

Asthma Guidelines Priority Topics: Intermittent Inhaled Corticosteroid Therapy and Inhaled Corticosteroids with Long Acting Beta-Agonists as Reliever Therapy

Kathryn V. Blake, PharmD,¹ and Hengameh H. Raissy, PharmD²

The National Asthma Education and Prevention Program Guidelines for the Diagnosis and Management of Asthma will update the guidelines on 6 topic areas. This review summarizes the findings for the charge to assess effectiveness of intermittent inhaled corticosteroid therapy with and without long-acting beta-agonist therapy in children 0 to 4 years of age, and children and adults 5 years and older. The complete report can be found on the Agency for Healthcare Research and Quality website.

Keywords: inhaled corticosteroid, long-acting beta-agonist, asthma, guidelines

THE NATIONAL ASTHMA Education and Prevention Program Guidelines for the Diagnosis and Management of Asthma will be updated on 6 selected topics as described in a past issue of this journal.¹ Previously, we reported on the Agency for Healthcare Research and Quality (AHRQ) topic of the efficacy of adding long-acting muscarinic antagonist to inhaled corticosteroids (ICS) with or without long-acting beta-agonist (LABA) in patients 12 years and older with uncontrolled persistent asthma and summarized results from additional recently published clinical studies in pediatric patients.² In this issue, we report on a second selected topic published by AHRQ on use of intermittent ICS and intermittent ICS with LABA.

The Evidence-based Practice Center of the AHRQ was tasked with reviewing those data on 3 key questions on the effectiveness of intermittent ICS use and intermittent ICS with LABA. These key questions, developed in collaboration between the Evidence-based Practice Center investigators, content experts, technical expert panel, and National Heart, Lung, and Blood Institute for the AHRQ protocol, were as follows:

Key Question 1a: What is the comparative effectiveness of intermittent ICS compared to no treatment, pharmacologic, or nonpharmacologic therapy in children 0 to 4 years old with recurrent wheezing?

Key Question 1b: What is the comparative effectiveness of intermittent ICS compared to ICS controller

therapy in patients 5 years of age and older with persistent asthma?

Key Question 1c: What is the comparative effectiveness of ICS with LABA used as both controller and quick relief therapy compared to ICS with or without LABA used as controller therapy in patients 5 years of age and older with persistent asthma?

For the AHRQ report, the following databases were searched: MEDLINE®, Embase®, Cochrane Central, and Cochrane Database of Systematic Reviews bibliographic databases from earliest date through March 23, 2017. In addition, manual searches from the references of relevant studies, as well as www.clinicaltrials.gov and the International Controlled Trials Registry Platform were performed. These results were further updated through November 28, 2017, but no new studies met the inclusion criteria. Data were abstracted, assessed for risk of bias, and graded on strength of evidence for each comparison and outcome.

Study risk of bias was an integral assessment of each trial. For each randomized clinical trial, assessment of risk of bias was based upon 7 components: sequence generation, allocation concealment, blinding of participants/personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. For each nonrandomized clinical trial, the risk of bias was based upon 8 components: representativeness of exposed cohort, selection of nonexposed cohort, ascertainment of exposure,

¹Department of Biomedical Research, Center for Pharmacogenomics and Translational Research, Nemours Children's Specialty Care, Jacksonville, Florida.

²Department of Pediatrics, Health Sciences Center, School of Medicine, University of New Mexico, New Mexico.

outcome of interest not present at start of study, comparability of cohorts, assessment of outcome, adequacy of follow-up duration, and adequacy of cohort follow-up. Each component was rated by 2 independent reviewers from the AHRQ Evidenced-based Practice Center as low, medium, high, or unclear, and for nonrandomized studies, “not applicable,” for the domain “Outcome of interest not present at start of study.” The overall risk of bias, classified as low, medium, or high, was based upon the collective risk of bias for each domain, and the confidence of the trial investigator in the results given the stated limitations of the study. If the majority of domains were unclear, then the overall risk of bias was classified as unclear.

The risk of bias informed the strength of evidence. The strength of evidence was graded for the following outcomes: asthma exacerbations, mortality, asthma control composite scores, spirometry, asthma-specific quality of life, and health care utilization. The 5 required domains to assess strength of evidence included study risk of bias, consistency, directness, precision, and publication bias. Strength of evidence was evaluated for each outcome within each comparison and was graded by 2 senior investigators independently and then discussed to arrive at the final grading using established guidance. Based on these elements, the strength of evidence was assessed as high, moderate, low, or insufficient for each comparison and outcome as shown in Table 1.

