a 52-week follow-up; and found no severe or fatal adverse events related to the drug. Mepolizumab reduced blood eosinophil counts and asthma exacerbations, and improved asthma control (11). Suggested levels of 'low' daily dose of inhaled corticosteroids have been updated. A cutoff for extra fine particle beclomethasone dipropionate has been added (50 mcg/day), and that for mometasone furoate has been updated to 100 mcg/day.

School-based programs for asthma control have been emphasized. A section of GINA discussed primary prevention of asthma and cited the importance of traffic-related air pollution (TRAP) and possibly obesity as risk factors for asthma. The change was brought about by citing recent evidence, which attributes up to 13% global asthma incidence to TRAP (12). The update also identifies obesity as a risk factor for pediatric asthma, and further states that obesity may increase risk of asthma. Step 1 management for age 6–11 years age is now the only "no controller required" recommendation in GINA 2020. Here the use of SABA alone as a reliever, remains the same as in earlier versions.

The definition of 'severe/life threatening' exacerbations in children 5 years of age and younger has been updated in terms of cutoffs for 'pulse rate'. The previous cutoffs were 200 and 180 beats per minute for 0–3 and 4–5 years of age respectively. These have been reduced to 180 and 150 beats per minute respectively, for early identification of severe exacerbations. The previously included, evidence of substernal retractions, was said to be subjective and has thus been removed. In its place, the update now includes a respiratory rate cutoff (greater than 40 breaths per minute) for severe exacerbations.

Caveats

Table 1 lists the evidence cited in GINA 2020 favoring the use of formoterol/budesonide combination as a reliever medication. These trials included asthmatics requiring GINA steps 1 and 2 treatment only. Even so, the recommendation has been made favoring the combination for all steps citing a risk of dependence on SABA. Although it may be pragmatic to apply the evidence by extension, more supportive data is required to conclusively support the benefit of using formoterol/budesonide over short acting bronchodilators as reliever therapy in steps 3–5. Furthermore, data collection in the SYGMA1 trial was based on sophisticated electronic inhalers, which may not be practical in the current day-to-day practice. Whereas the focus should be on regular treatment and follow up, recommending formoterol/budesonide as a controller-reliever combination in the early steps, promotes the concept of symptom-based treatment.

Conclusion

GINA gives periodical updates based on careful and extensive review of new evidence. Further, the updated flowcharts are concise and practical, and will be extremely valuable to health care providers at all levels, to apply the evidence-based strategies easily.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Author contribution

All the 3 authors contributed substantially to the conception and design of the work; or the acquisition, analysis, or interpretation of data for the work; or drafting of the work or critical revision for important intellectual content; and final approval of the version to be published. All authors are in final agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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