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# New asthma guidelines emphasize control, regular monitoring

## ABSTRACT

Updated asthma care guidelines have recently been released. This review will focus on several elements in the third Expert Panel Report (EPR3) guidelines that reflect substantial differences from recommendations of the second EPR (EPR2) guidelines, issued in 1997 and updated in 2002. A major difference is the emphasis on asthma control. Asthma control can be assessed serially by the use of validated instruments. The goal of asthma therapy is to achieve asthma control by reducing current impairment and future risk. Recommendations for asthma pharmacotherapy have also been revised since the release of the updated EPR2 guidelines. The revisions in asthma management proposed in these guidelines offer the potential for improved asthma care outcomes in the United States.

## KEY POINTS

The EPR3 recommends that management decisions be based initially on asthma severity, and subsequently on asthma control as assessed serially by validated tests.

Omalizumab, a monoclonal antibody against immunoglobulin E, is the only adjunctive therapy to demonstrate efficacy when added to high-dose inhaled corticosteroids plus long-acting beta agonists in patients with severe, persistent, allergic asthma.

The EPR3 guidelines recommend consideration of allergen immunotherapy for patients with mild or moderate persistent allergic asthma.

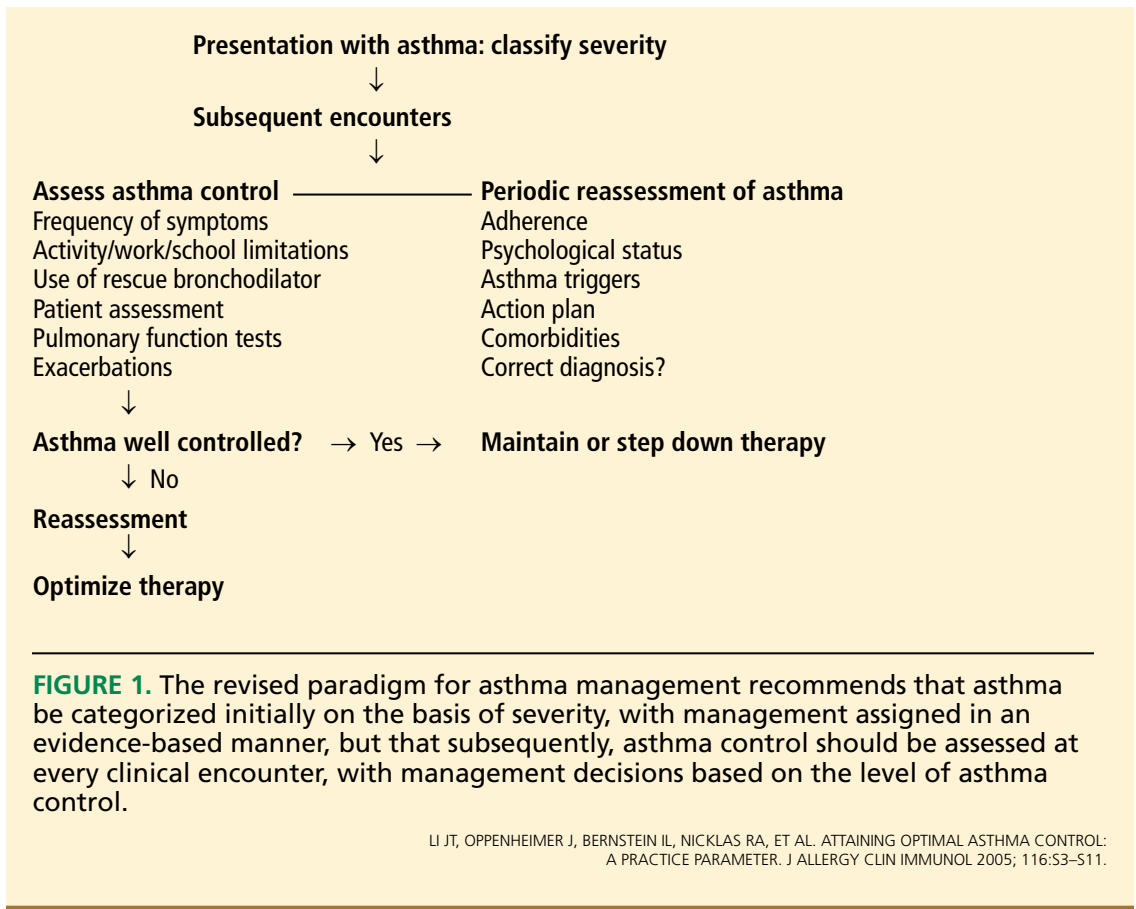
THIS REVIEW FOCUSES on several elements in the National Asthma Education and Prevention Program's new guidelines, the third Expert Panel Report (EPR3),<sup>1</sup> that differ substantially from those in EPR2,<sup>2</sup> issued in 1997 and updated in 2002.<sup>3</sup> These differences in approach to the management of asthma described in EPR3 offer a clear potential for reducing the gap between optimal asthma care outcomes as described in guidelines and normative asthma care outcomes in the "real world."

