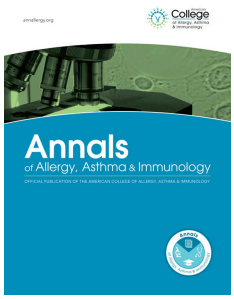
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GINA Updated 2019: Landmark Changes Recommended for Asthma Management

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9. **Figures.** 1 FIGURE 1. SUMMARY OF THE NEW GINA GUIDELINE RECOMMENDATIONS FOR PATIENTS > 12 YEARS.
10. **Tables.** 1 T ABLE 1: GINA 2019 COMPARED TO NHLBI 2007 GUIDELINES IN PATIENTS > 12 YEARS OLD

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Perspective from the Asthma Committee of the ACAAI

GINA Updated 2019: Landmark Changes Recommended for Asthma Management

GINA, Global Initiative for Asthma, was launched in 1993 in collaboration with the National Heart, Lung, and Blood Institute, National Institutes of Health, and the World Health Organization. to improve the prevention and management of asthma worldwide. Their science committee updates asthma guidelines yearly and the 2019[1] report's goals were to reduce the risk of serious asthma-related exacerbations: to avoid patient reliance on quick-relief medication: and to update asthma treatment goals. In the U.S., the NHLBI EPR-3 guidelines have not been updated since 2007. The purpose of this perspective is to delineate similarities and differences between the two.

Both recommend assessing asthma control and risk factors for future exacerbations which include addressing modifiable risk factors such as greater prescribing of ICS while, improving adherence to controller therapies, ensuring proper inhaler/spacer techniques, preventing overuse of SABAs and reducing indoor/ outdoor environmental exposures to allergens and air pollutants. These guidelines also recommend, monitoring pulmonary function tests every 3-6 months after starting initial controller therapy and at least every 1-2 years thereafter in all asthmatics. Children and patients at higher risk for exacerbations should have appropriate outpatient assessments with spirometry more often in conjunction with step-up or step-down therapy based on asthma control.

Unlike the NHBLI EPR-3 guidelines, GINA discourages as needed short-acting beta-agonists (SABA) as monotherapy. Inhaled corticosteroids (ICS) are now recommended to be started for mild intermittent asthma as needed with a SABA rather than using a SABA as needed alone.[2] Additional notable changes pertain to stepwise asthma treatment. It is now recommended that a low dose ICS-long-acting beta-agonist (ICS-LABA) combination therapy can be used as

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needed for all therapeutic steps for breakthrough symptoms in lieu of a SABA. This paradigm shift was in part based on the U.S. Food and Drug Administration (FDA) recent removal of the boxed warning for LABAs in December 2017 as well as four large clinical studies that found no increased serious asthma-related side effects using ICS-LABA compared to ICS monotherapy.[3-7]

Below, we review step by step changes in the GINA therapy guidelines that differ from current NHLBI guidelines.

STEP 1 RECOMMENDATIONS FOR PATIENTS ≥ 12 YEARS:

- **as needed low dose ICS-formoterol**
- **low dose ICS and SABA together as needed for symptoms**

Comment: Given the rapid onset of the LABA, formoterol and the poor patient adherence to controller therapy, ICS-formoterol is recommended as the preferred reliever option, replacing SABA. One study found that using 4 times the FDA approved dose for formoterol/budesonide was safe without evidence of side effects.

STEP 2 recommendations:

- **Daily low dose ICS with prn reliever (ICS-formoterol or SABA)**
- **Low dose budesonide-formoterol prn**
- **Low dose ICS used whenever SABA used**
- **Leukotriene receptor antagonist (LTRA) with prn reliever (ICS-formoterol or SABA)**

Comment: The results of two large trials (SYGMA 1 and SYGMA 2) compared using budesonide-formoterol as maintenance and reliever therapy (MART) versus fixed dose budesonide as maintenance and SABA as reliever therapy for patients with mild asthma.[3,4,5]

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Patients who at baseline used one or more puffs of a SABA experienced reduced asthma exacerbations if randomized to the budesonide-formoterol as needed versus a SABA as needed group. Using budesonide-formoterol as a MART was more effective for daily symptom control[4,5] compared to fixed dose budesonide with a SABA as a rescue medication. The budesonide–formoterol as needed group had approximately 25% less ICS exposure compared to the budesonide maintenance with as needed SABA group.

For patients with seasonal asthma, GINA recommends starting ICS at the beginning of the season and discontinuation 4 weeks after the season. Leukotriene antagonists can be used as an adjunctive agent.

