

## Current reviews of allergy and clinical immunology

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# Rationale for the major changes in the pharmacotherapy section of the National Asthma Education and Prevention Program guidelines

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Numerous changes have been incorporated into the new National Asthma Education and Prevention Program's Expert Panel Report 3. In the pharmacotherapy section of the report, many of these changes are minor in that they do not alter the basic philosophy of treatment recommendations from the previous Expert Panel Report but only add new formulations, change dosing or dosage forms, or add discussion of risks. However, 4 major changes have been identified, and the rationales for 3 are discussed in detail here. The treatment of childhood asthma is divided into 2 distinct age groups, infants less than 5 years of age and children 5 to 12 years of age, because of the availability of more data suggesting differences in response in these patients, as well as a relative paucity of quality data in the younger patients. Omalizumab, a humanized mAb to IgE, is the only new entity approved for the treatment of asthma since the previous guidelines, and its recommendations were reviewed. The indication for combination therapy with inhaled corticosteroids and long-acting inhaled  $\beta_2$ -agonists (LABAs) has been modified in lieu of the recent black box warning concerning the increased risk of severe asthma exacerbations and death associated with LABA use. However, the inhaled corticosteroids/LABAs are still recommended for patients with moderate-to-severe persistent asthma. The rationale for the continued recommendation is provided. (*J Allergy Clin Immunol* 2007;120:989-94.)

**Key words:** Asthma, treatment guidelines, pediatrics, childhood asthma, omalizumab, long-acting inhaled  $\beta_2$ -agonists, inhaled corticosteroids, adverse effects

### Abbreviations used

Arg: Arginine  
DPI: Dry-powder inhaler  
FDA: US Food and Drug Administration  
Gly: Glycine  
HFA: Hydrofluoroalkane  
ICS: Inhaled corticosteroid  
LABA: Long-acting inhaled  $\beta_2$ -agonist  
MDI: Metered-dose inhaler

The National Asthma Education and Prevention Program's Expert Panel Report 3 contains numerous changes and updates in the pharmacotherapy sections, and these are listed in [Table I](#).<sup>1</sup> Many of these involve updating of available drugs and dosage forms for both the management of chronic asthma and severe acute asthma exacerbations. Although these changes are important to consider in the day-to-day use of these medications, they do not constitute significant paradigm shifts in the management of asthma. On the other hand, 3 changes occurred that represent significant new approaches to asthma therapy and are highlighted in bold in [Table I](#). These changes involve recommendations for a new drug (omalizumab), altered status of long-acting inhaled  $\beta_2$  agonist (LABA)/inhaled corticosteroid (ICS) combinations, and division of the pediatric asthma recommendations to 5- to 11-year-olds and those less than 5 years of age. The purpose of this review is to give the practitioner the rationale for the 3 major changes.

## MINOR CHANGES

Numerous minor changes have been made, including the addition to the ICS comparative chart of mometasone furoate administered by means of dry-powder inhaler (DPI), as well as hydrofluoroalkane (HFA)-propelled

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**TABLE I.** Major and minor changes to the pharmacotherapy section of the asthma guidelines

| Major pharmacotherapy changes                                                                                                                                                                                                                                                                                                                   | Minor pharmacotherapy changes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ol style="list-style-type: none"> <li>1. Division of Pediatrics into 2 groups: 5-11 y and &lt;5 y</li> <li>2. Introduction of omalizumab into the therapy</li> <li>3. Readjustment of the LABA/ICS combination in therapy</li> <li>4. Change of the Stepwise approach with emphasis on control of asthma (see discussion elsewhere)</li> </ol> | <ol style="list-style-type: none"> <li>1. Addition of a new ICS to the dosing chart</li> <li>2. Addition of new inhaled formulations containing HFA propellant to dosing charts and tables</li> <li>3. Deletion of formulations no longer available in the United States</li> <li>4. Addition of new oral formulations to dosing tables</li> <li>5. Updated discussion of short-acting inhaled <math>\beta_2</math>-agonists</li> <li>6. Updated discussion and recommendations for aerosol delivery systems</li> <li>7. Updated discussion of immunomodulators for severe asthma</li> </ol> |

