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Selecting the Optimal Therapy for Mild Asthma

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Management of mild asthma has undergone a paradigm shift in recent years. Mild intermittent asthma has classically been treated with short-acting bronchodilators (primarily short-acting β_2-agonists [SABAs]) for as-needed symptomatic management with addition of a controller medication indicated for patients with persistent symptoms, prior exacerbations, or risk factors for acute exacerbations (1, 2). However, multiple recent studies have demonstrated that treatment with an inhaled corticosteroid (ICS) for patients with mild asthma is associated with improvement in asthma-related symptoms and reduced exacerbation frequency in comparison with SABA monotherapy (3–6). These studies prompted a change in the Global Initiative for Asthma (GINA) guidelines, which recommend treatment with an ICS as the preferred initial management strategy for patients with mild intermittent asthma

(step 1) (7). Several of these studies have also specifically compared the efficacy of scheduled daily use of an ICS and as-needed use of a SABA as a reliever medication versus as-needed use of a single combination inhaler containing an ICS and a fast-onset long-acting β_2-agonist (LABA) as both a controller and reliever medication. The results of these studies suggest that as-needed use of an ICS-LABA has similar efficacy (3, 4), and in some studies, higher efficacy (5, 6), in preventing acute exacerbations compared with a daily ICS regimen supplemented with a SABA as a reliever medication. These findings contributed to an update in the most recent GINA guidelines recommending as-needed low-dose ICS-formoterol as the preferred controller and reliever medication for mild intermittent asthma (step 1) and as an alternative to daily low-dose ICS and as-needed SABA use for mild persistent asthma (step 2) (7). This has prompted questions on the appropriate application of these recommendations to current patients with mild asthma, specifically selecting the optimal management strategy for stepping up therapy in patients managed only with as-needed SABA therapy and how best to step down therapy for patients with well-controlled symptoms on daily controller therapy.

In this issue of *AnnalsATS*, Bateman and colleagues (pp. 2007–2017) perform a *post hoc* secondary analysis of pooled data from two pivotal trials (SYGMA-1 and SYGMA-2) to compare the effects of treatment with as-needed ICS-LABA (budesonide-formoterol) (8), scheduled daily low-dose ICS with as-needed SABA, and as-needed SABA monotherapy among patients with mild asthma (3, 4). Critically, the analysis was conducted in subgroups based on preenrollment status, including those with uncontrolled disease on as-needed SABA therapy before study enrollment (subgroup 1) and those with previously well-controlled asthma managed on either daily low-dose ICS or a leukotriene receptor

antagonist (LTRA) (subgroup 2). Overall, there was a substantial reduction in exacerbation frequency among patients treated with either as-needed ICS-LABA or daily ICS in comparison with management with a SABA alone, which supports the GINA guideline recommendation and indicates that intermittent SABA use is inferior to treatment with either intermittent or daily use of an ICS for mild asthma.

The authors identified differential outcomes based on preenrollment status, most notably demonstrating superiority of as-needed ICS-LABA over daily ICS use for the specific endpoint of exacerbation frequency in the group of individuals with uncontrolled disease previously treated with as-needed SABA alone (subgroup 1). However, this effect was not observed in patients with previously well-controlled disease on preenrollment controller therapy (subgroup 2). The authors conclude that as-needed ICS-LABA therapy is superior to scheduled ICS therapy with use of an as-needed SABA for patients not previously treated with a controller medication and is a reasonable step-down option or alternative treatment strategy for patients with already well-controlled disease on low-dose ICS or LTRA. However, in contrast to the effects on exacerbation frequency that favored as-needed ICS-LABA therapy, several other outcomes favored daily ICS treatment regardless of preenrollment status. Specifically, the frequency of symptom-free days was significantly higher in patients on daily ICS treatment and there were small but statistically significant differences in lung function and the asthma control questionnaire-5 score favoring daily ICS use. These results suggest that broad application of intermittent ICS-LABA therapy may not be appropriate for all patients with mild asthma, particularly those with already well-controlled disease on either a low-dose ICS or LTRA. After transitioning from their effective preenrollment controller therapy to as-needed ICS-LABA, these patients not only experienced

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more frequent symptoms and small but significant reductions in lung function, but there was also an increased estimate of the rate of severe exacerbations, although this did not meet statistical significance.

In light of these results, it is worth revisiting the known paradoxical effects of chronic β_2-agonist use on disease control, airway physiology, and airway inflammation in asthma. Regular use of β_2-agonist treatment without concurrent ICS use has a well-documented association with increased asthma-related morbidity and mortality (9). In addition, multiple studies have demonstrated increased airway hyperresponsiveness to both direct (10–12) and indirect stimuli such as exercise and allergen challenges (13–15) with regular exposure to both short-acting and long-acting β_2-agonists. Importantly, patients enrolled in these physiologic studies had well-controlled disease and thus overall low preenrollment β_2-agonist exposure. In contrast, patients enrolled in a clinical trial for uncontrolled asthma typically require regular β_2-agonist therapy to manage ongoing symptoms. These physiologic studies identified that the adverse effects of β_2-agonist therapy occurred at modest doses of these drugs that are frequently encountered in patients with uncontrolled asthma. Thus, patients enrolled in clinical trials for uncontrolled asthma not previously