STEP 3 recommendations are unmodified from 2018:

- **Low dose ICS-LABA maintenance plus prn reliever (ICS-formoterol or SABA)**
- **Low dose ICS-formoterol maintenance plus ICS-formoterol also used as reliever**
- **Medium dose ICS plus prn reliever (ICS-formoterol or SABA)**
- **Low dose ICS plus LTRA plus prn reliever (ICS-formoterol or SABA)**

Comment: Patients who have had more than one exacerbation in the last year, using budesonide-formoterol as MART was more effective in reducing severe exacerbations than using a higher dose maintenance ICS with an as needed SABA or an ICS-LABA as maintenance with an as needed SABA.

STEP 4 recommendations are similar to 2018:

- **Medium dose ICS-LABA as maintenance plus prn reliever (ICS-formoterol or SABA)**

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- **High dose ICS with add on tiotropium or LTRA plus prn reliever (ICS-formoterol or SABA)**

Comment: These recommendations are similar to the previous GINA guidelines but theophylline and zileuton are no longer listed as treatment options.

STEP 5 recommendations are:

- **High dose ICS-LABA plus prn reliever (ICS-formoterol or SABA)**
- **Referral for phenotypic assessment**

Comment: Patients with uncontrolled asthma despite optimizing therapy, assessing adherence, and reducing contributory factors, may be considered for a biologic.[6] Biologics should be considered for patients with eosinophilic or allergic inflammatory biomarkers, poor symptom control, and asthma exacerbations while on high dose ICS-LABA with or without a long-acting muscarinic antagonist (LAMA) and/or maintenance oral CSs. Selection should be made based on the patient phenotype/endotype, payer eligibility, cost, dosing frequency, route of dosing and patient preference.

RECOMMENDATIONS FOR 6-11 YEARS WITH PRN SABA FOR EACH STEP:

STEP 1- low dose ICS taken with each dose of SABA or daily low dose ICS

STEP 2- daily low dose ICS. Other options include daily LTRA or low dose ICS taken whenever SABA taken

STEP 3- low dose ICS-LABA or medium dose ICS. Other options: low dose ICS plus LTRA

STEP 4- medium dose ICS-LABA or medium dose ICS. Referral for expert advice on managing difficult asthma. Other options: high dose ICS-LABA or add tiotropium or LTRA

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STEP 5 includes assessing for anti-IgE while addressing comorbidities and adherence issues

Comments: Recommendations for 6-11 y/o children are similar to NHLBI 2007 guidelines (5-11y/o) except for eliminating SABA "as needed" use as well as cromolyn, nedocromil or theophylline. [1,2]

Summary of Updated GINA Guidelines Versus NHLBI EPR-3 Guidelines:

Comparison of NHLBI Guidelines and GINA recommendations are summarized in Table 2. As discussed, the most notable recommendation for GINA 2019 is no longer using SABAs as monotherapy for mild asthma. This is an important nuance as patients frequently don't endorse clinical symptoms such as dyspnea and therefore, don't take medication. This can lead to an insidious progression of disease resulting in worsening lung function and poorer outcomes. Using an ICS with a SABA or an ICS-LABA as needed relieves symptoms while reducing airway inflammation. The balance is always when to step up or step-down therapy which is the reason why asthma patients require continuous monitoring over time to assess symptoms using objective validated questionnaires like the Asthma Control Test or Asthma Control Questionnaire in conjunction with spirometry at least once a year to ensure they are doing well clinically without decline in lung function. Although budesonide-formoterol may be a better quick reliever medication than albuterol, this indication is not currently approved in the U.S. making it difficult to implement as patients prescribed a scheduled combination ICS-LABA that also use it as needed will run out of their controller therapy before the next prescription cycle. This could create an untold economic burden for patients if add use of an ICS-LABA as needed is not endorsed by managed care companies.

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When updated NHLBI guidelines are published, it is anticipated that stringent GRADE methodology will be used to adopt or refute GINA guideline recommendations. In the moderate to severe asthma population, additional guidance on biologics use for patients based on their phenotype/endotype characteristics is needed beyond what has been recommended by GINA. This is unlikely to be improved upon by the NHLBI guidelines beyond describing FDA indications for use of each agent as there are no head to head comparison studies of these agents that would allow recommendation for one over another. It is anticipated that the NHBLI Guideline update will further emphasize the importance of personalized treatment approaches that include regular patient assessment and adjustment of medications until asthma symptoms are controlled in order to minimize risk and impairment.