metered-dose inhaler (MDI) preparations of flunisolide and fluticasone propionate. Additional HFA-propelled MDI preparations that have gained marketing approval and therefore are presented in the dosing charts and tables include ipratropium bromide, levalbuterol, and the LABA/ICS combinations salmeterol/fluticasone and formoterol/budesonide. Updated discussions have been provided for nearly all classifications of therapeutic agents, including a new section on immunomodulators that includes omalizumab, intravenous IgG, methotrexate, gold salts, and macrolide antibiotics. An updated discussion of the leukotriene modifiers montelukast, zafirlukast, and zileuton with the addition of new dosage forms and expanded indications is provided. An updated discussion of the short-acting inhaled  $\beta_2$ -agonists includes new data on enantiomeric differences and the potential role of genetic polymorphisms of the  $\beta_2$ -adrenergic receptor on response. Because of the rapidly changing environment surrounding aerosol delivery systems and their importance to asthma therapy, the discussion and table of recommendations has been updated. In addition, treatment of acute exacerbations has been provided its own chapter and is no longer a subdivision of the pharmacotherapy section.

Severe asthma uncontrolled on high-dose ICSs, systemic corticosteroids, or both, although relatively uncommon, accounts for a significant proportion of health care resource use. Numerous drugs that affect the immune system in differing ways have been tried in these patients, including compounds that have failed to gain approval. A new extensive review of the literature found that many of these "immunomodulators," with the exception of omalizumab, discussed below, lacked appropriate or sufficient data to support their use in the face of potential serious adverse effects.<sup>1</sup> An extensive amount of data continues to accumulate on the potential adverse effects of ICSs as they continue to be considered the most effective long-term control therapy for persistent asthma. When administered in low to medium doses, at which most patients derive maximum benefit, they have a wide safety margin, but at high doses, effects on bone mineral density and cataract formation might start becoming apparent, and therefore patients predisposed to those adverse effects should be appropriately monitored.<sup>1</sup>

## MAJOR CHANGES

### Pediatric divisions

Previous guidelines separated the pharmacotherapy into adults and children greater than 5 years of age versus children 5 years old or less.<sup>2</sup> This division was primarily based on the inability of young children to provide adequate lung function data to assess the efficacy of asthma drugs and the relative paucity of well-controlled clinical trials in children in general. Most pharmacotherapy trials for gaining US Food and Drug Administration (FDA) approval were performed in adults and children down to 12 years of age (although there were relatively small numbers of adolescents included in the trials). However, in the intervening years, a number of regulatory changes occurred, including the Pediatric Labeling and Extrapolation provision of 1994 and the final Pediatric Rule in 1998 and the Drug Modernization Act.<sup>3</sup> These provisions were further strengthened by the passage of the Best Pharmaceuticals for Children Act in 2002 and the Pediatric Research Equity Act in 2003.<sup>3</sup> In essence, these regulations provided an extension in exclusivity for testing marketed pharmaceuticals in children and mandated testing in children for new pharmaceuticals that would be used in diseases of childhood (ie, asthma and allergies). Thus with both a regulatory mandate and financial incentives, more controlled clinical trials were performed in children. The FDA provided guidance for obtaining approval in young children that allowed extrapolation of efficacy from studies in adults and older children, provided they were supplemented with safety and pharmacokinetic data in the specific pediatric age group.<sup>4</sup> This presumes that the disease and pharmacologic effect are not likely to vary significantly in younger age groups.

