Lessons Learned From the Asthma Clinical Research Network

By Brian Piazza, MS2 and Timothy J. Craig, DO

In 1993, the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health established the Asthma Clinical Research Network (ACRN) to answer vital questions about treatment for patients with asthma. To perform clinical research independent of that conducted by pharmaceutical companies, the ACRN includes multiple clinical research centers as well as a data-coordination center. The goals of this multicenter program are to conduct research for rapid evaluation of investigational and existing treatments and to disseminate the clinical findings to the greater health-care community.

The research reported by the ACRN has affected how physicians treat patients with asthma, and will continue to do so in the future. This article summarizes results from 19 ACRN studies that are useful for all physicians caring for patients with asthma.

Defining Asthma Control

Can peak expiratory flow rates, symptom scores, β-agonist use, mast cell biopsy, tryptase levels, or exhaled nitric oxide levels predict an exacerbation event, defined as a 20% decrease in forced expiratory volume in one second (FEV1)?

In an ACRN study by Leone et al., data collected from 313 participants were used to assess these outcomes. Of these participants, only 71 individuals met criteria for having active disease (ie, 20% decrease in FEV1). In a comparison of the use of albuterol in the active disease group with the nonactive disease group, neither asthma symptom scores, peak flow values, nor diurnal variation of peak flow were able to accurately predict patients who would have a 20% decline in FEV1.

The ability of peak flow measurement to predict a drop in FEV1 occurred in only 17% of patients. In viewing the data from the opposite direction, only 19% of patients who had a decrease in FEV1 also had a decrease in peak flow values. Results of the study by Leone et al.1 suggest that peak flow data, symptoms, and albuterol use may not be sensitive or specific enough (when used alone) to predict an asthma attack.1

Because of the inability of peak flow values to predict an asthma attack and the lack of patient compliance in using peak flowmeters, the NHLBI Guidelines for the Diagnosis and Management of Asthma are flexible regarding the need to monitor peak flow values. The exception to this flexibility is the patient with poor perception of his or her asthma severity. In that cohort, monitoring peak flow—with the goal of intensifying treatment before an exacerbation occurs—is important. An obvious question arises: Are more specific and sensitive tests available for predicting asthma exacerbation? Exhaled nitric oxide (eNO) measurements, sputum eosinophil counts, and challenge tests have been evaluated to determine if these tests could successfully predict asthma exacerbation—especially when altering corticosteroid treatment.

To determine the success of eNO, sputum eosinophil assessments and challenge tests in predicting loss of asthma control, Deykin et al.3 randomized 164 patients to receive an inhaled corticosteroid (ICS), the β-agonist salmeterol, or placebo. Neither the eNO test nor the methacholine challenge was able to predict loss of asthma control, but increasing eosinophil counts in sputum were predictive. Thus, assessment of sputum eosinophils may help predict which patients with asthma need to be restarted on ICS treatment to prevent loss of asthma control. Although monitoring sputum eosinophils may be effective in predicting an impending asthma exacerbation, monitoring techniques are difficult to perform, quality assurance is intense, and interpretation of the slides is complex—all of which limit the use of sputum eosinophil assessments in clinics.3

Analyzing mast cells and mast cell products (eg, tryptase levels) by bronchoscopy, biopsy, and bronchoalveolar lavage (BAL) can also be used to assess asthma control in patients. In a 28-week trial by Kraft et al.,4 45 patients underwent bronchoscopy, endobronchial biopsy, and BAL after a 6-week period in which all participants received the ICS triamcinolone acetonide. The patients were then randomly assigned to treatment with salmeterol, ICS, or placebo. At the end of the trial, they received a second bronchoscopy.