using a controller therapy (such as subgroup 1 described in this study) may already be experiencing the adverse effects of regular β_2-agonist therapy before enrollment. For these patients, exposure to intermittent ICS-LABA therapy may not incur additional detrimental effects on airway physiology and inflammation, whereas these effects may be more apparent in a population not previously treated with chronic β_2-agonist therapy (such as subgroup 2 in this study). Finally, although recent studies have provided reassuring evidence for the safety of chronic β_2-agonist therapy when combined with an ICS (16), short- (17, 18) and long-acting (11, 19–21) β_2-agonist use is associated with a loss of bronchoprotection, a reduction in the ability of β_2-agonists to protect against airway narrowing in response to stimuli known to promote bronchoconstriction, even with concurrent administration of an ICS (22).

With the recent changes in the GINA guidelines, it is likely that intermittent ICS-LABA therapy will be increasingly used by primary care providers, pulmonologists, and asthma specialists for management of mild asthma, both as an initial therapy and as a step-down option or alternative therapy for patients with persistent disease. As the authors point out, use of a single inhaler as both a controller and reliever medication is less complicated for both patients and providers, offers appropriate

treatment with an ICS for patients who previously overused their SABA reliever therapy, and may offer a preferred treatment schedule for patients with difficulty adhering to daily controller therapy. In addition, their analysis identifies a reduction in exacerbation frequency with intermittent ICS-LABA therapy versus scheduled daily ICS use among patients with uncontrolled disease not previously treated with controller therapy. This suggests the importance of initiating controller therapy at the earliest onset of worsening disease control to prevent an acute exacerbation and is potentially indicative of a reduced risk for additional negative effects on airway physiology and inflammation associated with intermittent ICS-LABA therapy for patients already experiencing the effects of chronic β_2-agonist therapy. However, the overall worsened symptom control and lung function in both subgroups with intermittent ICS-LABA use continues to provide a signal for the known detrimental effects associated with chronic β_2-agonist use. Providers should carefully consider these nuances when selecting treatment for patients with mild asthma, particularly for those with well-controlled disease and good adherence to controller therapy. ■

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What's to Be Found in the Wisdom of the Crowd?

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Despite the passage of two decades since the publication of Early Goal Directed Therapy (EGDT), the optimal resuscitation strategy for patients with sepsis and septic shock remains unclear (1). EGDT, as well as three subsequent studies, all compared an intervention to "usual care" (2–4). A common limitation in these subsequent trials is that usual care, where it was measured, often did not differ greatly from EGDT. The nature of other key interventions, such as when to start a second vasopressor or corticosteroids, were largely uncharacterized (5). Relatively little evidence exists to guide actual strategy and how best to apply this data beyond a "norepinephrine first" approach (6).

In this issue of *AnnalsATS*, Bosch and colleagues (pp. 2049–2057) have published a methodologically rigorous investigation describing current practice patterns for the use of adjunctive corticosteroids and vasopressors in the treatment of septic shock (7). Their study describes real-world practice and applies high-quality methods to evaluate factors associated with differences in the threshold at which providers utilize adjunctive therapies. The authors reported significant hospital-level practice variation for the threshold of norepinephrine, which triggers administration of an adjunctive therapy, including a ninefold difference between hospitals in the threshold at which a second vasopressor was started. They report similar variation in the threshold for adjunctive corticosteroids. Practices for adjunctive vasopressor initiation thus appear to be overly dependent on shared provider preferences within hospitals rather than evidence or patient factors. This variation is perhaps more disappointing than surprising, reflecting the dearth of papers addressing this issue in the 20 years that have elapsed since EGDT's publication (8). The only major trial of adjunctive vasopressor therapy in the last decade barely reported clinical outcomes, leaving an evidence vacuum for clinicians considering the role for the tested therapy in their patients (9).

Admittedly, it appears that intensivists are not entirely arbitrary. The favored second vasopressor was vasopressin, a practice supported by trial data and societal guidelines (6). Sicker and more comorbid patients were more likely to receive vasopressors before corticosteroids, which supports a pattern of using early additional vasopressors to meet hemodynamic endpoints in extreme acute illness. The pattern of later utilization of corticosteroids is also supported by evidence for their use in patients who do not respond to vasopressors (10). The greatest contribution of this study is the report of the commonalities observed, which comprises usual care. Most hospitals added vasopressin at around 10–30 μg/min of norepinephrine about 7 hours after starting norepinephrine, whereas corticosteroids were added around 5–15 μg/min of norepinephrine about 18 hours after starting norepinephrine.

Trial design is difficult. One challenge facing investigators is the design of a control arm. Proponents of usual care as a control contend that for an intervention to be deemed superior and to be adopted, it must be tested against usual care, which allows for determining safety and effectiveness. However, usual care is subject to unexplained clinical variation, may change with secular trends, and may be