As a result of the new regulations, more drugs have gained FDA-approved labeling for younger children based on efficacy studies: budesonide nebulizer suspension for 1- to 8-year olds; fluticasone propionate administered by means of DPI for 4- to 11-year-olds; beclomethasone dipropionate administered by means of MDI with HFA propellant for 5- to 11-year-olds; cromolyn nebulizer solution for 2- to 12-year-olds; formoterol administered by means of DPI for 5- to 11-year-olds; montelukast, 5 mg,

for 6- to 14-year-olds; zafirlukast for 7- to 11-year-olds; and levalbuterol HFA for 4- to 11-year-olds. In addition, some drugs have gained FDA-approved labeling based on extrapolation of efficacy and safety from studies on adults and older children plus safety and pharmacokinetic data in the children and some limited efficacy data: fluticasone propionate HFA for 4- to 11-year olds (efficacy and safety from DPI studies in same age); fluticasone/salmeterol administered by means of DPI for 4- to 11-year olds; salmeterol administered by means of DPI for 4- to 11-year-olds; and montelukast, 4 mg, for 1- to 5-year-olds.

Although the age ranges for approvals might seem to indicate that the cut-off point of 5 years is somewhat arbitrary, it was believed that 5 years still represented the age at which one could obtain reproducible spirometric measures for assessing an objective outcome from clinical trials and thus evaluate whether these children respond in a similar manner to adults.<sup>5</sup> In addition, there has been a significant increase in data for this age group. Under the age of 5 years, more subjective outcome criteria, such as symptoms and as-needed use of rescue medication, are needed.<sup>6-8</sup> Most 4-year-olds are able to generate sufficient peak inspiratory flows to achieve adequate dosing from DPIs.<sup>9</sup> However, at less than 4 years of age, many children are unable to cooperate fully with DPIs or MDIs and will require the parent to assist with the use of an MDI plus a valved holding chamber or nebulizer, both with a facemask.<sup>6,8,10</sup> In the younger infants the use of a facemask in combination with low tidal volumes results in lower delivery of aerosols.<sup>11,12</sup> Finally, there are some data suggesting that young children with predominantly virus-induced wheezing might respond differently to therapy, and many therapies have not even been studied in children less than 5 years of age.<sup>1</sup>

### Omalizumab placement in therapy

Omalizumab is the newest entity for the treatment of asthma. It is a recombinant DNA-derived humanized mAb to the Fc portion of the IgE antibody that prevents the binding of IgE to its high-affinity receptor (FcεRI) on mast cells and basophils.<sup>13</sup> The decreased binding of IgE on the surface of mast cells leads to a decrease in the release of mediators in response to allergen exposure. In addition, omalizumab decreases FcεRI expression on basophils and airway submucosal cells.<sup>14</sup> Omalizumab was approved for the treatment of moderate-to-severe persistent atopic asthma in adults and children 12 years and older whose symptoms were inadequately controlled with ICSs.<sup>13</sup> However, the Expert Panel Report 3 recommended the use of omalizumab as adjunctive therapy for adult patients with severe persistent asthma whose symptoms were inadequately controlled with high-dose ICSs plus LABAs.<sup>1</sup> The basis of that decision is outlined below.

As with most new entities, there are limited efficacy and safety trials and no comparator trials with other adjunctive therapies. The majority of patients in pivotal clinical trials of omalizumab had moderate-to-severe persistent asthma incompletely controlled with ICSs.<sup>15-17</sup> All patients had atopy and proved sensitivity to an aeroallergen. Most

trials were designed with a 16-week stable corticosteroid period, followed by a 12-week tapering corticosteroid phase.<sup>15-18</sup> Adding omalizumab to ICS therapy generally produced a reduction in asthma exacerbations,<sup>15,16,19</sup> although not always.<sup>17,18</sup> Omalizumab also had a modest steroid-sparing effect, allowing a median reduction of 25% over that of placebo in the trials.<sup>15-18</sup> In addition, at least 50% of patients receiving placebo in the trials were able to achieve a significant reduction in corticosteroid dose ( $\geq 50\%$ ). In 2 trials, one open-label, of patients with severe persistent asthma inadequately controlled with ICSs plus LABAs, omalizumab reduced asthma exacerbations and emergency department visits.<sup>20,21</sup>