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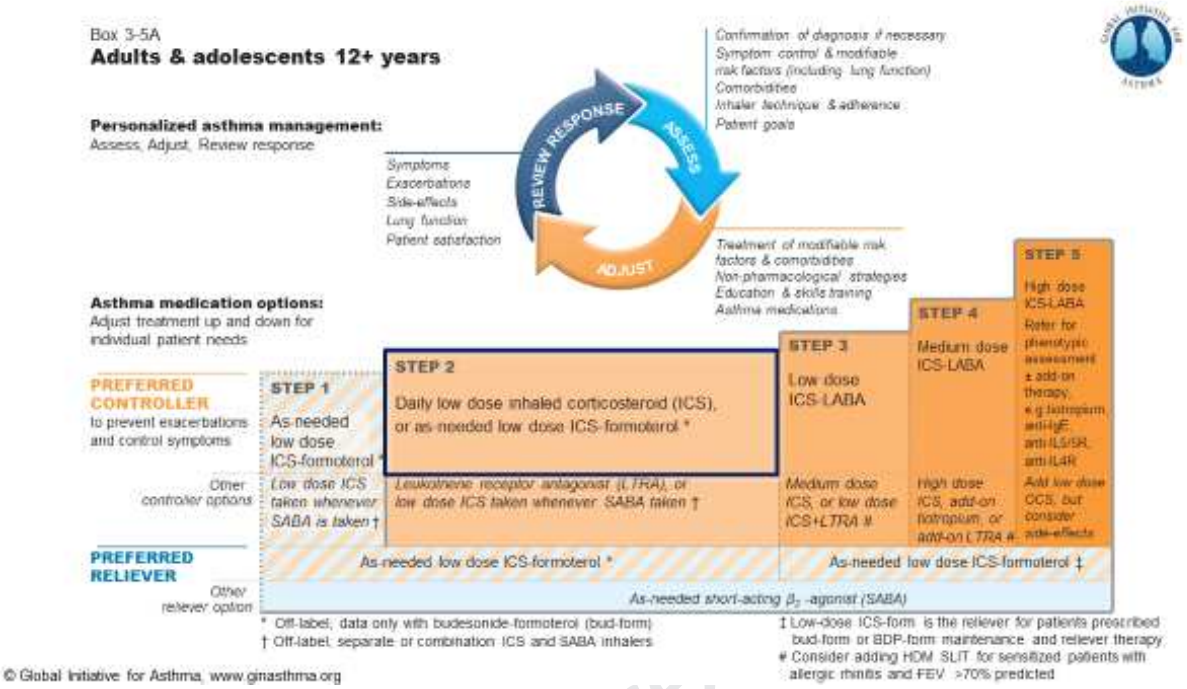
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FIGURE 1. SUMMARY OF THE NEW GINA GUIDELINE RECOMMENDATIONS FOR PATIENTS > 12 YEARS.



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T ABLE 1: GINA 2019 COMPARED TO NHLBI 2007 GUIDELINES IN PATIENTS ≥ 12 YEARS OLD

	NHLBI 2007 Preferred Therapy	GINA 2019 Preferred Therapy
STEP 1	• **prn** SABA	• **prn** low dose ICS-formoterol • Other options: low dose ICS and SABA together **prn** for symptoms
STEP 2	• Daily low dose ICS with **prn** SABA • **Other options:** with **prn** SABA • Cromolyn • Nedocromil • Leukotriene receptor antagonist (LTRA) • Theophylline	• Daily low dose ICS with **prn** reliever (ICS-formoterol or SABA) • **prn** low dose budesonide-formoterol **Other options:** • Low dose ICS used whenever SABA used • Leukotriene receptor antagonist (LTRA) with **prn** reliever (ICS-formoterol or SABA)
STEP 3	• Low dose ICS-LABA with **prn** SABA • Medium dose ICS with **prn** SABA • **Other options:** low dose ICS with **prn** SABA plus • LTRA or • Theophylline or • Zileuton	• Low dose ICS-LABA maintenance plus **prn** reliever (ICS-formoterol or SABA) • Low dose ICS-formoterol maintenance plus ICS-formoterol also used as reliever **Other options:** • Medium dose ICS plus **prn** reliever (ICS-formoterol or SABA) • Low dose ICS plus LTRA plus **prn** (ICS-formoterol or SABA)
STEP 4	•Medium dose ICS-LABA with **prn** SABA •**Other options**: medium dose ICS with **prn** SABA plus • LTRA or • Theophylline or • Zileuton	• Medium dose ICS-LABA as maintenance plus **prn** reliever (ICS-formoterol or SABA) **Other options:** • add on tiotropium • add on LTRA • High dose ICS plus **prn** reliever (ICS-formoterol or SABA)
STEP 5	• High dose ICS-LABA with **prn** SABA • Consider omalizumab for allergic asthma	• High dose ICS-LABA as maintenance plus **prn** reliever (ICS-formoterol or SABA) • Referral for phenotypic assessment and possible biologicals **Other options:** •Add on tiotropium •low dose oral corticosteroids
STEP 6	• High dose ICS-LABA and oral corticosteroid with **prn** SABA • Consider omalizumab	• No step 6

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T ABLE 1: GINA 2019 COMPARED TO NHLBI 2007 GUIDELINES IN PATIENTS ≥ 12 YEARS OLD

Abbreviations: ICS, inhaled corticosteroid; LTRA, Leukotriene receptor antagonist; prn , as needed; SABA, short-acting beta agonist

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