Medication Regimens for Managing Stable Asthma

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Guideline-based management of asthma was developed as a means of standardizing asthma therapies and of improving outcomes. The National Asthma Education and Prevention Program and the Global Initiative for Asthma guidelines provide recommendations to care providers about the routine management of asthma. There has been rapid development of new therapies for asthma, specifically with the advent of new drug delivery devices and biologic therapies for severe asthma. We are increasingly recognizing that asthma is a heterogeneous disease with a diverse underlying pathophysiology, and therefore, it is imperative for care providers to begin to understand asthma phenotypes and endotypes, and the implications of these classifications on management, especially of severe refractory asthma. This article serves as a review of guideline-based therapy for asthma and includes updates on alternative therapies, new approaches that use previously recognized therapies, and special populations with asthma. Key words: asthma; management; phenotypes; guidelines. [Respir Care 2018;63(6):759–772. © 2018 Daedalus Enterprises]

Introduction

Asthma is a heterogeneous disease that is characterized by both inflammation and airways hyper-responsiveness. Asthma affects millions of adults and children worldwide and is associated with a significant degree of morbidity. Guideline-based management of asthma has been recommended since the 1990s as a means of standardizing asthma treatment across the age spectrum and

as a way of summarizing the best available evidence on the management of asthma. The National Asthma Education and Prevention Program¹ (NAEPP) and the Global Initiative for Asthma² (GINA) guidelines are meant to empower care providers with tools to help manage asthma, with specific recommendations about selecting initial therapies, systematically assessing response, and adjusting therapies based on the individual response to medications.

The NAEPP guidelines¹ were last updated in 2007 and included a key change in asthma management priorities. The NAEPP 2007 guidelines¹ shifted from a focus on severity-based asthma treatment recommendations to one that is focused on achieving optimal asthma control regardless of underlying severity. Asthma severity is an inherent feature of the disease, and there has been increased recognition that severity cannot always be altered; however, asthma control can be optimized regardless of the underlying severity of disease. Per the NAEPP guidelines,¹ good control for patients >12 y old includes the following: asthma symptoms ≤ 2 days/wk, nighttime awakenings ≤ 2 times a month, short-acting β_2 agonist (SABA) use ≤ 2 days/wk, no interference with normal activity, and FEV₁ of $\geq 80\%$ predicted.

The current guidelines^{1,2} recommend systematic approaches to determining the degree of asthma symptoms and then assessing impairments caused by these symptoms with standardized questionnaires such as the Asthma Control Test and the Asthma Control Questionnaire. These instruments can be administered during clinician visits, and adjustments in therapy are made based on the degree to which the individual patient's asthma is controlled or uncontrolled. The GINA guidelines² (2017) included the addition of newer asthma therapies that were not in the previous guidelines, including the use of tiotropium and anti-interleukin-5 targeted therapies. Both guidelines are consistent in the recommendation that corticosteroid-based anti-inflammatory therapies are the baseline treatment for all patients with asthma, with the addition of bronchodilators (both short acting and long acting), leukotriene antagonists, and targeted biologic therapies as adjunctive therapies if asthma control is not achieved.^{1,2} This paper reviews current recommendations and approaches to care per the current guidelines, and suggests that treatment, both now and in the future, should also be driven by consideration of phenotypes and endotypes associated with an individual's

asthma. These classifications may significantly impact the management of asthma, especially refractory asthma.^{1,2}

Asthma Phenotypes and Endotypes

Asthma is a heterogeneous disease composed of a combination of symptoms, inflammation, and lung function impairments. However, it is being increasingly recognized that a variety of pathophysiologic mechanisms lead to the manifestation of asthma symptoms. Phenotypes are defined as the observable properties of an organism that are produced by the interaction of genotype and the environment. Endotype is proposed to be a subtype of a condition defined by a distinct pathophysiologic mechanism.³ For example, eosinophilic asthma is the phenotype but the endotype would be late onset eosinophilic asthma driven by interleukin-5. The primary inflammatory mediator of asthma was previously thought to be underlying allergic and eosinophilic inflammation, and led to the recommendation that inhaled steroids should be the cornerstone of therapy in persistent asthma.

We now understand that a large proportion of patients with asthma (up to 50% of patients with mild-to-moderate asthma) do not have underlying eosinophilic inflammation, which makes it unlikely that a response to inhaled steroids will occur.⁴⁻⁶ This indicates that a significant number of patients would benefit more from initial therapy with bronchodilators, such as long acting muscarinic antagonists monotherapy, or by using alternative anti-inflammatory therapies, such as theophylline, roflumilast, or leukotriene modifiers. Although, the evidence that supports alternative approaches is mounting, it is too early to make changes to the asthma guidelines. The fact that patients may receive therapies that are both expensive and highly unlikely to be beneficial underscores the importance of correctly identifying asthma phenotypes, particularly in severe asthma when targeted therapies can be administered.