Omalizumab has not been compared in clinical trials with the other adjunctive therapies for moderate persistent asthma (LABAs, leukotriene modifiers, and theophylline), all of which improve outcomes and allow reduction of corticosteroid dose. The one study in children 6 to 12 years of age produced nonsignificant reductions in exacerbations and no improvement in lung function but did allow a reduction in ICS dose compared with that seen with placebo.<sup>17</sup> However, omalizumab is the only adjunctive therapy to demonstrate added efficacy to high-dose ICSs plus LABAs in patients with severe persistent allergic asthma.<sup>21,22</sup>

### Adjustment of the placement of combination ICSs/LABAs

The 2002 update of the guidelines placed the ICS/LABA combinations as preferred therapy for patients with moderate and severe persistent asthma in adults because of the demonstration of improved lung function, symptom control, and reduced exacerbations compared with that seen with higher doses of ICSs (usually double) alone.<sup>23</sup> For infants and children less than 5 years of age, preferred therapy for moderate persistent asthma included both medium-dose ICSs and a combination of low-dose ICSs and LABAs because of the lack of data on combination therapy in this age group. The new guidelines place increasing the dose of ICSs from low to medium at equal weight with ICSs/LABAs for those patients whose symptoms are not controlled with low-dose ICSs, regardless of age. As discussed below, this is primarily a result of studies suggesting an increased risk of serious asthma exacerbations, including asthma deaths, in patients prescribed LABAs in addition to their standard therapy, in particular the Salmeterol Multicenter Asthma Research Trial (SMART).<sup>24-26</sup> This association with severe asthma exacerbations has resulted in a black box warning and change in FDA-approved labeling for all products containing LABAs.<sup>27</sup> Both the significance of the findings and potential mechanisms for the adverse outcomes have been extensively debated in the literature and will not be repeated in detail here.<sup>28-30</sup> Rather, the reasoning behind the current consensus will be outlined.

Numerous studies and meta-analyses of adults and children 12 years and older have established that the ICS/LABA combination therapy is more effective at controlling symptoms, improving lung function, and reducing moderate-to-severe asthma exacerbations than increasing

the dose of ICS by 2-fold.<sup>23,31-35</sup> Indeed, a large prospective trial found a greater proportion of patients were able to gain guideline-defined control from combination therapy than from increasing the dose of ICS.<sup>35</sup> Thus there is no evidence for a general increased risk of severe asthma exacerbations in adult patients receiving combination ICSs/LABAs. In children 4 to 11 years old, combination therapy improves lung function and symptom control; however, evidence for a positive effect on exacerbations is lacking.<sup>36</sup> Combination ICSs/LABAs have not been studied in children less than 4 years old nor has any other combination. Thus any recommendation in infants and children requires extrapolation of data from older children.

Evidence for an increased risk of severe exacerbations from LABAs originates from studies that compared monotherapy with LABAs with monotherapy with ICSs or compared the addition of LABAs with the patients "usual therapy," which might or might not have included ICSs.<sup>24-26,30,36-39</sup> Large systematic reviews comparing LABAs with placebo and short-acting inhaled  $\beta_2$ -agonists found a reduced risk of severe exacerbations compared with placebo (odds ratio, 0.78; 95% CI, 0.69-0.88) and a similar risk compared with short-acting  $\beta_2$ -agonists (odds ratio, 0.90; 95% CI, 0.78-1.03).<sup>40</sup> The previous guidelines stated that LABAs "should not be used in place of anti-inflammatory therapy," and that they should be "added to anti-inflammatory therapy."<sup>2</sup> Thus the 2 large trials suggesting an increased risk of death from asthma in patients prescribed LABAs, although consistent with approved labeling, were not in line with guideline recommendations.<sup>25,39</sup> It bears mentioning that although the SMART trial demonstrated a statistically significant increased risk of asthma-related deaths in the entire population, an increased risk of death was not seen in the subset of patients reporting ICS use at baseline ( $n = 12,265$ ).<sup>25</sup> However, the study was not powered to assess subsets and therefore was insufficient by itself to determine whether ICS therapy obviates the risk from LABAs.