Similar to sputum eosinophils, mast cells were found by Kraft et al.4 to be an important predictor of asthma exacerbation in patients withdrawn from ICS and in others whose symptoms exacerbated while taking salmeterol or placebo. Patients whose symptoms exacerbated after stopping ICS had higher
numbers of mast cells on biopsy despite therapy, and they also had higher levels of tryptase on BAL. Patients whose symptoms exacerbated while taking salmeterol or placebo also had higher levels of tryptase on BAL. These data suggest that assessment of mast cells or their products may help predict individuals who need ICS to maintain well-controlled asthma. 4

Despite the beneficial findings represented by these data, use of sputum eosinophil tests and bronchoscopy are not practical in many clinical settings. The collection of sputum and counting of sputum eosinophils is time-consuming and difficult to perform even in an experienced research laboratory. Adequate collection of sputum requires a well-trained technician and—even with such training—results can be inconsistent. Similarly, the use of bronchoscopy includes inherent risk and cost. Because of these factors, these procedures are unlikely to gain widespread use in the clinical setting.

Patient response to ICSs can be predicted by many parameters. In a dose-ranging study of 2 ICSs by Szefler et al,5 patients who had a greater than 15% increase in FEV₁ level were more likely to have a high eNO level, a high degree of reversal of FEV₁ with albuterol, and a low FEV₁/forced vital capacity (FVC) ratio, compared to patients who had a minimal response in FEV₁ level. Of particular interest, methacholine suppression, eNO reduction, albuterol rescue use, symptom reduction, peak flow, and FEV₁ level all improved maximally with a low to medium dose of ICS. Increasing the ICS dose further provided only minimal improvement, despite the increase in cortisol suppression. The only parameter that required higher doses of ICS for maximal suppression was sputum eosinophil count.5

Based on these studies,1-5 no single parameter or variable that can be assessed routinely in the clinical setting provides sufficient information to determine risk of future asthma exacerbations. Thus, it is necessary to use multiple variables, as outlined by the NHLBI asthma guidelines,2 to determine asthma severity, control, and treatment for a patient. The NHLBI asthma guidelines2 suggest the consideration of daytime symptoms, nighttime symptoms, albuterol use, exercise tolerance, exac-

<table>
<thead>
<tr>
<th>Components of Severity</th>
<th>Classification of Asthma Severity (Age ≥ 12 years of age and adults)</th>
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<tbody>
<tr>
<td></td>
<td>Intermittent</td>
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<td></td>
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<tr>
<td>Impairment</td>
<td></td>
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<tr>
<td>Normal FEV₁/FVC:</td>
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<tr>
<td>8-19 y 85%</td>
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<tr>
<td>20-39 y 80%</td>
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<tr>
<td>40-59 y 75%</td>
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<tr>
<td>60-80 y 70%</td>
<td></td>
</tr>
<tr>
<td>Nighttime awakenings</td>
<td>≤ 2x/month</td>
</tr>
<tr>
<td>Short-acting β-agonist use for symptom control</td>
<td>≤ 2 days/week</td>
</tr>
<tr>
<td>Interference with normal activity</td>
<td>None</td>
</tr>
<tr>
<td>Lung function</td>
<td>Normal FEV₁ between exacerbations</td>
</tr>
<tr>
<td>Exacerbations requiring oral systemic corticosteroids</td>
<td>0-1/year</td>
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Risk

Relative annual risk of exacerbations may be related to FEV₁

Figure 1. National Heart, Lung, and Blood Institute’s guidelines for classifying asthma severity in adults. Adapted from the National Heart, Lung, and Blood Institute.5 Abbreviations: FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.
erbations in the past year, and spirometry to classify asthma severity (Figure 1), to assess asthma control options (Figure 2), and to determine asthma management methods (Figure 3).