The key barrier to correct identification of asthma phenotypes and endotypes in clinical settings is the inability to access a readily available clinical test that accurately categorizes the type of inflammation present in the lungs of patients with asthma. Sputum remains the accepted standard to identify the presence of eosinophils and neutrophils in the lungs of patients with asthma, but, with few exceptions, sputum testing remains a research tool, and many centers do not have the capability to perform sputum differential cell counts in patients with asthma as a means of guiding therapy. Until these challenges can be addressed and further evidence to guide medical decision-making can be accumulated, there is little chance that personalized medicine in asthma management will be fully realized. Alternative approaches to help identify phenotypes and endotypes of asthma are being developed, including the use

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Fig. 1. National Asthma Education and Prevention Program stepwise approach to managing asthma in patients >12 y old. ICS = inhaled corticosteroid; LABA = long-acting β agonist; SABA = short-acting β agonist; LTRA = leukotriene receptor antagonist; PRN = prescribed as needed. From Reference 1, with permission.

of sputum-based proteomics; nasal brushings; transcriptomics; and surrogate measurements of inflammation, such as the fraction of exhaled nitric oxide, blood eosinophils, and serum immunoglobulin E levels. Most of these markers require additional validation before being widely used. The closest we have come to personalized medicine in asthma is in severe asthma in which targeted biologic therapies are administered based on serum immunoglobulin E (omalizumab) and peripheral eosinophils (reslizumab, mepolizumab, and benralizumab). Phenotyping is critical in the management of severe asthma, and clinicians should strongly consider incorporating this into routine practice at this time.^{7,8}

Review of a Stepwise Approach for Managing Stable Asthma

Both the NAEPP and GINA guidelines^{1,2} rely on a stepwise approach to managing asthma symptoms. The NAEPP guidelines¹ include 6 steps based on asthma severity, which is defined on the basis of lung function impairments, exacerbations, and medication utilization (Fig. 1). Step 1 asthma is mild and intermittent, and typically requires “as needed” bronchodilator therapy; step 2 asthma is encompassed by more persistent symptoms but contin-

ues to be associated with normal lung function.¹ The persistent symptoms require the addition of daily therapies aimed at decreasing these symptoms, which include low doses of inhaled steroids or theophylline or leukotriene antagonists.¹ As the steps increase, the patient’s asthma is characterized by more persistent symptoms and abnormalities in lung function, with an increased likelihood of having exacerbations, nighttime symptoms, daily symptoms, and use of bronchodilator therapies for rescue (steps 3, 4).¹

As asthma worsens, inhaled steroid doses are increased and the addition of maintenance bronchodilator therapies is encouraged. In the NAEPP guidelines,¹ the bronchodilator that is recommended is long-acting β agonist (LABA), although there is a significant amount of evidence available to support the use of tiotropium as an alternative to LABA or as adjunctive therapy. The data on tiotropium will be discussed further in long acting muscarinic antagonists (long acting anticholinergic) section of this paper. Steps 5 and 6 asthma are severe persistent and often refractory to inhaled steroids and bronchodilators in isolation.¹ These patients have the most significant burden of disease in asthma and also have the highest risk of poor outcomes. In these patients, whose asthma is not con-

Fig. 2. Global Initiative for Asthma stepwise approach to control asthma symptoms and reduce risk. ICS = inhaled corticosteroid; LABA = long-acting β agonist; OCS = oral corticosteroid; SLIT = sublingual immunotherapy; HDM = house dust mite. From Reference 2, with permission.

trolled on high-dose inhaled steroids and LABA, there are several alternatives, including the use of tiotropium, biologic therapies that target interleukin-5 and immunoglobulin E, and bronchial thermoplasty.

The GINA guidelines² use a similar stepwise approach to asthma management, and there are 5 steps included in the recommendations (Fig. 2). Step 1 patients require intermittent therapy with consideration for the addition of daily maintenance therapy if there are persistent symptoms that remain uncontrolled; in step 2 therapy, the addition of maintenance inhaled steroids is important in achieving asthma control.² Steps 3 and 4 require the addition of maintenance bronchodilators, with increasing doses of inhaled steroids, and step 5 encompasses severe asthma, and these patients may require oral corticosteroids and biologic therapies, in addition to their

inhaled combination therapies.² Unlike the NAEPP guidelines,¹ the GINA guidelines² include the use of tiotropium in steps 4 and 5 asthma as a means of achieving asthma control. In addition, use of inhaled steroids and/or LABA therapy for rescue is included. The GINA guidelines² recommend a continuum that is encompassed by assessing patients, adjusting therapies, reviewing response, and reassessing patients to determine if further adjustments are required. In addition, adherence, medication tolerance, management of comorbid conditions, and contributing factors are recommended. Interestingly, the latest GINA guidelines² include the use of sublingual immunotherapy for a target population of patients with allergic rhinitis, exacerbations, FEV₁ > 70% predicted and house dust mite allergen sensitivity (Fig. 2).