A direct physiologic or pharmacologic mechanism for LABAs worsening asthma pathology has not been established. The regular sustained use of all  $\beta_2$ -agonists induces tolerance by decreasing binding affinity, as well as through downregulation of the  $\beta_2$ -adrenergic receptor.<sup>41,42</sup> Although the tolerance results in a decreased duration of bronchoprotection from contractile stimuli, such as exercise, a standard dose of short-acting inhaled  $\beta_2$ -agonists administered before exercise still blocks bronchospasm.<sup>43,44</sup> Tolerance induced from LABAs reduces the response to short-acting  $\beta_2$ -agonists after moderate bronchospasm induced by methacholine, but it only takes one additional dose to produce the same degree of bronchodilation.<sup>45-47</sup> In addition, a trial in patients presenting to the emergency department demonstrated no difference in bronchodilator response to short-acting  $\beta_2$ -agonists in patients previously receiving LABAs and those not receiving LABAs.<sup>48</sup> Neither short- nor long-term administration of LABAs induces an increase in bronchial responsiveness similar to that seen with administration of short-acting  $\beta_2$ -agonists.<sup>40-42</sup> Finally, neither the

characteristics of lung function deterioration leading to an acute exacerbation nor their recovery are different in patients receiving LABAs compared with those seen in patients receiving ICSs alone.<sup>49</sup>

Findings from large studies and meta-analyses cannot rule out the potential for a direct effect producing worsening of asthma caused by a relatively rare phenotypic or genotypic predisposition. The most extensively studied polymorphism of the  $\beta_2$ -adrenergic receptor has been the homozygous single nucleotide substitution of arginine (Arg) for glycine (Gly) at codon 16 that affects about 15% of the white population but could approach 30% in black and Asian subjects.<sup>50</sup> Early studies applying retrospective genetic analysis to previous prospective clinical trials reported decreased lung function and increased exacerbations with chronic regular use of the short-acting albuterol in homozygous Arg/Arg patients but not for other genotypes.<sup>51,52</sup> This was followed by a prospective trial stratified by genotype (Arg/Arg and Gly/Gly) that reported somewhat lower peak flows and increased symptoms in the Arg/Arg group that received albuterol compared with placebo as a result of the improvement in the placebo group and a marked improvement in peak flow and symptoms in the Gly/Gly group that received albuterol compared with placebo.<sup>53</sup> Because of the improvement in lung function and symptoms in the Gly/Gly group, the secondary comparison of the 2 genotypes with albuterol was highly significant.

Data on the effect of the Arg/Arg genotype during regular use of LABAs are inconclusive. Unlike albuterol, salmeterol therapy was not associated with an increase in exacerbations compared with placebo in the Arg/Arg group.<sup>52</sup> A retrospective genetic analysis of a small number of patients from 2 trials of the National Institutes of Health-sponsored Asthma Clinical Research Network reported lower morning peak flows in the Arg/Arg group compared with those in the Gly/Gly group receiving salmeterol because of both improvement in the Gly/Gly group and a decrease in the Arg/Arg group in the one study.<sup>54</sup> However, the differences between genotypes in the second study were driven by the improvement in lung function and symptoms in the Gly/Gly genotype and not because of significant deterioration from baseline in the Arg/Arg group.<sup>54</sup> A retrospective genetic analysis of multiple trials assessing tolerance to the bronchoprotective effects of formoterol and salmeterol reported a significant association with loss of bronchoprotection with the Arg genotype, both homozygous and heterozygous, compared with Gly/Gly homozygotes.<sup>55</sup> A more recent retrospective genetic analysis of outcomes from 2 trials comparing the ICS/LABA combination with montelukast in patients with mild-to-moderate persistent asthma reported no difference in response to LABA/ICS between Arg/Arg, Arg/Gly, and Gly/Gly patients.<sup>56</sup> A cross-sectional survey of 546 children and young adults reported an increased risk of exacerbations in the past 6 months in Arg/Arg patients compared with that seen in Gly/Gly patients, particularly in those patients treated with salmeterol.<sup>57</sup> However, as seen from the above, it is not clear

whether this is due to improvement in the Gly/Gly population or worsening in the Arg/Arg population.