Because of the difficulty of performing sputum eosinophil counts and the poor prediction of risk from using a single variable (eg, spirometry, peak flow, eNO, symptoms, methacholine), the NHLBI guidelines provide the most appropriate tool for managing the patient with asthma in the clinical setting.2

<table>
<thead>
<tr>
<th>Components of Severity</th>
<th>Classification of Asthma Control (Age ≥12 years of age and adults)</th>
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<tbody>
<tr>
<td></td>
<td>Well Controlled</td>
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<tr>
<td>Impairment</td>
<td></td>
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<tr>
<td>Symptoms</td>
<td>≤2 days/week</td>
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<tr>
<td>Nighttime awakenings</td>
<td>≤2/month</td>
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<tr>
<td>Interference with normal activity</td>
<td>None</td>
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<tr>
<td>Short-acting β-agonist use for symptom control</td>
<td>≤2 days/week</td>
</tr>
<tr>
<td>FEV₁ or peak flow</td>
<td>&gt;80% predicted/ personal best</td>
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<tr>
<td>Validated questionnaires</td>
<td></td>
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<tr>
<td>ATAQ</td>
<td></td>
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<tr>
<td>ACQ</td>
<td></td>
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<tr>
<td>Exacerbations</td>
<td>0-1/year</td>
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<tr>
<td>Progressive loss of lung function</td>
<td>Evaluation requires long-term follow-up care.</td>
</tr>
<tr>
<td>Treatment-related adverse effects</td>
<td>Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.</td>
</tr>
</tbody>
</table>

Figure 2. National Heart, Lung, and Blood Institute’s guidelines for assessing asthma control in adults. Adapted from the National Heart, Lung, and Blood Institute.2 Abbreviations: ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; ATAQ, Asthma Therapy Assessment Questionnaire; FEV₁, forced expiratory volume in 1 second; N/A, Not available.

Special Cohorts of Patients with Asthma Hypersensitivity

Asthma can be triggered by exercise, occupational exposures, respiratory irritants (eg, air pollution, tobacco smoke), viral infections, atypical bacteria, cold dry air, and active rhinosinusitis. In addition to these factors, various allergens may be triggers in many patients.

Aeroallergen sensitivity was formerly thought to play only a minimal role in asthma. However, data reported by the ACRN demonstrates a high rate of skin test sensitivity to aeroallergens in patients with mild to moderate asthma (which accounts for approximately 85% of asthma cases).6 In a large assessment of multiple ACRN studies involving such patients, Craig et al6 reported that aeroallergen sensitivity was as high as 95%. However, results of that study are limited because skin testing—not aeroallergen challenge—was used to determine hypersensitivity to aeroallergens.

Despite this limitation, Craig et al6 found that increasing immunoglobulin E serum levels, eNO values, bronchial hyperresponsiveness (as defined by methacholine concentration), and minority ethnicity all correlated with the number of skin tests that had positive results. In addition, 89% of study participants older than age 60 years continued to have hypersensitivity, although those patients with late-onset asthma were less likely to be hypersensitive. Of note is that 93% of the studied patients had a positive reaction to an indoor perennial allergen test. These data suggest that allergens may be an aggravating factor for a large portion of the asthmatic population, and avoidance of allergens should be part of the therapeutic interventions in this population.6
Smoking

Tobacco smoke is a known irritant for respiratory diseases, including asthma, bronchitis, chronic obstructive pulmonary disease, otitis media, and sinusitis. The unique effects of tobacco on treatment for patients with asthma suggest that interventions for patients who smoke may differ from interventions for patients who do not smoke. Smokers are often excluded from clinical trials on asthma. Thus, treatment outcomes are unknown in this cohort. However, because previous data suggested a decrease in response of FEV₁ with ICS use in patients with asthma who smoke, the ACRN conducted a study comparing treatment with ICS to treatment with the leukotriene receptor antagonist (LTRA) montelukast in such patients.7

Lazarus et al7 found that despite similar baseline FEV₁ values and similar bronchodilator responses to albuterol and methacholine, smokers had more asthma symptoms, poorer quality of life, and lower peak flow values than nonsmokers. Although use of an ICS decreased eosinophil levels in both smokers and nonsmokers, FEV₁ did not improve after addition of an ICS in smokers (while it did improve in nonsmokers, as expected). By contrast, use of montelukast improved peak flow values in smokers, suggesting that this LTRA agent may have some benefit over ICS use in smokers.7

Caution is necessary when interpreting these trial results, because the small sample size of this study (N=83) did not allow researchers to determine if use of an ICS or montelukast could reduce exacerbations or protect against accelerated loss of lung function.7 Thus, larger studies are needed to further explore leukotriene inhibitors as treatment for patients with asthma.