## GREATER EMPHASIS ON CONTROL

The EPR2 guidelines<sup>2</sup> recommended that asthma management be carried out in an algorithmic manner. Patients were classified into four severity categories: mild intermittent, mild persistent, moderate persistent, and severe persistent asthma, based on assessment of the level of symptoms (day/night), reliance on "reliever" medication, and lung function at the time of presentation. Pharmacologic management was then assigned according to each respective categorization in an evidence-based fashion.

In an ideal world, this would result in patients with asthma receiving appropriate pharmacotherapeutic agents associated with favorable asthma care outcomes, which were also advantageous from both cost- and risk-benefit standpoints. In the real world, however, this paradigm was flawed, as it relied on accurate categorization of patients in order for pharmacotherapy to be prescribed appropriately. Both providers and patients are prone to underes-

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**Both providers and patients tend to underestimate asthma severity; this encourages undertreatment of asthma**

timate asthma severity,<sup>4,5</sup> and for this reason many patients managed on the basis of this paradigm were undertreated.

A new paradigm, based on the assessment of asthma control, has been encouraged in the EPR3 guidelines.<sup>1</sup>

**Severity and control are not synonymous**

More than a decade ago, Cockcroft and Swystun<sup>6</sup> pointed out that asthma control (or lack thereof) is often used inappropriately to define asthma severity: ie, well-controlled asthma is seen as synonymous with mild asthma, and poorly controlled asthma with severe asthma.

Asthma severity can be defined as the intrinsic intensity of the disease process, while asthma control is the degree to which the manifestations of asthma are minimized. Asthma severity is clearly a determinant of asthma control, but its impact is affected by a variety of factors, including but not limited to:

- Whether appropriate medication is prescribed

- Patterns of therapeutic adherence
- The degree to which recommended measures for avoiding for clinically relevant aeroallergens are pursued.

Health care utilization, including hospitalizations and emergency department visits, correlates more closely with asthma control than with asthma severity.<sup>7-9</sup> Indeed, a patient with severe persistent asthma who is treated appropriately with multiple “controller” medications and who takes his or her medications and avoids allergens as directed can achieve well-controlled or totally controlled asthma, and is not likely to require hospitalization or emergency department management, to miss school or work, or to experience nocturnal awakening or limitation in routine activities due to asthma. This patient has severe persistent asthma that is well controlled.

In contrast, a patient with mild or moderate persistent asthma who does not receive appropriate instructions for avoiding allergens or taking controller medication regularly or

TABLE 1

### Classification of asthma severity (patients 12 years old and older)

COMPONENTS OF SEVERITY <sup>a</sup>		CLASSIFICATION OF ASTHMA SEVERITY			
		INTERMITTENT	MILD	MODERATE	SEVERE
<b>Impairment</b>	Symptoms	≤ 2 days/week	> 2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤ 2 times/month	3-4 times/month	> Once a week but not nightly	Often 7 times/week
	Short-acting beta agonist use for symptom control (not prevention of exercise-induced bronchospasm)	≤ 2 days/week	> 2 days/week but not daily, and not more than once on any day	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	Normal FEV <sub>1</sub> between exacerbations	FEV <sub>1</sub> > 80% predicted	FEV <sub>1</sub> > 60% but < 80% predicted	FEV <sub>1</sub> < 60% predicted
		FEV <sub>1</sub> > 80% predicted FEV <sub>1</sub> /FVC normal	FEV <sub>1</sub> /FVC normal	FEV <sub>1</sub> /FVC reduced ≤ 5%	FEV <sub>1</sub> /FVC reduced > 5%
<b>Risk</b>	Exacerbations requiring oral systemic corticosteroids	0–1/year	≥ 2/year <sup>b</sup>		
<p>Consider severity and interval since last exacerbation.</p> <p>Frequency and severity may fluctuate over time for patients in any severity category.</p> <p>Relative annual risk of exacerbations may be related to FEV<sub>1</sub>.</p>					
<b>Recommended step for initiating treatment</b>	Step 1	Step 2	Step 3	Step 4 or 5	
			And consider short course of oral systemic corticosteroids		