Because of the lack of a definitive direct pharmacologic effect for LABAs producing severe asthma exacerbations, it has been posited that patients prescribed LABAs might delay seeking medical care for exacerbations, thus resulting in poorer outcomes.<sup>25</sup> Although this is as plausible a hypothesis as a direct effect of the LABAs producing asthma deterioration, it is similarly supported by only circumstantial evidence. Various epidemiologic studies have not found an increased risk of death from LABA use, including a large prescription event surveillance study and a case-control study of 532 asthma deaths, both from the United Kingdom.<sup>58,59</sup> These inconsistencies might be due to a lack of power in these somewhat smaller trials or to a lack of a definitive cause for the association and are therefore fodder for debate. Regardless, the SMART trial was a large randomized prospective trial with a placebo control that raised concern over the safety of LABAs. This increased level of concern about LABAs combined with the results of 2 large clinical trials showing that a number of patients could be adequately controlled with ICS therapy alone resulted in the addition of medium-dose ICSs as a second preferred alternative in patients whose symptoms are inadequately controlled with low-dose ICSs.<sup>35,60</sup>

Finally, a recent meta-analysis seemed to support that LABAs produced excess serious asthma exacerbations and claimed that LABAs were responsible for 4000 deaths per year in the United States.<sup>30</sup> However, this meta-analysis included the SMART trial and the formoterol studies cited by the FDA, and the results of death and life-threatening asthma were primarily driven by the SMART trial, and the analysis of hospitalizations were primarily driven by the formoterol studies cited by the FDA; thus it did not provide new evidence over that assessed by the FDA advisory panel. In addition, this meta-analysis failed to include studies of the addition of LABAs to ICSs or to recognize other meta-analyses on this subject that all reported significant reductions in exacerbations from the addition of LABAs to ICSs.<sup>31-34,40</sup> Finally, evidence for LABAs producing 4000 deaths per year is lacking. Over the past 10 years, since the introduction of LABAs, both hospitalizations and deaths from asthma have been decreasing, and therefore there were only 3780 deaths reported for 2004 in the United States.<sup>61</sup>

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## Continuing Medical Education examination

# Rationale for the major changes in the pharmacotherapy section of the National Asthma Education and Prevention Program guidelines

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### Learning objectives: "Rationale for the major changes in the pharmacotherapy section of the National Asthma Education and Prevention Program guidelines"

1. To understand the rationale for dividing children into 2 distinct age ranges in the new National Asthma Education and Prevention Program (NAEPP) guidelines.
2. To be able to define the role of omalizumab in the long-term control of moderate to severe asthma.
3. To understand the evidence supporting the rationale for using inhaled corticosteroid/long-acting inhaled  $\beta_2$ -agonist (ICS/LABA) combination therapy in moderate to severe asthma.

### CME items

**Question 1.** Which of the following is true concerning achieving Food and Drug Administration (FDA) approval of drugs in young children (less than 6 years old) based on the Best Pharmaceuticals for Children Act in 2002 and the Pediatric Research Equity Act in 2003?

- A. Approval in young children requires 2 randomized, placebo-controlled trials in the age group of interest demonstrating both safety and efficacy.
- B. Approval in young children requires sufficient data in the literature suggesting efficacy and safety, either uncontrolled trials or case series.
- C. Approval in young children requires safety and limited pharmacokinetic studies that supplement extrapolation of efficacy data from older children and adults.
- D. Approval in young children is required at the time of approval in older children if the drug is likely to be used to treat younger children.

**Question 2.** Which of the following controllers has been approved for children as young as 1 year of age based on randomized, placebo-controlled clinical trials of efficacy and safety?

- A. montelukast 4 mg granules
- B. budesonide nebulizer suspension
- C. levalbuterol nebulizer solution
- D. cromolyn nebulizer solution

**Question 3.** Which of the following statements concerning children with asthma less than 5 years of age is the most accurate?