The outcomes for the key questions reported in this article are on exacerbation reduction for the composite and separate endpoints: oral corticosteroid use, emergency department (ED) visits, hospitalizations, and fall in Peak Expiratory Flow <70% from baseline. The full AHRQ report details other outcomes such as rescue medication use, asthma control scores, quality of life, and spirometry. Citations for all the studies described herein can be found in the full AHRQ report at (<https://effectivehealthcare.ahrq.gov/>)

TABLE 1. STRENGTH OF EVIDENCE GRADE FOR EACH STUDY OUTCOME

High	High confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. Believe that findings are stable, that is, another study would not change the conclusions.
Moderate	Moderate confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. The findings are likely to be stable, but some doubt remains.
Low	Limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). Believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	No evidence, unable to estimate an effect, or have no confidence in the estimate of the effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

topics/asthma-pharmacologic-treatment/research-2017). In this article, the main topic for each key question is bolded and the specific comparators within that main topic are in italics.

Four trials meeting eligibility were evaluated for the effectiveness of **intermittent ICS in children 4 years and younger with recurrent wheezing**. In 3 trials comparing *intermittent ICS with as-needed short-acting beta-agonist versus as-needed short-acting beta-agonist (SABA)* initiated at the start of a respiratory tract infection in children with recurrent wheezing, there was a 33% reduced risk of asthma exacerbations requiring oral corticosteroids [relative risk, RR: 0.67 (95% confidence interval, CI: 0.46–0.98)] in favor of intermittent ICS. There was no significant difference for acute care visits or hospitalizations related to asthma.

One trial evaluated *intermittent ICS with as-needed SABA versus ICS controller with as-needed SABA* in children 0 to 4 years old and found that there was no difference between treatments on the risk of exacerbation requiring oral corticosteroid or the risk of hospitalization, but the strength of evidence was low.

A single trial evaluated *intermittent ICS versus no therapy* in children 0 to 4 years but the evidence was insufficient to draw a conclusion.

Seven randomized controlled trials (RCTs) meeting eligibility criteria were evaluated for the effectiveness of **intermittent ICS with or without ICS controller therapy compared with ICS controller therapy in patients 5 years and older with persistent asthma**. In the 2 trials in children 4 to 11 years old that compared *intermittent ICS with ICS controller versus ICS controller*, there was insufficient evidence to draw conclusions.

In the 4 trials that compared *intermittent ICS with ICS controller versus ICS controller* in patients 12 years and older evaluating effect on oral corticosteroid use, there was no difference in effect on the risk of exacerbations requiring oral corticosteroids in the study population as a whole [RR: 0.68 (95% CI: 0.31–1.49)] nor in the subpopulation of patients who actually initiated intermittent ICS [RR: 0.64 (95% CI: 0.26–1.57)].

There was only a single trial in children 4 to 11 years old evaluating *intermittent ICS versus ICS controller*; but the strength of evidence was graded insufficient to draw a conclusion.

Twenty-four trials meeting eligibility evaluated the effectiveness of **ICS with LABA therapy used as controller and quick relief therapy compared with ICS with or without LABA as controller therapy in patients 5 years and older with persistent asthma**. However, only 2 trials enrolled children as young as 4 years of age. Asthma severity and presence of symptoms (versus asymptomatic) at baseline of enrolled participants varied across studies.

In the 3 trials (2 of which included adolescents) that compared *ICS and LABA as controller and quick relief versus ICS controller at the same comparative ICS dose* (all with budesonide/formoterol versus budesonide) and included a composite exacerbation event (oral corticosteroid use, ED visit, or hospitalization, or a peak expiratory flow <70%), composite events were reduced by 35% to 51% with the use of ICS and LABA controller with quick relief.