Fig. 3. Proposed personalized approach to asthma therapy. SABA = short-acting β agonist; ICS = inhaled corticosteroid; LABA = long-acting β agonist; LTRA = leukotriene receptor antagonist.

Assessment of Contributing Factors

A well-rounded approach to mitigating contributing factors must be included in the management of patients with asthma if optimal control is to be achieved. It is imperative to assess comorbidities, such as gastroesophageal reflux disease, allergic rhinitis and atopy, sinus disease, sleep apnea, vocal cord dysfunction, and obesity, throughout all the steps of asthma management. In addition, management of environmental exposures and/or triggers, tobacco use, and irritants is essential.

Asthma Follow-up, Assessing Adherence, and Education Are Essential to Asthma Outcomes

The guidelines recommend assessing patients by obtaining baseline lung function measurements and establishing the level of asthma control, managing contributing factors and comorbid conditions, and then making adjustments to therapy if indicated.^{1,2} Patients should then be followed up at 3-month intervals to determine if asthma control has been achieved and if there are opportunities to either further optimize therapy or to step-down treatment. The ultimate goal is to determine the right amount of medication required to achieve control without exposing patients to the risks associated with the use of unnecessarily high doses or excessive numbers of medication.

An additional key issue that must be addressed is asthma education and the improvement of health literacy in patients with asthma. Practitioners must ensure that patients are adherent to asthma therapies, and it is imperative not only to identify non-adherence but to address the issues

that are causing non-adherence to improve adherence and thus asthma outcomes. The complex issues of adherence are addressed in an article Titled: Patient Adherence Issues in this edition of the journal.

As the landscape of inhaled therapies and comfort level regarding devices used to deliver medications becomes more complex, the gaps in knowledge of patients, providers, and care teams is an added concern. There currently are multiple devices on the market, including the Respimat (Boehringer Ingelheim, Germany), dry powder inhaler, pressurized metered-dose inhaler, Diskus and Ellipta devices, each with a unique actuation, priming, and administration approach. Improper technique when using these devices is a common issue and leads to poor drug delivery and to predictably poor treatment response rates. Advances must be made in teaching patients how to correctly use the devices prescribed to them to improve asthma outcomes. It is often challenging for a busy practitioner to address inhaler teaching, but this must be a key component of any asthma management program.

New Approaches to Managing Stable Asthma

Intermittent Dosing of Controller Therapies in Asthma

The guidelines recommend regular rather than intermittent use of long-term controllers (inhaled steroids and long-acting bronchodilators) in patients with persistent asthma.^{1,2} However, there has been growing interest in intermittent dosing of controller medications. In a recent study, the intermittent use of short-acting albuterol combined with

inhaled steroids was associated with similar rates of asthma exacerbations as regular use of beclomethasone or combination therapy (albuterol-beclomethasone) in subjects with mild persistent asthma.⁹ Furthermore, in this study, regular use of inhaled steroid therapy had no additive benefits over intermittent “as needed” use with regard to the reduction of asthma exacerbations, which required oral steroids in adults and children with persistent asthma.¹⁰ Regular use of inhaled steroids resulted in improvements in asthma control and symptom-free days. However, it did not confer additional benefits with regard to FEV₁, quality of life, airway hyper-reactivity, adverse events, hospitalizations, and emergency department visits for asthma.¹⁰ Based on the available data, clinicians can consider the use of intermittent inhaled steroid or combination therapies in carefully selected patients with mild persistent asthma.

Alternative Medications for the Management of Asthma

The use of bronchodilator-based and inhaled corticosteroid (ICS) based therapies for asthma are reviewed in other articles Bronchodilators and Inhaled and Systemic Corticosteroids in this issue of the Journal. There are several other new promising therapies, including anticholinergic and alternative anti-inflammatory medications that are not currently widely used to treat asthma.

Long Acting Muscarinic Antagonists (Long-Acting Anticholinergic): Tiotropium and Umeclidinium

Tiotropium is an anticholinergic drug that targets the muscarinic receptors and results in bronchodilatory effects in the lungs of patients with asthma and COPD. Tiotropium has been shown to improve FEV₁ in addition to ICS or as an additive therapy to inhaled steroids and LABA combination therapy^{11,12} (see Table 1 for multiple other studies). In addition, tiotropium increases the time to first exacerbation and decreases severe exacerbations when added on to combination therapy in severe asthma.¹³ In African-American subjects, tiotropium was non-inferior to LABAs and did not demonstrate any differences in safety measures and adverse events.¹⁴ The initial studies used the HandiHaler (Boehringer Ingelheim, Germany) device, and more recent trials included the Respimat device, which was shown to be efficacious in improving FEV₁ in children, adolescents, and adults with asthma.¹⁵⁻¹⁷ The FDA cleared the use of the Spiriva Respimat (Boehringer Ingelheim, Germany) for treatment of adult and pediatric patients with asthma. The use of tiotropium as monotherapy in asthma is an ongoing area of investigation. Tiotropium has been included in the GINA guidelines² as an alternate add-on treatment option for steps 4 and 5 in adult patients with a history of exacerbations and will undoubtedly be