- A. Young children with viral-induced wheezing appear to respond to therapy in a similar way as older children and adults with asthma.
- B. Children as young as 2 and 3 years old can cooperate and use dry-powder inhalers.
- C. Young children using a spacer and facemask are likely to receive a lower dose of aerosol than older children using a mouthpiece.
- D. Most short-acting inhaled  $\beta_2$ -agonists delivered by metered-dose inhaler are approved for use in children provided they are used with a spacer device.

*Question 4.* Omalizumab has been approved for the treatment of atopic asthma in children more than 12 years of age and adult patients still symptomatic on chronic corticosteroid therapy, but it is recommended only in the guidelines for atopic patients with severe asthma not completely responding to combination ICS/LABA therapy. The rationale for this is that —

- A. omalizumab has not been compared to other adjunctive therapy to ICSs, such as LABAs, leukotriene modifiers, or theophylline.
- B. omalizumab is too expensive to justify its use in patients taking ICSs only.
- C. omalizumab has been more extensively studied in patients with severe asthma receiving combination therapy.
- D. omalizumab has been shown to be more effective than ICS dosing in allowing a reduction in oral corticosteroid dosing.

*Question 5.* Which of the following statements is true concerning the use of ICS/LABA combination therapy in children?

- A. Fluticasone propionate/salmeterol is not approved for children under 12 years of age.
- B. ICS/LABA combination therapy has been studied in children under 4 years of age.
- C. ICS/LABA therapy has not yet demonstrated a reduction in exacerbations in children.
- D. ICS/LABA combination is not recommended in children less than 5 years of age.

*Question 6.* Which of the following statements best describes the placement of ICS/LABA combinations in the new NAEPP's Expert Panel Report 3 guidelines?

- A. Patients not adequately controlled on low-dose ICS and other adjunctive therapy should be placed on ICS/LABAs.
- B. Patients not adequately controlled on medium-dose ICS should be placed on ICS/LABAs.
- C. Patients inadequately controlled on high-dose ICS should be placed on ICS/LABAs plus other adjunctive therapy.
- D. Patients inadequately controlled on low-dose ICS should have their ICS dose increased or should be placed on ICS/LABAs.

*Question 7.* The US FDA has mandated “black box” warnings on all preparations containing LABAs. The basis for this comes from studies of —

- A. the addition of LABA monotherapy versus placebo to standard care therapy at the time.
- B. the addition of LABAs to ICS versus placebo or increasing the dose of ICS.
- C. meta-analyses of LABA/ICS combination versus ICS monotherapy on exacerbations.
- D. comparisons of LABA to ICS, each as monotherapy.

*Question 8.* The subset of patients in SMART who reported taking an ICS on entry into the study did not show an increase in death and life-threatening exacerbations in the salmeterol group compared with the placebo group. Which of the following statements is the most appropriate conclusion based on this information?

- A. The use of ICS mitigates against any adverse consequence of LABAs.
- B. The use of ICS would appear to prevent the decreased responsiveness caused by chronic  $\beta_2$ -agonist use.
- C. LABAs likely enhance the inflammatory response in asthma, leading directly to severe exacerbations.
- D. Because of power limitations, these data are insufficient to conclude that ICSs mitigate the risk from LABAs.

*Question 9.* Which of the following best describes the physiologic mechanism underlying the increased risk of severe exacerbations from LABA use?

- A. no physiologic mechanism
- B. increased bronchial hyperresponsiveness secondary to chronic  $\beta_2$ -agonist administration.
- C. decreased smooth muscle responsiveness secondary to  $\beta_2$  adrenergic receptor tolerance.
- D. enhanced inflammation secondary to proinflammatory effect of  $\beta_2$ -agonists.

*Question 10.* Which of the following best describes the effect of ICS/LABAs on the frequency of asthma exacerbations in adults?

- A. The combination increases the risk of asthma exacerbations over that of ICS alone.
- B. After control is achieved with the combination, exacerbation will continue to be suppressed with LABA monotherapy.
- C. The combination lowers the risk of exacerbations at lower ICS doses than ICS therapy alone.
- D. Doubling the dose of ICS is usually sufficient to produce the same reduction in exacerbations seen with ICS/LABA.