Obesity

In a large retrospective study of patients (N = 1256) recruited into ACRN studies, Sutherland et al8 conducted a comparison of overweight and obese individuals with asthma to nonoverweight individuals with asthma. The researchers found minimal differences between the 2 groups in asthma parameters. However, results favored the lean body type in terms of higher FEV₁ value, higher FEV₁/FVC ratio, lower eN0 level, improved methacholine response, and better quality of life. In response to particular treatments, the lean population responded to ICS with a greater reduction of eN0 level. In addition, the lean cohort had greater improvement of spirometric values when treated with the combination of ICS and long-acting β-agonist.
(LABA). Both cohorts responded equally to montelukast.

Although the study by Sutherland et al. found that clinical impairment is not significantly increased with an increase in BMI in patients with asthma, the study does suggest that future prospective studies are warranted for closer examination of treatment responses in overweight and obese individuals with asthma.

**Safety Studies**

**Methacholine**

A lower FEV₁ limit has not been well established for the safe evaluation of bronchial hyperresponsiveness on methacholine, and most suggestions on the use of the methacholine challenge are derived from expert opinion. Some experts suggest using this challenge only when a patient’s FEV₁ exceeds 80% of the predicted value, while other experts suggest that this challenge can be safely performed when the FEV₁ exceeds 1 liter.

To help define the safety of the methacholine challenge, Martin et al. assessed the use of this technique in patients (N=88) with FEV₁ below 60% predicted. Only 4 of the 88 patients who were challenged failed to return to at least 90% of their baseline FEV₁ with 1 treatment of the short-acting β-agonist (SABA) albuterol. These 4 individuals each required 1 additional treatment with albuterol to achieve a good response and no statistically significant adverse events.

These data suggest that the methacholine challenge can be safely performed even in individuals with moderate to severe asthma that is not well controlled. This result has research implications. However, because methacholine is only 1 tool for determining how treatment affects bronchial hyperresponsiveness, the use of methacholine is probably best limited in the clinical setting to patients with controlled asthma and FEV₁ above 60% predicted.

**Sputum Induction**

To determine the safety and reproducibility of sputum induction in patients with moderate to severe asthma, Fahy et al. enrolled 79 participants in a multicenter study. Providers at all centers underwent training and adhered to a manual of operation to ensure that the sputum induction technique was performed correctly and consistently in each center. Analyses of the sputum were performed at a single center.

In 14% of the patients, the change in FEV₁ resulting from the sputum induction procedure equaled or exceeded a 20% decrease. This FEV₁ decrease was observed in 25% of patients with a baseline FEV₁ value between 40% and 60% of the predicted value. Despite this FEV₁ drop, all study participants responded well to 2 puffs of albuterol with correction of the FEV₁.

No statistically significant adverse events occurred during the trial by Fahy et al., suggesting that sputum induction can be safely performed in individuals with moderate to severe asthma without expected poor outcomes. Data recovered from the induction—including measurements of sputum eosinophils, eosinophil cationic protein, and tryptase—were found to be reliable, reproducible, and consistent from center to center. The data also indicated that the sputum induction was equivalent in safety to that of the methacholine challenge.

These positive outcomes must be viewed in light of the fact that a well-developed manual of operations, pre-procedural training and testing, and ongoing quality assurance were used by Fahy et al. Without such rigor, it is doubtful that sputum eosinophil testing will be helpful in clinical practice, though this testing does appear to be safe to perform and useful for multicenter clinical trials.