considered for addition to future revisions of the NAEPP guidelines.¹

Umeclidinium, a newer addition to this class of drugs, has been studied as both monotherapy and add-on therapy to inhaled steroids in asthma. There was a modest improvement in trough FEV₁ in subjects who were steroid naive and treated with umeclidinium monotherapy¹⁸ and umeclidinium resulted in improvements in FEV₁ in addition to inhaled steroids when compared with inhaled steroids alone, an effect that was reportedly more prominent in those subjects with fixed obstruction.¹⁹ Studies to determine the role of umeclidinium and glycopyrrolate in asthma are ongoing, and it is still unclear about how these medications will be incorporated in the future. Umeclidinium is currently not FDA-cleared for asthma.

Phosphodiesterase-4 Inhibitor: Roflumilast

Roflumilast is a phosphodiesterase-4 inhibitor that has both bronchodilatory and anti-inflammatory effects, and is currently cleared by the FDA for the treatment of adult patients with COPD associated with chronic bronchitis and a history of frequent exacerbations. Roflumilast has been studied in asthma as monotherapy as well as add-on therapy to inhaled steroids (Table 2 for multiple studies). There are studies that demonstrated non-inferiority when compared with inhaled steroids with improvements in FEV₁ in patients with mild-to-moderate persistent asthma. In addition, roflumilast results in increased time to first exacerbations and has some effects on improvement in asthma quality of life and symptoms. The drug is associated with nausea and gastrointestinal adverse effects that are transient and improve with time. In addition, roflumilast results in weight loss in some patients. The potential weight loss and possibility of associated improvements in asthma control in those who are obese may be a desirable effect of roflumilast therapy in this subpopulation of patients with asthma.²⁰ However, in a large clinical trial in asthma, roflumilast did not result in significant changes in weight.²¹ Although roflumilast is a promising therapy for asthma, phase 3 studies have not been completed and the drug is currently not cleared by the FDA for treatment of asthma. The main limitation has been the vexing adverse effects of therapy that must be balanced with the potential benefits and weighed against better tolerated alternatives.

5-Lipoxygenase Antagonists: Zileuton

Montelukast (Singulair, Merck, Kenilworth, NJ) is a more commonly used leukotriene receptor antagonist cleared by the FDA for treatment of asthma in patients ages ≥12 months and is considered step 2 therapy in the NAEPP guidelines¹ with anti-inflammatory properties. The less-familiar drug, zileuton is a 5-lipoxygenase inhibitor

Table 1. Review of Clinical Trials Assessing Efficacy of Tiotropium in Asthma

Clinical Trial With Tiotropium	Comparators	Results	Other Considerations
Peters et al ⁵⁷	Tiotropium vs formoterol add-on therapy in asthma (NAEPP Step 3)	Tiotropium was non-inferior to salmeterol and superior to doubling the dose of ICS	Improved peak expiratory flow improved proportion of ACDs; improved FEV ₁ ; decreased daily symptoms
Kerstjens et al ⁵⁸	Tiotropium as an add-on to ICS/LABA (GINA/NAEPP Step 5)	Tiotropium significantly improved lung function in severe uncontrolled asthma	Significant improvement in FEV ₁ (86 mL for a 5-μg dose and 113 mL for a 10-μg dose); no significant difference in QOL measurements
Bateman et al ⁵⁹	Tiotropium vs salmeterol add-on therapy in patients uncontrolled on ICS with B16-Arg/Arg mutation (Bateman NAEPP Step 3,4)	Tiotropium was non-inferior to salmeterol in maintaining improved lung function when added to ICS	Improvements in peak expiratory flows and patient-reported outcomes
Kerstjens et al ¹³	Tiotropium as an add-on to ICS/LABA (step 5)	Tiotropium significantly increased time to the first exacerbation and FEV ₁	Overall 21% reduction in severe exacerbation (hazard ratio 0.79, <i>P</i> = .03); significant increase in FEV ₁
Beeh et al ¹⁵	Tiotropium add-on to the medium-dose ICS in patients with symptoms and with moderate persistent asthma	Significant improvement in FEV ₁	Mean 188 mL improvement in FEV ₁ (the maximal improvement was noted with the 5-μg dose)
Vogelberg et al ¹⁶	Tiotropium Respimat (1.25 μg, 2.5 μg, and 5 μg) add-on to ICS in adolescents symptomatic when on ICS	Significant improvement in FEV ₁ with a 2.5-μg and 5-μg dose	Similar adverse events across dose ranges, well tolerated
Kerstjens et al ⁶⁰	Tiotropium Respimat or salmeterol as add-on therapy to ICS in moderate persistent asthma	Significant improvements in FEV ₁ with both tiotropium and salmeterol	ACQ7 response improved in tiotropium and salmeterol compared with placebo
Vogelberg et al ¹⁷	Dose-ranging tiotropium Respimat therapy in children 6–11 y old with persistent symptoms while on inhaled steroids with or without leukotriene antagonists	Significant improvements in FEV ₁ 272 mL with a 5-μg dose, 290 mL with a 2.5-μg dose, 261 mL with a 1.25-μg dose in comparison with placebo	No significant safety events were reported
Wechsler et al ¹⁴	Anticholinergic vs LABA add-on therapy to inhaled steroids in black adults with asthma	No difference in LABA + ICS vs tiotropium + ICS in time to first exacerbation; no differences in FEV ₁ , QOL measurements, ACQ, or responses based on the Arg16Gly alleles	Addition of tiotropium to ICS is non-inferior to the addition of salmeterol in black adults with moderate asthma
Paggiaro et al ⁶¹	Effect of tiotropium in symptomatic asthma on low- to medium-dose inhaled steroids	Tiotropium 2.5-μg and 5-μg doses were superior to placebo in increasing FEV ₁	Significant improvement in FEV ₁ after 12 wk of therapy
Hamelmann et al ⁶²	Tiotropium add-on in adolescents (age 12–17 y) with moderate asthma, on ICS with or without leukotriene antagonist for 52 wk	Improvements in FEV ₁ with 2.5-μg and 5-μg doses at 24 wk	Trend toward improvement in asthma control and health-related QOL measures

