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Outpatient Management of Chronic Asthma in 2020

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Asthma is a chronic airway disease with recurrent symptoms of wheezing, chest tightness, dyspnea, and cough. Asthma is characterized by airway inflammation, airflow obstruction, and variable respiratory symptoms.[1] The 2007 Expert Panel Report-3 Guidelines for the Diagnosis and Management of Asthma[1] suggest a stepwise approach for managing asthma based on symptom severity. The stepwise approach consists of escalating or deescalating asthma therapy as needed to control symptoms and prevent adverse asthma outcomes, such as exacerbations and accelerated loss of lung function. Traditionally, chronic asthma treatments have been categorized as *relievers*, short-acting β_2-agonists (SABAs; eg, albuterol) used to acutely relieve symptoms, and *controllers*, inhaled corticosteroids (ICSs) and ICSs in combination with long-acting β_2-agonists (LABAs) used daily to prevent symptoms, reduce exacerbations, and improve lung function. Recently, this paradigm of asthma management has been challenged by evidence supporting novel approaches using conventional controller medications (**Box**).

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Box. Approaches to Asthma Management

- Low-dose daily inhaled corticosteroids improve asthma outcomes in patients with asthma regardless of asthma severity.
- Symptom-driven therapy with budesonide-formoterol reduces exacerbations and is appropriate for individuals with mild asthma, defined as intermittent asthma (symptoms <2 days per week) and mild persistent asthma (symptoms ≥2 days per week, but not daily, and normal lung function).
- In individuals with moderate persistent asthma, single maintenance and reliever therapy with low-dose budesonide-formoterol decreases exacerbation rates.
- Long-acting muscarinic antagonists, such as tiotropium, can be added to inhaled corticosteroids instead of a long-acting β_2-agonist (formoterol or salmeterol).

Current Approach to Chronic Asthma Management

Current guidelines emphasize 2 treatment goals: improved symptom control (reduced symptom frequency and nocturnal waking, as-needed SABA use, and activity limitation) and reduced risk of adverse asthma outcomes (asthma exacerbations, hospital admissions, accelerated loss of lung function, and death).

Traditionally, a distinction has been made between intermittent and persistent asthma based on the frequency of asthma symptoms, and this distinction has been used to determine appropriate treatment. For patients with asthma symptoms occurring more than 2 days per week (ie, persistent asthma), which can vary in severity, US guidelines recommend daily controller therapy with ICS, which reduces symptoms and prevents adverse outcomes. Intermittent asthma is defined as mild symptoms occurring 2 days per week or less, rare exacerbations, and normal lung function while receiving no daily controller therapy, for which US guidelines recommend as-needed SABA alone.

However, recent evidence suggests that daily controller ICS benefits all individuals with asthma, regardless of symptom frequency.[2] A post hoc analysis of the Steroid Treatment as Regular Therapy (START) study (N = 7138) showed that even in individuals with recent-onset (ie, diagnosed within the past 2 years) mild intermittent asthma, once-daily low-dose budesonide (400 µg daily or 200 µg daily if younger than 11 years) was associated with fewer emergency department visits, hospital admissions, deaths, and exacerbations requiring systemic corticosteroids; reduced decline in lung function; and improved symptom control compared with placebo plus usual asthma care (ie, SABA).[2] These findings challenge current guidelines recommending ICS only for patients with persistent asthma (ie, symptoms more than twice a week). However, poor adherence to daily ICS controller therapy is common, and this treatment strategy may be associated with poor adherence in patients with mild asthma.

New Evidence Regarding Treatment of Persistent Asthma

The single maintenance and reliever therapy (SMART) treatment approach includes use of an inhaler combining ICS and rapid-onset LABA (ie, formoterol) for both control (ie, maintenance; used daily to prevent symptoms and adverse outcomes) and for acute symptom relief. In this approach, the rapid onset of formoterol provides prompt symptom relief that lasts longer than SABA, while the ICS has anti-inflammatory properties that are introduced earlier during an episode of worsening symptoms, resulting in both symptom relief and fewer exacerbations. In a meta-analysis of 16 randomized clinical trials using SMART therapy in patients 12 years and older, SMART was associated with fewer asthma exacerbations compared with treatment that included similar or higher doses of combined ICS and LABA administered daily as controller therapy with SABA used as needed to relieve symptoms.[3] SMART was also associated with fewer asthma exacerbations compared with ICS as controller therapy and SABA as quick relief. Therefore, ICS combined with rapid-onset LABAs, such as formoterol, used as both controller and reliever therapy is a reasonable approach in patients 12 years and older with persistent asthma and is included in the most recent Global Initiative for Asthma guidelines.[4]