**Treatment Agents**

**Short-acting β-Agonists**

Short-acting β-agonists should be used only before exercise and as needed for bronchospasm. Concerns exist about the regular use of SABAs, especially when albuterol is necessary for reversal of exercise-induced bronchospasm (EIB). Regular use of albuterol has been shown to result in blunted effects when the drug is used for rescue from EIB. The ACRN designed and completed a genotype-stratified, crossover, placebo-controlled, multicenter study comparing 126 patients using albuterol on a regular basis to 129 patients using albuterol on an as-needed basis for symptoms. Differences in neither beneficial nor deleterious effects were apparent between the 2 cohorts. Of note, there was no evidence of an increase in exacerbations when using albuterol regularly. There was only one distinction between the two groups—greater financial cost for individuals using albuterol regularly.

Although the study by Drizen et al. enhanced knowledge about regularly scheduled albuterol use, concerns continued regarding use of albuterol for specific populations. Because patients with certain β-receptor genotypes may be at risk when using albuterol regularly, the ACRN designed and completed a genotype-stratified, crossover, placebo-controlled trial to further explore the ramifications of scheduled use.

Israel et al. compared clinical outcomes and the objective parameter of airflow between patients who were homozygous for glycine (gly/gly) and patients who were homozygous for arginine (arg/arg) at the sixteenth amino acid of the β-receptor. This amino acid...
was selected based on data suggesting that adverse effects to regular use of β-agonists were greater in individuals with the arg/arg genotype. Patients were randomly assigned to regular use of albuterol or placebo, and they were crossed over after 16 weeks to the opposite arm. All patients had mild asthma and were matched by FEV₁ and genotype in the 2 groups. To reduce variables, albuterol was replaced by ipratropium bromide for rescue use during the study.¹⁷

As expected, results between the 2 genetic groups differed, with regular use of albuterol increasing peak flow in patients with the gly/gly genotype and decreasing peak flow in patients with the arg/arg genotype.¹⁷ Similar changes were observed between the groups in FEV₁, symptoms, and use of rescue medications. In contrast to the albuterol study by Drazen et al,¹⁶ which was not randomized by genotype and which demonstrated that albuterol was equally safe and effective when used regularly or as needed, data from the genotype-stratified study by Israel et al.¹⁷ showed adverse effects in the arg/arg cohort—suggesting less safety and efficacy of the LABA in patients with the arg/arg genotype.¹⁷ Similary, patients with the arg/arg genotype required higher doses of methacholine than did patients with the arg/arg genotype.¹⁷ Similar changes were observed between the groups in FEV₁, symptoms, and use of rescue medications. In contrast to the albuterol study by Drazen et al,¹⁶ which was not randomized by genotype and which demonstrated that albuterol was equally safe and effective when used regularly or as needed, data from the genotype-stratified study by Israel et al.¹⁷ showed adverse effects in the arg/arg cohort—suggesting less safety and efficacy of the LABA in patients with the arg/arg genotype.¹⁷

A secondary outcome in the Israel et al¹⁷ study demonstrated that ipratropium can substitute for albuterol as a rescue medication, despite a longer time to effect and smaller improvement in FEV₁ with ipratropium. In addition, ipratropium is more expensive than albuterol. Thus, its use should be limited to patients who are intolerant to albuterol.

Long-acting β-Agonists
Concerns regarding the safety of LABAs led the US Food and Drug Administration (FDA) to mandate a large safety trial in 2011 for these agents.¹⁸-²⁰ Over the past decade, the ACRN has addressed both the safety and efficacy of LABAs in genotype-stratified and nongenotype-stratified studies. Two ACRN studies with a common goal of assessing the safety and efficacy of the LABA salmeterol were the Salmeterol Off Corticosteroids (SOCS) trial²¹ and the Salmeterol +/− Inhaled Corticosteroids (SLICS) trial.²²