ICS = inhaled corticosteroid
ACD = asthma control day
LABA = long-acting β agonist
ACQ7 = Asthma Control Questionnaire, 7-point scale
QOL = quality of life

Table 2. Review of Clinical Trials Assessing the Efficacy of Roflumilast in Asthma

Clinical Trial With Roflumilast	Comparators	Results	Other Considerations
Bousquet et al ⁶³	Roflumilast 500 µg once daily compared with inhaled beclomethasone 200 µg twice daily for 12 wk in patients with asthma (499 subjects)	Roflumilast and beclomethasone significantly increased FEV ₁ (270 mL and 320 mL, respectively); significant improvements in FVC with both therapies; small improvements in asthma symptom scores and rescue medication use	No significant differences existed between roflumilast and beclomethasone effects in asthma
Bateman et al ⁶⁵	Roflumilast 100-, 250-, and 500-µg doses in patients with asthma (12-wk dose-ranging study, 693 subjects)	Significant improvements in FEV ₁ compared with baseline for the three doses of roflumilast 100-, 250- and 500 µg resulted in increases of 260, 300 and 400 mL respectively; significant improvements in peak flow	Roflumilast was well tolerated with all doses with mild-to-moderate adverse events that were transient in nature
Bateman et al ⁶⁴	Analysis of seven phase 2 or 3 studies comparing roflumilast with beclomethasone and montelukast in asthma (3,802 subjects)	Roflumilast was non-inferior to beclomethasone and montelukast with regard to improvement in FEV ₁ , asthma symptom scores, or rescue medication use	Roflumilast improves FEV ₁ and asthma symptoms
Meltzer et al ⁶⁶	Analysis of data from 10 studies with 4,873 subjects who received roflumilast vs placebo either alone or as add-on therapy to ICS (2 studies: fluticasone and beclomethasone)	Roflumilast increased FEV ₁ in 9/10 studies with significant improvements reported in 3 studies; addition of roflumilast to ICS resulted in increases in FEV ₁	Roflumilast improves FEV ₁ ; roflumilast increased time to first exacerbation in comparison with placebo; most common adverse events were gastrointestinal in nature (nausea and diarrhea) with minimal changes in weight (Chervinsky <i>P</i> et al 2015)(16)
Bateman et al ⁶⁷	Roflumilast combined with montelukast vs montelukast alone as an add-on in patients with moderate-to-severe asthma on at least medium dose ICS + LABA (64 patients)	Addition of roflumilast + montelukast resulted in a minimally clinically significant difference in FEV ₁ compared with montelukast + placebo; improvements in patient-related outcomes were noted	The most common adverse event was headache; no changes in sputum or blood neutrophils and eosinophils

ICS = inhaled corticosteroid

LABA = long-acting β agonist

that significantly decreases the production of leukotrienes. It has effects on both lung function and inflammation, which result in significant improvements in FEV₁, asthma quality of life, and exacerbations (see Table 3 for multiple studies). Furthermore, zileuton decreases inflammation in the lungs of patients with asthma. The drug has been cleared by the FDA for the treatment of asthma in persons ≥ 12 y and is included in the NAEPP guidelines¹ for treatment of patients with step 3 or higher asthma. Zileuton is associated with a small risk of causing elevated liver function test results; this is more likely to occur within the first 3 months of treatment. Elevations in liver function test results are transient and resolve with discontinuation of therapy; therefore, it is recommended that liver function be monitored on a regular basis after the initiation of zileuton therapy.²² In spite of the addition of zileuton into the guidelines, its widespread use has been hampered by concerns over liver-related adverse effects and short half-life that require frequent dosing.²³ In addition, poor insurance coverage for the medication coupled with its high costs resulted in decreased utilization.