FEV<sub>1</sub> = forced expiratory volume in 1 second, FVC = forced vital capacity

<sup>a</sup> Level of severity is determined by assessment of both impairment and risk. Assess impairment domain by patient's and caregiver's recall of previous 2–4 weeks and spirometry. Assign severity to the most severe category in which any feature occurs.

<sup>b</sup> At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (eg, requiring urgent, unscheduled care, hospitalizations, or intensive care unit admission) indicate greater underlying disease severity. For treatment purposes, patients who had two or more exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

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who is poorly adherent will likely have poor asthma control. This patient is more likely to require hospitalization or emergency department management, to miss school or work,

and to experience nocturnal awakening or limitation in routine activities due to asthma. This patient has mild persistent asthma that is poorly controlled.

**TABLE 2**

**Classification of asthma control (patients 12 years old and older)**

COMPONENTS OF CONTROL <sup>a</sup>	CLASSIFICATION OF ASTHMA CONTROL		
	WELL CONTROLLED	NOT WELL CONTROLLED	VERY POORLY CONTROLLED
<b>Impairment</b>			
Symptoms	≤ 2 days/week	> 2 days/week	Throughout the day
Nighttime awakenings	≤ 2 times/month	1-3 times/week	≥ 4 times/week
Interference with normal activity	None	Some limitation	Extremely limited
Short-acting beta agonist use for symptom control (not prevention of exercise-induced bronchospasm)	≤ 2 days/week	> 2 days/week	Several times/day
FEV <sub>1</sub> or peak flow	> 80% predicted or personal best	60%–80% predicted or personal best	< 60% predicted or personal best
<b>Validated questionnaires <sup>b</sup></b>			
ATAQ	0	1–2	3–4
ACQ	≤ 0.75 <sup>b</sup>	≥ 1.5	NA
ACT	≥ 20	16–19	≤ 15
<b>Risk</b>			
Exacerbations requiring oral systemic corticosteroids	0–1/year Consider severity and interval since last exacerbation.	2–3/year <sup>c</sup>	> 3/year
Progressive loss of lung function	Evaluation requires long-term follow-up care.		
Treatment-related adverse effects	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.		

ATAQ = Asthma Therapy Assessment Questionnaire, ACQ = Asthma Control Questionnaire, ACT = Asthma Control Test, FEV<sub>1</sub> = forced expiratory volume in 1 second.

<sup>a</sup>The level of control is based on the most severe impairment or risk category. Assess impairment domain by patient’s recall of previous 2–4 weeks and by spirometry or peak flow measures. Symptom assessment for longer periods should reflect a global assessment, such as inquiring whether the patient’s asthma is better or worse since the last visit.

<sup>b</sup>ACQ values of 0.76–1.4 are indeterminate regarding well-controlled asthma.

<sup>c</sup>At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (eg, requiring urgent unscheduled care, hospitalization, or intensive care unit admission) indicate poorer disease control. For treatment purposes, patients who had two or more exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have not-well-controlled asthma, even in the absence of impairment levels consistent with not-well-controlled asthma.

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**Assess asthma severity in the first visit, and control in subsequent visits**

The revised algorithm for asthma management (FIGURE 1) recommends that asthma care providers categorize asthma severity at the

initial visit (TABLE 1) and assess asthma control in subsequent visits (TABLE 2).