In SOCS,²¹ patients with mild asthma were randomly assigned to receive salmeterol, a low dose of ICS, or placebo, while patients with moderate asthma (now referred to as poorly controlled asthma) were randomly assigned to receive salmeterol, ICS, or a combination of salmeterol and ICS with a tapering dose of the ICS. As expected, the SOCS results demonstrated that the SOCS results demonstrated that the SOCS results demonstrated that solo use of a LABA is not effective for controlling asthma, with the cohort receiving only salmeterol having more asthma exacerbations and more treatment failures than the cohort receiving a low dose of ICS. Salmeterol showed no benefit, compared to placebo, on the 3 inflammatory markers used in the study (ie, sputum eosinophils, sputum tryptase, eNO).²¹

The SOCS results²¹ confirmed that salmeterol fails to suppress inflammation and provides no benefit greater than placebo when used as solo treatment in patients with asthma. (This is probably true for all LABAs.) Of major importance is that asthma exacerbations and treatment failures were fewer, but not statistically significant, in the salmeterol group compared to the placebo cohort.²¹

In SLICS,²² salmeterol and ICS combination treatment was compared to ICS solo treatment in patients with moderate persistent asthma. As several industry-sponsored studies have found, the addition of a LABA to an ICS can improve multiple asthma parameters, in addition to lowering the dose of ICS needed to preserve asthma control. In SLICS,²² decreasing the ICS dose by 50% led to a treatment failure rate of 2.8% in patients treated with low-dose ICS plus salmeterol, while the failure rate was 8.3% in the ICS only group. When the ICS was eliminated, the treatment failure rate increased to 46.3% in the ICS solo group, compared to 13.7% of those on combination treatment.

The conclusion drawn from SLICS²² was that salmeterol can allow the dose of ICS to be reduced without loss of control of asthma. However, treatment failures were more than 3 times higher in the cohort in which steroid doses were reduced. This finding was not considered clinically relevant by study authors.

As was the case with albuterol, much interest regarding the association of genotypes with response to LABAs has emerged. Retrospective data from SOCS²¹ and SLICS²² revealed different outcomes in arg/arg vs gly/gly genotypes. To further investigate this association, Wechsler et al.²³ performed a prospective-randomized, genotype-stratified, placebo-controlled, crossover trial. The asthma parameters assessed included albuterol rescue and ipratropium bromide rescue, eNO, immunoglobulin E, methacholine, peak flow, pH in exhaled breath condensate, skin tests, spirometry, and symptom scores and exacerbations.

The only variable difference that Wechsler et al.²³ observed between groups was that the gly/gly cohort receiving ICS plus salmeterol required higher doses of methacholine than did the arg/arg cohort—suggesting less bronchial hyperresponsiveness in the gly/gly participants receiving combination treatment. No other variables, including exacerbations, differed between the groups. The benefits noted with the addition of salmeterol to ICS...
included increased peak flow, increased FEV₁, less need for rescue therapy, and reduced symptoms. However, these benefits were surprisingly greater when salmeterol was given to the arg/arg genotype group.

In summary, genotype differences at the sixteenth amino acid position of the β-receptor does not appear to have a statistically significant effect on asthma control when a LABA is added to an ICS.²¹

Inhaled Corticosteroids
Most clinical trials performed by the ACRN involved ICSs in chlorofluorocarbon-propelled metered-dose inhalers. Since the change in propellant to hydrofluoroalkane, some of these studies no longer have clinical application. The following section focuses on those ACRN studies of ICSs that continue to be clinically relevant.

Guidelines suggest using ICS on a daily basis to control mild persistent asthma.² However, the effectiveness of these guidelines is limited by patient noncompliance. Can use of an as-needed ICS be effective if instituted at times of loss of asthma control? Can an ICS be used successfully for a brief but defined period of time? Can an as-needed ICS be effective compared to regular daily use of an ICS in patients with mild persistent asthma?