Macrolide Antibiotic: Azithromycin

Azithromycin is an azalide antibiotic, closely related to macrolides, that possesses antimicrobial and immunomodulatory effects, and there has been growing interest in using it as a therapy in severe persistent asthma. There have been mixed results from clinical trials that assessed the use of macrolides as adjunctive therapy in asthma with a recent study that demonstrated no effects in asthma overall but a subgroup analysis indicated that perhaps macrolides may still have effects on exacerbation reduction in patients with severe non-eosinophilic asthma.^{24,25} There are conflicting results with regard to the effect of azithromycin on asthma exacerbations. Although azithromycin reportedly decreased the number of exacerbations and improved quality of life in one study,²⁶ therapy did not decrease the duration of acute symptoms or the time to resolution of acute asthma symptoms. In addition, in a separate exacerbation study (AZALEA), azithromycin did not result in improvement in asthma control, quality of life, or lung function.²⁷ There is uncertainty about the long-term role of macrolides in asthma, unlike in COPD in which these therapies demonstrated efficacy in reducing exacerbations in select patients with COPD with frequent exacerbations.²⁸ A recent meta-analysis demonstrated an increased risk of hearing loss and antimicrobial resistance in subjects with chronic lung disease treated with long-term macrolides, and, therefore, these issues need to be taken into consideration as the role of macrolides in asthma is defined in the future.²⁹

Special Population Considerations

Asthma COPD Overlap

Asthma and COPD were previously thought to be 2 distinct diseases without any significant overlap. However, recently, a new phenomenon was described, and the term asthma COPD overlap was coined to encompass a disease in which these disorders may co-exist, with features of both being present.³⁰ Asthma COPD overlap accounts for approximately 15–25% of obstructive airway diseases and is associated with worse outcomes than either asthma or COPD alone.^{31–35} Patients with asthma COPD overlap have an increased risk of exacerbations; pharmacologic implications exist when determining the appropriate therapies for these patients.³⁶

The exact definition of asthma COPD overlap continues to be a topic of ongoing discussion,^{37–40} and the origin of the disease may be asthma with the subsequent development of chronic obstruction or COPD with allergic features.^{41,42} Patients with asthma and with a lack of reversible air flow obstruction and with a significant tobacco use history are excluded from asthma clinical trials, which thus limits the generalizability of therapies cleared by the FDA for the treatment of asthma to this unique group of patients. This holds true for patients with COPD with any history of asthma or allergic disease and reversibility. In 2014, the GINA guidelines² first addressed the issue of asthma COPD overlap, stressing the importance of assessing risk factors for exacerbations, including nonpharmacologic therapies and strategies in this subgroup of patients.⁴³

Therapeutic approaches in patients with asthma COPD overlap require an increased ability to accurately define the potential underlying mechanisms of inflammation (endotypes) that can allow for targeted therapies.⁴⁴ Biomarkers are desperately needed to help characterize these phenotypes and to deal with the inherent inflammatory heterogeneity that is present in asthma COPD overlap.⁴⁵ For instance, some patients with COPD predominantly have eosinophilic inflammation and, as such, should be treated with inhaled steroids rather than with bronchodilators alone, contrary to the current recommended guidelines for the treatment of COPD (the Global Initiative for Chronic Obstructive Lung Disease).^{46,47}

Tobacco cessation and vaccinations are cornerstones of therapy in asthma COPD overlap, and the use of ICS and bronchodilators is important. Further research is required to determine the role of biologic medications in asthma COPD overlap.⁴⁸ The impact of asthma COPD overlap on asthma and COPD outcomes will continue to be an area of active investigation, and clinical trials are needed to help define the most appropriate interventions for these patients who bear a more significant burden of disease.

Table 3. Review of Clinical Trials Assessing the Efficacy of Zileuton in the Treatment of Asthma