**How to assess severity**

The previous guidelines proposed that asthma

severity be assessed before starting long-term therapy. However, many patients are already taking controller medications when initially seen. In the EPR3 guidelines,<sup>1</sup> asthma severity can be inferred on the basis of response or lack of response to drug therapy. Responsiveness is defined as the ease with which asthma control can be achieved by therapy. At the initial visit, severity is assessed on the basis of impairment and risk (TABLE 1), whether or not the patient is regularly taking controller medication. In assessing impairment, we focus on the present, eg, ascertaining symptom frequency and intensity, functional limitation, lung function, and whether the patient follows the treatment and is satisfied with it.

In assessing risk, we focus on the future, with the aim of preventing exacerbations, minimizing the need for emergency department visits or hospitalizations, reducing the tendency for progressive decline in lung function, and providing the least amount of drug therapy required to maintain control in order to minimize risk of untoward effects. The impairment and risk domains may respond differently to treatment.

### How to measure control

For all patients with asthma, regardless of severity, the goal is the same: to achieve control by reducing both impairment and risk. Asthma is classified as well controlled, not well controlled, or poorly controlled (TABLE 2).<sup>1</sup>

### Validated tests are available to assess control

Asthma control is multidimensional<sup>9</sup> and can be assessed by use of validated tests such as the Asthma Control Questionnaire (ACQ), Asthma Therapy Assessment Questionnaire (ATAQ), and the Asthma Control Test (ACT) (TABLE 3). These tests were designed to gauge asthma control over time in a user-friendly fashion. They are valid, reliable, and responsive to asthma control over time.<sup>9-13</sup>

In the case of the ACT (TABLE 4), the patient answers five questions (each on a scale of 1 to 5) about symptoms and the use of rescue medications in the previous 4 weeks. In general, the higher the score (range 5–25), the better the control of the asthma; a cut-point of 19 yields the best balance of sensitivity (71%)

TABLE 3

### What asthma control questionnaires measure

	ASTHMA CONTROL TEST	ASTHMA CONTROL QUESTIONNAIRE	ASTHMA THERAPY ASSESSMENT QUESTIONNAIRE
Daytime symptoms	✓	✓	
Nocturnal symptoms	✓	✓	✓
Activity restriction	✓	✓	✓
Reliever use	✓	✓	✓
Lung function		✓	
Self-perception of control	✓		✓
Symptom severity		✓	
Time frame	Previous 4 weeks	Previous week	Previous 4 weeks and previous 12 months
No. of dimensions	5	7	4

and specificity (71%) for classifying asthma as well controlled or not well controlled.<sup>13</sup>

### Serial testing as a quality indicator

Serial ACT scores give an objective measure of the degree to which the goals of management<sup>1</sup> are being achieved, and in so doing can encourage optimal outcomes.<sup>14</sup>

Another use of these tests is to document whether asthma control improves over time when patients receive care from a particular physician or group. This use may become increasingly important in view of efforts underway to implement a pay-for-performance model for asthma care, in which providers will be financially rewarded for improved patient care outcomes and adherence to standards of practice based on Health Plan Employer Data and Information Set measures.<sup>15</sup>

We have used the ACT in the Section of Allergy/Immunology at Cleveland Clinic for 3 years on a routine basis. All patients with asthma being seen either for the first time or as follow-up complete the ACT, which has been entered in a flow sheet in our electronic medical record, at the same time they undergo spirometry. We have shown that care in the Section of Allergy/Immunology is associated with improvement in asthma control over

**'Poor perceivers' may have substantial ventilatory impairment, but little or no subjective awareness of it**

**TABLE 4**

**The Asthma Control Test (ACT)**

1	2	3	POINTS	4	5	YOUR SCORE
<b>In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, at school, or at home?</b>						
All of the time	Most of the time	Some of the time		A little of the time	None of the time	_____
<b>During the past 4 weeks, how often have you had shortness of breath?</b>						
More than once a day	Once a day	3 to 6 times a week		Once or twice	Not at all a week	_____
<b>During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness, or pain) wake you up at night, or earlier than usual in the morning?</b>						
4 or more nights a week	2 or 3 nights a week	Once a week		Once	Not at all or twice	_____
<b>During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication such as albuterol (Proventil)?</b>						
3 or more times per day	1 or 2 times per day	2 or 3 times		Once a week per week	Not at all or less	_____
<b>How would you rate your asthma control during the past 4 weeks?</b>						
Not controlled at all	Poorly controlled	Somewhat controlled		Well controlled	Completely controlled	_____
<b>Total score</b>						_____

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time, in patients who have completed serial ACT measurements at initial visits and at follow-up visits (FIGURE 2).