A single trial of patients 12 years and older compared *ICS and LABA as controller and quick relief versus ICS controller at a higher comparative ICS dose* and found that

TABLE 2. SUMMARY OF MAJOR FINDINGS FOR EXACERBATION ENDPOINTS

Comparator groups [KQ]	Age range specified for inclusion for the KQ [actual age range]	Number of trials	Major findings for exacerbation endpoint
<i>KQ1a: Comparative effectiveness of intermittent ICS compared with no treatment, pharmacologic, or nonpharmacologic therapy in children 0 to 4 years old with recurrent wheezing</i>			
Intermittent ICS with as-needed SABA versus as-needed SABA [KQ1a]	0 to 4 years old	3	There was a 33% reduced risk of asthma exacerbations requiring oral corticosteroids in favor of intermittent ICS (moderate strength of evidence)
Intermittent ICS with as-needed SABA versus ICS controller with as-needed SABA [KQ1a]	0 to 4 years old	1	No difference between treatments on the risk of exacerbation requiring oral corticosteroid (low strength of evidence)
Intermittent ICS versus no therapy [KQ1a]	0 to 4 years old	1	Evidence was insufficient
<i>KQ1b: Comparative effectiveness of intermittent ICS compared with ICS controller therapy in patients 5 years of age and older with persistent asthma</i>			
Intermittent ICS with ICS controller versus ICS controller [KQ1b]	5 years and older [4 to 11 years old]	2	Evidence was insufficient
Intermittent ICS with ICS controller versus ICS controller [KQ1b]	5 years and older [12 years and older]	4	There was no difference in effect on the risk of exacerbations requiring oral corticosteroids in the study population as a whole nor in the subpopulation of patients who actually initiated intermittent ICS (low strength of evidence)
Intermittent ICS versus ICS controller [KQ1b]	5 years and older [4 to 11 years old]	1	Evidence was insufficient
<i>KQ1c: Comparative effectiveness of ICS with LABA used as both controller and quick relief therapy compared with ICS with or without LABA used as controller therapy in patients 5 years of age and older with persistent asthma</i>			
ICS and LABA as controller and quick relief versus ICS controller at the same comparative ICS dose [KQ1c]	5 years and older [12 years and older]	2	Composite exacerbation events (oral corticosteroid use, ED visit, or hospitalization, or a peak expiratory flow <70%) were reduced by 35% to 51% with the use of ICS and LABA controller and quick relief (moderate strength of evidence)
ICS and LABA as controller and quick relief versus ICS controller at a higher comparative ICS dose [KQ1c]	5 years and older [12 years and older]	1	Composite exacerbation events were reduced by 42% with ICS and LABA as controller and quick relief (low strength of evidence)
ICS and LABA as controller and quick relief versus ICS controller at a higher comparative ICS dose [KQ1c]	5 years and older [4 to 11 years]	1	Composite exacerbation events also favored ICS and LABA controller and quick relief (reduced events by 45%) (low strength of evidence)
ICS and LABA as controller and quick relief versus ICS and LABA controller at the same comparative ICS dose [KQ1c]	5 years and older [12 years and older]	5	The composite exacerbation endpoint was reduced by 32% and exacerbations were also reduced by 31% when only considering ED and hospitalizations (high strength of evidence)
ICS and LABA as controller and quick relief versus ICS and LABA controller at the same comparative ICS dose [KQ1c]	5 years and older [4 to 11 years]	1	The composite exacerbation endpoint also favored ICS and LABA controller and quick relief (reduced events by 62%) (low strength of evidence)
ICS and LABA as controller and quick relief on exacerbation endpoints when compared with ICS and LABA controller at a higher comparative ICS dose [KQ1c]	5 years and older [12 years and older]	3	Composite exacerbation endpoint was reduced by 25% (high strength of evidence)
ICS and LABA as controller and quick relief versus ICS and LABA controller at a lower comparative ICS dose [KQ1c]	No trials in children or adolescents	0	
ICS and LABA as controller and quick relief versus conventional best practice [KQ1c]	5 years and older [12 years and older]	6	22% reduction in the composite exacerbation endpoint with ICS and LABA as controller and quick relief versus conventional best practice (moderate strength of evidence)

ED, emergency department; ICS, inhaled corticosteroids; KQ, key question; LABA, long-acting beta-agonist; SABA, short-acting beta-agonist.

composite exacerbation events were reduced by 43% with ICS and LABA as controller and quick relief but the strength of evidence was low. In another study, a subgroup analysis of children 4 to 11 years of age found that the composite exacerbation endpoint also favored ICS and LABA controller and quick relief (reduced events by 45%), but the strength of evidence was low because the ICS dose was lower than the labeled indication dose, as well as lower than the dose considered by Expert Panel Report-3 as low dose.