Clinical Trial With Zileuton (Zyflo, Chiesi, Cary, NC)	Comparators	Outcomes	Other Considerations
Israal et al ⁶⁸	Zileuton 400 µg and 600 µg vs placebo in mild-to-moderate asthma on β agonist only; <i>N</i> = 401, 13-wk treatment period	Significant reduction in asthma exacerbations that required corticosteroid therapy, RR 2.6 (600-µg dose); significant increase in FEV ₁ and asthma QOL assessments (600-µg dose)	Elevated liver function tests in some patients that resolved with discontinuation of drug
Liu et al ⁶⁹	Zileuton (400 µg, 600 µg vs placebo; <i>N</i> = 373) in patients with asthma with regular use of β agonist alone	Significant improvement in FEV ₁ with both zileuton doses compared with placebo; significant decrease in nocturnal symptoms, β agonist use, and proportion that required steroid rescue medication decreased by 62%	Similar adverse events across groups
Schwartz et al ⁷⁰	Zileuton vs theophylline in mild-to-moderate asthma (<i>N</i> = 471)	No significant difference between zileuton and theophylline on asthma outcomes, including FEV ₁ , peak flow β agonist use, and QOL; both zileuton and theophylline improved these outcomes when compared with placebo	
Lazarus et al ⁷¹	Open label study to assess efficacy of zileuton when added to usual asthma care vs usual care alone (<i>N</i> = 2,947)	Zileuton resulted in significantly lower steroid rescues, less emergency care, fewer hospitalizations, and greater increases in FEV ₁ ; significant improvement in asthma symptoms	Increased risk of elevated LFTs (4.6% in zileuton group vs 1.1% in the usual care group); resolved with discontinuation of therapy
O'Connor et al ⁷²	Zileuton added to low-dose inhaled betamethasone versus doubling the dose of betamethasone in moderate-to-severe persistent asthma (<i>N</i> = 388, 12-wk treatment period)	Adding zileuton showed no significant difference in FEV ₁ compared with doubling ICS dose; all 3 groups had significant improvements in FEV ₁ compared with baseline	No significant changes in salbutamol use, acute asthma exacerbations, and requirement for steroids
Wenzel et al ⁷³	Zileuton CR added to usual care vs placebo (<i>N</i> = 926) in patients with moderate asthma	Improvements in peak expiratory flow with zileuton compared with placebo	Increased abnormalities in LFTs improved within 21 days of discontinuing therapy
Nelson et al ²²	Zileuton CR compared with placebo in moderate asthma treated with β agonist only (<i>N</i> = 613, 12-wk study)	Improvements in FEV ₁ noted within 2 wk and sustained throughout (390 mL in the zileuton group); decline in β agonist use and exacerbations	Elevations in liver function tests in 2.5% zileuton group and 0.5% placebo, resolved with discontinuation of zileuton therapy

RR = relative risk
QOL = quality of life
ICS = inhaled corticosteroid
CR = controlled release
LFT =

African-American Patients and Safety of LABAs

LABAs are a mainstay of asthma therapy for patients with persistent asthma who remain uncontrolled on inhaled steroid monotherapy. In 2006, the SMART trial was published and raised concern about a potential for increased adverse events in patients of African descent who had asthma.^{43,49} The SMART trial included 26,355 subjects who received salmeterol or placebo for the management of asthma.⁴⁹ In interim analyses, the study was terminated secondary to a small but statistically significant increase in overall mortality with regular use of salmeterol. Furthermore, there were increased respiratory-related events and asthma-related deaths with salmeterol that seemed to occur predominantly in African-American subjects, who represented 18% of the study population.⁴⁹

Meta-analysis confirmed the significant benefits of LABA therapy in asthma; however, safety concerns remained.⁵⁰ In 2007, the FDA issued a black box warning on any drug formulations that contains LABAs that mandated against using these medications as monotherapy without concomitant inhaled steroids.⁵¹ In addition, safety studies were mandated to determine if, in fact, there were residual safety concerns when LABA used in combination with inhaled steroids was prescribed to African-American patients.⁵²

Since the SMART trial,⁴⁹ multiple large clinical trials have been completed that demonstrated efficacy of LABAs in combination with ICS in decreasing exacerbations⁵³ and asthma control in African-Americans with an acceptable safety profile and no indication of increased mortality.^{14,54,55} Based on these studies, the FDA recently removed the black box warnings on LABAs.⁵⁶ What is yet undetermined is whether increased doses of inhaled steroids will be superior to adding on LABAs in African-Americans, and this is an area of ongoing investigation.

Summary Recommendations for Clinicians Providing Care to Patients With Stable Asthma

Clinicians who care for patients with asthma need to be increasingly aware of the implications of phenotypes and endotypes on disease activity and response to therapy. Increased recognition of the underlying pathophysiology that drives a patient's symptoms and level of control can help guide decision-making regarding asthma therapies in a more tailored way (Fig. 3). Comorbid conditions and contributing factors should be taken into consideration and mitigated. A structured approach to the management of patients with asthma in the clinical setting should be developed, including the use of standardized questionnaires to routinely assess the 2 important domains: risk (exacerbations) and control. This approach allows clinicians to determine if adjustments to therapy are warranted. Fur-

thermore, it is essential to discern whether patients have been non-adherent with their asthma therapies and to identify and target reasons for non-adherence. Asthma education is an essential part of care delivery, particularly given the inhaler confusion that exists and is worsening with the ever-expanding number of devices that are on the market. Ultimately, the goal is to decrease exacerbations, optimize lung function, and decrease symptoms that negatively impact each patient's quality of life.

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Discussion

Williams: Very nice summary. I don't think the final answer will be coming out in terms of what the next NIH Expert Panel Report version looks like, but I think there is a good summary of the evidence coming from the Agency for Healthcare Research and Quality. Some of the things we can expect, such as the issue of the use of inhaled steroids alone versus inhaled steroids plus as needed steroids when necessary reportedly showed no benefit. They feel comfortable and, thus, they recommend inhaled steroids alone versus intermittent steroids for those

≥12 y old but not for 5-11 y olds because of incomplete evidence. I'm not quite sure I understand what the concern is about triple therapy versus combination therapy, you feel like an inhaled steroid with a LABA is still going to be available to the patient. Is that correct?