**Objective measurement of lung function is also important**

Serial monitoring of lung function at every patient visit with spirometry is also important, as some patients may be “poor perceivers,”<sup>16</sup> ie, they may have little or no subjective awareness of moderate or even severe ventilatory impairment. A number of studies<sup>17,18</sup> support the contention that symptoms and lung function are separate and independent dimensions of asthma control, and that both of them need to be assessed.

**Responding to changes in control**

If the disease is well controlled, the provider, in collaboration with the patient, may consider continuing the current regimen or “step-

ping down” to a less aggressive treatment. If the patient’s asthma is not well controlled, it is appropriate to “step up” the treatment. The EPR3 guidelines outline a stepwise approach to therapy (TABLE 5), from intermittent asthma (step 1) to severe persistent asthma (steps 5 and 6).<sup>9</sup> If asthma is poorly controlled, the patient is at risk of exacerbation of asthma and on this basis is clearly a candidate for intervention.<sup>11–13,19</sup>

**THE STEP 3 CONTROVERSY**

**Salmeterol Multicenter Asthma Research Trial**

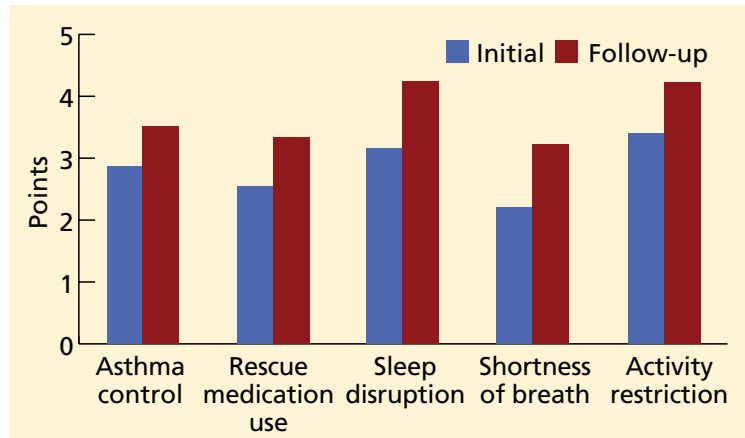
In the Salmeterol Multicenter Asthma Research Trial (SMART), patients randomized to the long-acting beta agonist (LABA) salmeterol (Serevent)—particularly African Americans—had a statistically significant increase in the risk of untoward asthma care outcomes.<sup>20</sup>

SMART was launched in 1996. Patients

were randomized in a double-blind fashion to receive either salmeterol 42 µg twice a day or placebo in addition to their usual asthma therapy for 28 weeks. The rate of the primary outcome (respiratory-related deaths or life-threatening experiences) was not significantly different with salmeterol than with placebo (relative risk [RR] = 1.40, 95% confidence interval [CI] 0.91–2.14). However, in 2003, the study was halted prematurely because of difficulty enrolling the targeted number of 60,000 patients, and an interim analysis that revealed significantly higher rates of secondary outcomes in subjects randomized to salmeterol. Compared with the placebo group, the salmeterol group had significantly higher rates of respiratory-related deaths (RR 2.16, 95% CI 1.06–4.41), asthma-related deaths (RR = 4.37, 95% CI = 1.25–15.34), and combined asthma-related deaths or life-threatening experiences (RR = 1.71, 95% CI 1.01–2.89). There were 13 asthma-related deaths and 37 combined asthma-related deaths or life-threatening experiences in the salmeterol group, compared with 3 and 22, respectively, in the placebo group. Of the 16 asthma deaths in the study, 13 (81%) occurred in the initial phase of SMART, when patients were recruited via print, radio, and television advertising; afterward, patients were recruited directly by investigators.

Statistically significant differences in outcomes occurred primarily in African Americans. African Americans who received salmeterol had higher rates of respiratory death or life-threatening experiences (RR = 4.10, 95% CI 1.54–10.90), the primary end point for the study, as well as higher rates of combined asthma-related deaths or life-threatening experiences (RR = 10.46, 95% CI 1.34–81.58), a secondary end point. No statistically significant differences were observed in white patients randomized to salmeterol with respect to the primary end point (RR = 1.05, 95% = 0.62–1.76); the secondary end point of combined asthma-related deaths or life-threatening experiences (RR = 1.08, 95% CI 0.55–2.14); or other end points.