Two randomized trials published after the meta-analysis described above support a symptom-driven approach, using as-needed combination therapy with ICS and a rapid-onset LABA as an alternative to daily therapy. Whereas SMART evaluated combination ICS-formoterol as both daily controller and symptom-driven reliever therapy, the Symbicort Given as Needed in Mild Asthma (SYGMA) 1 and 2 trials evaluated a symptom-driven approach using combination budesonide-formoterol without the use of a daily controller treatment.[5,6] The SYGMA trials evaluated this symptom-driven approach in patients with mild asthma (ie, asthma not well controlled with SABA reliever therapy alone or asthma well controlled with an ICS for controller therapy or leukotriene receptor antagonists plus SABA as reliever therapy). In SYGMA 1,[5] patients 12 years and older (N = 3849) were randomized to receive 200 µg of budesonide and 6 µg of formoterol as needed, 0.5 mg of terbutaline as needed, or 0.5 mg of terbutaline as needed plus 200 µg of

Table. Asthma Treatment Options Based on Asthma Severity

Asthma Severity	Current Treatment Options
Mild asthma (intermittent asthma [symptoms <2 d per week] and mild persistent asthma [symptoms ≥2 d per week, but not daily, and normal lung function])	Symptom-driven approach with as-needed low-dose budesonide-formoterol or low-dose daily ICS
Moderate asthma (moderate persistent asthma [daily asthma symptoms and nocturnal awakenings more than once per week])	SMART approach with low-dose budesonide-formoterol used as both daily controller and as-needed reliever therapy
Severe asthma (severe persistent asthma [symptoms throughout the day and nightly awakenings due to asthma])	Medium- to high-dose ICS-LABA and referral to asthma specialist for add-on therapy (eg, LAMA, anti-IgE)

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; SMART, single maintenance and reliever therapy.

budesonide twice daily as controller therapy. As-needed budesonide-formoterol was superior to as-needed terbutaline, but was inferior to daily budesonide controller therapy combined with as-needed terbutaline regarding the outcome of asthma symptom control. Exacerbation rates were similar between the 2 budesonide groups, but the budesonide-formoterol group had significantly lower glucocorticoid exposure than the group receiving budesonide controller therapy combined with as-needed terbutaline. SYGMA 2 evaluated as-needed budesonide-formoterol compared with budesonide controller therapy. Patients 12 years and older (N = 4215) were randomized to receive either 200 µg of budesonide and 6 µg of formoterol as needed or twice-daily 200 µg of budesonide and 0.5 mg of terbutaline as needed. As-needed budesonide-formoterol was noninferior to twice-daily budesonide controller therapy for the outcome of asthma exacerbations, but did not meet noninferiority criteria for the outcome of symptom control.[6] Exacerbation rates were similar despite significantly less exposure to glucocorticoids in the budesonide-formoterol group. Based on results of these trials, symptom-based therapy with budesonide-formoterol may be suitable for patients with mild asthma (ie, intermittent and mild persistent asthma). This symptom-based approach (**Table**) is included in Global Initiative for Asthma guidelines for asthma management.[4]

Both SMART and symptom-driven therapy in the SYGMA 1 and 2 trials evaluated combination ICS-LABA therapy. In 2010, the US Food and Drug Administration (FDA) placed a black box warning on medications containing LABAs.[7,8] This warning was removed in December 2017 after results of 4 large FDA-mandated postmarketing trials showed that combination therapy with ICS-LABA did not significantly increase asthma-related hospitalization, intubation, or death compared with ICS alone, and that combination therapy resulted in fewer asthma exacerbations.[9] Most studies of SMART and symptom-driven as-needed therapy evaluated budesonide combined with rapid-onset LABA (ie, formoterol). Currently, the FDA product labeling for budesonide-formoterol does not recommend this use; however, US clinicians should be educated about these effective novel therapies.

For persistent asthma, defined as symptoms more than twice a week or more than 2 asthma-related nocturnal awakenings per month, there are few alternatives to ICS and ICS-LABA combination therapy. Leukotriene receptor antagonists, theophylline, oral corticosteroids, and omalizumab are the only guideline-based alternatives. However, the long-acting muscarinic antagonist (LAMA) tiotropium has been shown to be effective as add-on controller therapy for individuals with persistent asthma. A systematic review and meta-analysis showed that adding LAMA to ICS therapy was associated with reduced asthma exacerbations compared with placebo in patients older than 12 years with uncontrolled, persistent asthma.[10] However, adding LAMA, LABA, and combined LABA-LAMA to ICS therapy had similar rates of exacerbation. Add-on LAMA therapy may be an alternative effective controller therapy for uncontrolled, persistent asthma. In the United States, the tiotropium soft-mist inhaler is the only FDA-approved LAMA for asthma; trials of other LAMAs for managing asthma are under way.

Conclusions

Asthma is a chronic inflammatory disease that requires long-term monitoring and therapy. Recent evidence has identified more effective alternatives to traditional asthma therapy.

ARTICLE INFORMATION

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