Nine RCTs (all but 1 included adolescents) compared *ICS and LABA as controller and quick relief versus ICS and LABA controller at the same comparative ICS dose*. Six trials used budesonide/formoterol for each comparator, and 2 trials compared budesonide/formoterol as controller and quick relief versus fluticasone/salmeterol controller. In 5 trials of ICS and LABA as controller and quick relief, the composite exacerbation endpoint was reduced by 32% [RR: 0.68 (95% CI: 0.58–0.80)] and exacerbations were also reduced by 31% when only considering ED and hospitalizations [RR: 0.69 (95% CI: 0.63–0.76)]. In a single study of children 4 to 11 years of age, the composite exacerbation endpoint also favored ICS and LABA controller and quick relief [reduced events by 62%; (RR: 0.38 [95% CI: 0.23–0.63])] but the strength of evidence was low because the ICS dose was lower than the labeled indication dose, as well as lower than the dose considered by Expert Panel Report-3 as low dose.

The effect of *ICS and LABA as controller and quick relief* on exacerbation endpoints when compared with *ICS and LABA controller at a higher comparative ICS dose* was less pronounced. The composite exacerbation endpoint in 3 RCTs, all of which included adolescents, was reduced by 25% [RR: 0.75 (95% CI: 0.59–0.96)] with ICS and LABA controller and quick relief but was not reduced when only considering ED and hospitalizations. All studies used budesonide/formoterol for controller and quick relief, which was compared with either fluticasone/salmeterol or budesonide/formoterol controller.

There were no trials in children or adolescents that compared *ICS and LABA as controller and quick relief versus ICS and LABA controller at a lower comparative ICS dose*.

Six trials (all including adolescents) were included in the analysis of *ICS and LABA as controller and quick relief versus conventional best practice*. Conventional best practice comprised at a minimum, ICS with/without LABA, and the medications and doses were adjusted during the trial at physician discretion. There was a 22% reduction in the composite exacerbation endpoint [RR: 0.78 (95% CI: 0.64–0.95)] with ICS and LABA as controller and quick relief versus conventional best practice but there were no differences when evaluating the endpoints of oral corticosteroid use, ED visits, or hospitalizations separately.

These data in the AHRQ (Table 2) report suggest that in children 0 to 4 years of age, intermittent ICS initiated at the start of an RTI reduces exacerbation events when compared with SABA as-needed use but there is not an effect, or the evidence is insufficient, when compared with ICS controller or no therapy. In patients 5 years and older, intermittent ICS with or without additional ICS controller appears to provide no additional benefit against exacerbation risk compared

with ICS controller therapy. ICS and LABA as controller and quick relief reduce composite exacerbation events when evaluated against the following comparators: ICS alone; ICS at a similar dose with LABA; ICS at a higher dose with LABA; and conventional best practice. Many trials do include adolescents but typically the data from adolescents in specific trials are not analyzed separately from adults and, therefore, are not presented separately in this AHRQ report. Data on children 0 to 4 years are even more sparse except when the trial is specifically designed to evaluate outcomes in this age group (as with the effect of intermittent ICS in children with recurrent wheezing). Additional studies on intermittent ICS and ICS and LABA controller and quick relief have been published since this AHRQ report was released.^{3–5} The Expert Panel Report-4 working group will evaluate the AHRQ report findings in conjunction with newly published trials as well as data from other sources in determining the revision to the guidelines.

Author Disclosure Statement

K.V.B., PharmD, served as a paid consultant to the Evidence-based Practice Center for the topic “Systematic Review of Intermittent Inhaled Corticosteroids and of Long-acting Muscarinic Antagonists for Asthma.” Dr. K.V.B. is a member of the National Asthma Education and Prevention Program Working Group for the Expert Panel Report-4. H.H.R., PharmD, has no conflicts of interest to report.

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Address correspondence to:
Kathryn V. Blake, PharmD
Biomedical Research Department
Center for Pharmacogenomics
and Translational Research
Nemours Children’s Specialty Care
807 Children’s Way
Jacksonville, FL 32207

E-mail: kathryn.blake@nemours.org

Received for publication January 15, 2019; accepted after revision February 21, 2019.