

JAMA Clinical Guidelines Synopsis

Therapy for Mild to Moderate Asthma

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GUIDELINE TITLE Global Strategy for Asthma Management and Prevention (GINA Strategy Report)**RELEASE DATE** April 26, 2021**PRIOR VERSION** April 3, 2020**DEVELOPER AND FUNDING SOURCE** The Global Initiative for Asthma (GINA)**TARGET POPULATION** Patients aged ≥ 12 y with asthma**MAJOR RECOMMENDATIONS**

- Short-acting β -agonist (SABA) monotherapy is no longer recommended (level of evidence: A).
- There is no distinction between mild-intermittent and mild-persistent asthma; inhaled corticosteroid (ICS)-containing therapies are recommended for both. ICS-formoterol is recommended as the preferred reliever inhaler (level of evidence: A).
- For treatment of moderate asthma, GINA recommends ICS-formoterol maintenance and reliever therapy in the preferred track (level of evidence: A).

Summary of the Clinical Problem

Asthma is a disease characterized by recurring, reversible airways obstruction due to underlying inflammation and bronchial hyper-responsiveness. Asthma is one of the most common chronic non-communicable diseases, affects an estimated 260 million people globally, and is associated with significant morbidity and mortality.¹ Asthma with usually mild or infrequent symptoms (50%-75% of patients with asthma) contributes to 30% to 40% of exacerbations leading to emergency care; asthma-related death may occur in persons with asthma that is usually mild.²

Characteristics of the Guideline Source

GINA is a collaboration of the National Institutes of Health, National Heart, Lung, and Blood Institute (NHLBI), and World Health Organization. The GINA Science Committee, composed of international leaders in asthma research and clinical practice, meets twice yearly to review new literature and assess its influence on management guidelines. Reviewers of published research must be neither an author nor have a declared conflict of interest (Table). GINA states that the guideline goes through extensive external review prior to publication. GINA assigns evidence ratings based on the NHLBI scale. Recommendations with evidence level A are based on data supported by multiple large randomized clinical trials (RCTs), systematic reviews, or observational studies in the target population. This guideline synopsis discusses 3 recommendations supported by level A evidence.

Evidence Base

In 2019, GINA altered its framework, recommending against the use of monotherapy with SABA. This change was motivated by evidence from retrospective studies that suggested increased use of SABA canisters, or use of SABA-only therapy, was associated with a higher risk of exacerbation and death. This risk is reduced with the addition of ICS. In a study from 2012, each additional SABA canister dispensed was associated with an 18% (OR, 1.18 [95% CI, 1.16-1.21]) increased risk of ED visit or hospitalization.³ Absolute reductions were not reported. On the other hand, in a case-control study from 2000, ICS use was associated with a decreased risk of death of 21% (adjusted rate ratio, 0.79 [95% CI, 0.65-0.97]) for every additional canister of ICS used.⁴

Most asthma guidelines, except that of the National Asthma Education and Prevention Program (NAEPP), now recommend some form of ICS as part of the treatment regimen (step 1-2) for mild asthma: either (1) ICS as needed whenever SABA is used, (2) scheduled twice-daily maintenance ICS and SABA as needed, or (3) the use of ICS-formoterol as needed. Formoterol, a long-acting β -agonist (LABA), is unique in that its rapid onset of action enables its use as an effective reliever medication. It has also been proven to be safe when used multiple times daily.

This GINA 2021 Strategy Report suggests 2 treatment tracks: "preferred track" and "alternative track." In the preferred track, ICS-formoterol is the reliever of choice. SABA relievers, along with an ICS-containing inhaler, are used in the alternative track, where track 1 is not possible, or not preferred by a patient with no exacerbations while taking their current therapy. These recommendations are based on RCTs that demonstrated lower rates of exacerbation with preferred track therapy and lower overall use of ICS.⁵⁻⁷ In 2 representative studies, cumulative ICS dose in the as-needed ICS-formoterol groups was 17% to 24% of the dose in the maintenance to ICS groups, with a 60% to 64% reduction in exacerbations (absolute risk reduction [ARR], 22%) among those taking ICS-formoterol as needed vs SABA monotherapy.^{5,6} All 3 cited RCTs used budesonide-formoterol formulations.

Table. Guideline Rating

Standard	Rating
Establishing transparency	Good
Management of conflict of interest in the Guideline Development Group (GDG)	Fair
Guideline development group (GDG) composition	Poor
Clinical practice guideline-systematic review intersection	Good
Establishing evidence foundations for, and rating strength, for each of the guideline recommendations	Good
Articulation of recommendations	Good
External review	Good
Updating	Good
Implementation Issues	Fair

For moderate and severe asthma, requiring step 3-4 and step 5 treatment, respectively, the GINA 2021 guidelines recommend ICS-formoterol inhaler maintenance and reliever therapy (MART; also referred to as single maintenance and reliever therapy [SMART]) as the preferred approach. Data suggest a decreased exacerbation risk of 32% (ARR, 6.4%) for patients with moderate asthma who used MART therapy compared with the same dose of ICS-LABA maintenance controller therapy. There is no direct evidence comparing MART and maintenance ICS plus SABA regimens for the severe asthma group.⁸

Benefits and Harms

Treatment using a single ICS-formoterol inhaler for both maintenance and rescue symptom relief provides a streamlined, effective approach for improving asthma care and also enables patients to self-titrate ICS according to symptom severity. Although the guidelines strongly advocate for the use of ICS-formoterol with robust evidence for reduced exacerbation risk, this treatment regimen may not be optimal for all patients. This led GINA to provide the "alternative track." Although ICS inhalers are safe and there was no increased risk of adverse effects among those assigned to the ICS-formoterol as-needed groups in the studies cited above, certain individuals may be more susceptible to adverse effects such as dysphonia or thrush and have difficulty tolerating ICS, compared to therapy without ICS.

Discussion

The 2020 NAEPP guidelines still recommend SABA monotherapy for step 1 asthma treatment; however, SABA alone does not address underlying airways inflammation leading to asthma pathophysiology. Convincing data to suggest reduced morbidity and mortality with ICS have led GINA to advocate for the addition of ICS in all asthma treatment plans since 2019. Evidence from multiple RCTs

supports the use of ICS-formoterol as the preferred maintenance and reliever therapy in the treatment of patients with mild or moderate asthma. Regardless of the chosen treatment track, GINA guidelines recommend careful attention be paid to ensuring that patients have ICS as part of their regimen to prevent harm caused by overreliance on SABA monotherapy. Careful assessment for alternative diagnoses, modifiable risk factors, and incorrect inhaler technique remain critical in asthma care.

Areas Needing Future Study or Ongoing Research

With a few exceptions, most studies of single maintenance and reliever therapy have used budesonide-formoterol. The guideline recommendations include other ICS-formoterol formulations; however, more data supporting this approach would be welcome. While the current literature demonstrates the advantage of ICS-formoterol as reliever therapy and MART therapy, access to and cost of these medications remain a barrier to guideline implementation.⁹ Clinician implementation remains a barrier to guideline adherence, as demonstrated by survey data from 736 primary care clinicians in Australia, Canada, China, and the Philippines, indicating that while 70.3% were aware of these guidelines, 47.4% would still consider SABA monotherapy for initial therapy of mild asthma.¹⁰ Research into ways to overcome this barrier is needed.

Associated Guidelines and Other Resources

National Asthma Education and Prevention Program (NAEPP). 2020 Focused Updates to the Asthma Management Guidelines <https://www.nhlbi.nih.gov/health-topics/all-publications-and-resources/2020-focused-updates-asthma-management-guidelines>

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