The Improving Asthma Control Trial (IMPACT)²⁴ addressed such questions about ICS use on a daily vs as-needed basis in patients with mild persistent asthma. In IMPACT,²⁴ 225 adults were randomly assigned to 1 of 3 treatment groups: (1) use of an ICS in a symptom-based action plan; (2) daily use of an ICS plus use of an ICS in an action plan; or (3) daily use of zafirlukast (an LTRA) plus an ICS action plan. The action plan consisted of budesonide 800 micrograms twice daily for 10 days for asthma-worsening symptoms.

The 3 treatment groups in IMPACT²⁴ did not differ in daily peak flow or exacerbations. However, regular use of an ICS resulted in statistically significant improvements, compared with the other 2 groups, in asthma control scores, asthma-free days, bronchial reactivity, eN O , FEV₁, and sputum eosinophils. The as-needed ICS group and the zafirlukast group did not differ in the asthma parameters analyzed. The as-needed strategy resulted in substantially reduced use of ICS and lower costs. Thus, this strategy may be worth using for the cost-consciousness or nonadherent patient with mild persistent asthma who is reliable enough to use an asthma action plan.²⁴

Approximately 25% of patients will have minimal benefit from ICSs. The ability to predict patient response would help direct physicians’ selections of alternate treatments. In the Predicting Response to Inhaled Corticosteroid Efficacy (PRICE) trial,²⁵ ACRN researchers assessed multiple variables to determine those that would predict response to ICS treatment. Of importance, patients who had good responses to ICSs (ie, >5% increase in FEV₁) continued to require ICSs, with loss of asthma control when they discontinued treatment. By comparison, failure to respond to short-term use of ICSs (ie, <5% change in FEV₁) indicated that such patients may not need ICSs in their treatment plans. The majority of poor responders to ICSs continued to be refractory to the benefit of an ICS over a longer period of time, with no change in their asthma control after discontinuing ICS treatment.²⁵

Of all the parameters tested in the PRICE trial,²⁵ the 3 with greatest predictive value of ICS success were a low FEV₁/FVC ratio, a low FEV₁ value, and a large FEV₁ improvement with albuterol. Because of the brief duration of the study (ie, <6 months), the benefits of ICSs in terms of exacerbations, hospitalizations, and death could not be ascertained. Thus, despite the reported results of PRICE,²⁵ caution is necessary regarding the elimination of ICSs in poor responders.

Steroid Sparing Strategies
One of the earliest ACRN trials was an ICS sparing study with colchicine.²⁶ The outcome of that study failed to demonstrate benefits. The ACRN has considered conducting studies with omalizumab as an ICS sparing strategy, but the high cost of this medication has prevented such studies to date. The use of ICSs on as-needed or as-necessary bases would decrease ICS use, but it would also give mixed messages to patients about asthma being a chronic disease with persistence of inflammation even during asymptomatic periods. Use of alternate treatments in patients who are poor ICS responders would reduce corticosteroid exposure, but alternate agents for patients with asthma are few—and most such alternatives are more costly than ICSs.

The use of a LABA in combination with an ICS to reduce, but not eliminate, the ICS dose is the most logical corticosteroid sparing strategy. Research has demonstrated the effectiveness of LTRAs, but their use as a single agent is limited to patients with mild asthma, in whom beneficial response rates are approximately 65%.²⁷ The following question arises: Can an LTRA be combined with a LABA to provide benefits approximating those expected from an ICS plus a LABA?

The ACRN attempted to answer that question by using a combination of the LTRA montelukast and the LABA salmeterol. In a randomized, placebo-
controlled, crossover study of 192 patients with moderate persistent asthma, Deykin et al\(^28\) compared the montelukast-salmeterol combination to a combination of the ICS beclomethasone with salmeterol. The results indicated that the LTRA-LABA combination was not as effective as the ICS-LABA combination, with treatment failures in the LTRA-LABA group exceeding those in the ICS-LABA arm. In addition, daytime peak expiratory flow rates and asthma control scores were markedly worse in the LTRA-LABA group than in the ICS-LABA group. Thus, the use of an LTRA as add-on treatment to a LABA should not be considered as a steroid sparing strategy.\(^28\)