Lugogo: Yes.

Williams: Maybe that there's just going to be some confusion about it?

Lugogo: For example, there are patients who do very well with tiotropium, and they like the delivery with

the Respimat device but are not doing as well when they combine tiotropium with a fixed combination ICS/LABA. In some instances, all the formulations on the market have been tried. Some patients do well combining inhaled steroids and LABA plus long acting muscarinic antagonists (eg, one of my patients did best with beclomethasone combined with Tiotropium plus olodaterol [Stiolto, Boehringer Ingelheim, Germany]). I recognize that this is off-label use, so I'm not recommending this approach; however, the more inhalers we have on the market, the higher the number of possible combinations. There may be some bene-

fits to using combination bronchodilator therapy. For example, if you are on LABA plus long-acting anti-muscarinic antagonists, then you can really ramp up the ICS dosage during exacerbations. Therefore, if the patient takes beclomethasone propionate all the time, then he or she could quadruple the dose during acute asthma episodes. Of course, the FDA is currently still mandating that, if you use a LABA, it needs to be in a fixed combination inhaler. The other thing we find is that patients are completely overwhelmed by the different types of devices; for instance, one patient may have a rescue pMDI, a Respi-mat inhaler with tiotropium, and inhaled steroids or fixed combination medication in an Ellipta device. This introduces a significant amount of inhaler confusion. The large number of delivery devices is also a big burden on providers who are managing these patients. Especially for primary care physicians; I don't know how a provider would find the time to really educate a patient on the use of 3 different devices during an already time-constrained visit.

MacIntyre: Njira, I don't treat asthma. But say you have a relatively mild patient with asthma who only has intermittent symptoms, what drives you to just give the patient albuterol when necessary versus something simple, like montelukast, versus the ICS/SABA combination? What drives those choices in your mind?

Lugogo: I would recommend prescribing SABA only to patients with exercise-induced asthma or with very mild intermittent asthma, with rare use of SABA, once a month or something. If you have any kind of atopy or allergic rhinitis and exercise-induced symptoms not fully controlled on

SABA, then I would add on a leukotriene inhibitor as first-line therapy. But if you have a little bit more in the way of symptoms, for example, you have seasonal symptoms, or when you get upper respiratory infections, you cough for 3-4 weeks at a time, or you're very aware that, for a month and half in the spring, you'll have issues, then you would qualify for intermittent treatment with ICS. The 2 ways I approach this group of patients is as follows: One subgroup of patients receives intermittent asthma therapy that is administered seasonally. So I'll say, "you're always sick in April, start your ICS in March, take it for 2 months and then you can stop it for the next 9 months, and if you get sick with any upper respiratory infection, go on your inhaled therapy." The other subgroup is of those without seasonal variation but who really fall off a cliff when they get sick and it takes them forever to recover in spite of oral corticosteroids and other interventions. In those patients, I'll prescribe intermittent SABA/ICS dosing that is initiated the moment they get sick with an upper respiratory infection. This is meant to reduce the morbidity and protracted course.

Mann: I think there's a fair number of patients with fairly severe asthma who really only have problems when they get a cold. My son was a perfect example. He would be fine and stable, but, with a cold, he would be blue and in the emergency department. I eventually started putting him on prednisone when he had a cold. So, I managed my son in a possibly unorthodox way by giving him prednisone during colds and nothing in between. I'm not sure even treatment guidelines would concur with such an approach, but my son's clinicians frankly agreed with my approach. He eventually outgrew

his asthma and did fine. I think that supports my second and more significant comment, which is I think it's important to understand the difference between treatment guidelines and the FDA and drug labels. The FDA functions under regulatory standards that require a very strong level of evidence for efficacy; we call it substantial. A substantial level of evidence usually means 2 randomized double-blind trials that replicate efficacy. You also have to have a very full and thorough understanding of safety to clear a drug, and FDA cleared indication and label that goes on new medications. Clinical treatment guidelines are different. They can perform a literature review and their experience and attempt to inform clinicians on the practice of medicine. They can go, if you will, beyond the label. I am glad the practice of medicine allows for clinicians to be understanding of various ways to use drugs more broadly. I think the FDA says as well that it's absolutely fine with us, the practice of medicine is important and we don't regulate that. I wouldn't want to go to a clinician who says, "I only prescribe FDA-cleared therapy." That would make me very nervous because there are a lot of gaps and holes. I just want to clarify, when folks criticize the FDA and say: How come you haven't cleared this or that? Everyone is doing it! How come we don't have as-needed use based on this study? Why don't you clear the use of this drug for this population when it's helpful? Such data often fall more appropriately into clinical guidelines or the practice of medicine and only if the data meet regulatory standards and are submitted to the FDA can they be implemented in labeling.