Because of concerns about LABA alternate treatment, ICS sparing combination treatments have been investigated. In a recently published study by Peters et al\(^29\), the muscarinic receptor antagonist tiotropium bromide was found to be as effective as salmeterol when added to an ICS to control asthma. This study was a 3-way, double-blind, triple-dummy, crossover trial with 210 patients. The 3 arms of the study were: (1) beclomethasone 80 mcg twice daily plus tiotropium 18 mcg each morning, (2) beclomethasone 80 mcg twice daily plus salmeterol 50 mcg twice daily, and (3) beclomethasone 160 mcg twice daily.

Peters et al\(^29\) found that the combination of ICS with tiotropium was more effective than doubling the dose of ICS, as made evident by greater peak flow improvement, increased number of asthma control days, improved FEV\(_1\) rate, and improved daily symptom scores. When compared to the LABA-ICS arm, the tiotropium-ICS combination was equivalent in all monitored outcomes except prebronchodilator FEV\(_1\), which was greater in the tiotropium-ICS intervention arm. The trial by Peters et al\(^29\) confirmed that tiotropium is effective as add-on treatment to ICS to achieve asthma control and as an alternative to increasing the dose of an ICS or to adding a LABA to an ICS.

Sutherland et al\(^30\) assessed strategies for improving asthma control without increasing ICS dose by adding the antibiotic clarithromycin 500 mg twice daily for mild to moderate persistent asthma not well controlled by low-dose ICS. Patients entering the study received bronchoscopy to determine if they had positive or negative polymerase chain reaction (PCR) results for Mycoplasma pneumonia or Chlamydia pneumonia, the 2 microorganisms known to colonize the airway and possibly cause unstable asthma. The primary outcome of the study was the patient’s score on the Asthma Control Questionnaire. Patients were stratified based on their PCR findings. They were then treated for 16 weeks with clarithromycin plus the ICS fluticasone or placebo plus fluticasone.

The data reported by Sutherland et al\(^30\) demonstrated that the addition of clarithromycin did not improve the Asthma Control Questionnaire scores in either the PCR-negative or PCR-positive cohorts. In fact, lung function and inflammatory markers were unchanged by the addition of clarithromycin. The only variable that was affected by the addition of clarithromycin was methacholine concentration, which improved by approximately 1 doubling dose (P = .02). The primary conclusion of the trial was that there is little evidence to support the use of antibiotics to spare or replace the use of ICSs.\(^30\) However, more data are necessary, especially in patients who are PCR-positive, to confirm these findings.

**Final Notes**

Much clinically significant information can be derived from the research performed by the ACRN, including the following 8 points:

- Asthma control is best assessed as recommended in the National Heart, Lung, and Blood Institute’s Guidelines for the Diagnosis and Management of Asthma.
- Albuterol should be used only before exercise and as needed for bronchospasm.
- The use of albuterol, but not LABAs, in patients with the arg/arg genotype can result in a decrease in asthma control.
- The use of as-needed or as-necessary ICS treatment combined with an asthma action plan is as effective as using a daily LTRA.
- A LABA can be used in addition to an ICS to reduce the dose of ICS needed, and a LABA-ICS combination can improve clinical outcomes with little increase in risk.
- An LTRA is not acceptable in place of an ICS to be used in combination with a LABA.
- Tiotropium is as effective as salmeterol as add-on treatment to an ICS.
- Antibiotics do not appear to be effective in improving asthma control.

**References**


Brian Piazza is a 2nd-year medical student at Pennsylvania State University (PSU) in Hershey. Mr. Piazza can be reached by e-mail at bpiiazza@hmc.psu.edu.

Timothy J. Craig, DO, is professor of medicine and pediatrics in the allergy and immunology department at PSU. Dr. Craig can be reached by e-mail at: tcraig@hmc.psu.edu.