Medication exposures were not tracked during the study, and allocation to inhaled corticosteroids combined with salmeterol was not randomized, so the effect of concomitant



**FIGURE 2.** Mean scores on the Asthma Control Test (ACT) from patients seen in the Section of Allergy/Immunology at Cleveland Clinic in 2005. Among patients who accomplished initial and follow-up ACT measurements, mean scores reflecting self-reported asthma control increased from 14.54 to 19.06.

inhaled corticosteroid use cannot be determined from these data.

As a result of SMART, medications that contain either of the two LABAs, salmeterol or formoterol (Foradil), carry a black-box warning.

#### LABAs: Risks and benefits

Two studies<sup>21,22</sup> have suggested that asthmatic patients who are homozygous for Arg/Arg at codon 16 of the beta-2 adrenergic receptor are predisposed to untoward asthma outcomes with regular exposure to LABAs. However, other data<sup>23–25</sup> do not support the contention that B16 Arg/Arg patients experience adverse asthma outcomes with LABA exposure. In two recently published studies, no difference in rates of exacerbations, severe exacerbations, lung function, frequency of reliance on SABA, or nocturnal awakenings was observed in patients receiving formoterol combined with budesonide<sup>24</sup> or salmeterol combined with fluticasone<sup>25</sup> according to genotype. A prospective study<sup>26</sup> also found no statistically significant difference in exacerbation rates according to beta adrenergic receptor genotype in individuals randomized to LABA monotherapy, or LABA combined with inhaled corticosteroids.

The updated EPR2 asthma guidelines,<sup>3</sup>

**SMART results:  
More asthma  
deaths were  
observed in  
African  
Americans  
randomized to  
salmeterol than  
to placebo**

**TABLE 5**

**Stepwise approach for managing asthma (patients 12 years and older)**

**ASSESS CONTROL**

Step up if needed (first, check adherence, environmental control, and comorbid conditions).  
Step down if possible (and asthma is well controlled for at least 3 months).

**INTERMITTENT ASTHMA**

**Step 1**

Preferred: Short-acting beta agonists as needed

**PERSISTENT ASTHMA: DAILY MEDICATION**

Consult with asthma specialist if step 4 care or higher is required.  
Consider consultation at step 3.

**Step 2**

Preferred: Low-dose inhaled corticosteroids

Alternatives: Cromolyn, leukotriene antagonists, nedocromil (Alocril), or theophylline

**Step 3**

Preferred: Low-dose inhaled corticosteroids and long-acting beta agonists, or medium-dose inhaled corticosteroids

Alternatives: Low-dose inhaled corticosteroids plus either leukotriene antagonists, theophylline, or zileuton (Zyflo)

**Step 4**

Preferred: Medium-dose inhaled corticosteroids plus long-term beta agonists

Alternatives: Medium-dose inhaled corticosteroids plus either leukotriene antagonists, theophylline, or zileuton

**Step 5**

Preferred: High-dose inhaled corticosteroids plus long-acting beta agonists

AND

Consider omalizumab (Xolair) for patients who have allergies

**Step 6**

Preferred: High-dose inhaled corticosteroids plus long-acting beta agonists plus oral corticosteroids

AND

Consider omalizumab for patients who have allergies

**Each step:** Patient education, environmental control, and management of comorbidities

**Steps 2–4:** Consider subcutaneous allergen immunotherapy for patients who have allergic asthma.

**Quick relief medication for all patients**

Short-acting beta agonists as needed for symptoms. Intensity of treatment depends on severity of symptoms. Up to three treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.

Use of short-acting beta agonists more than 2 days a week for symptom relief (not prevention of exercise-induced bronchospasm) generally indicates inadequate control and the need to step up treatment.

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published in November 2002, stipulated that LABAs were the preferred controller agent to “add on” to low-dose inhaled corticosteroids for patients with moderate persistent asthma,

and that the combination of low-dose inhaled corticosteroids and LABA was associated with superior outcomes: reduction of symptoms, including nocturnal awakening, increase in lung



function, improvement in health-related quality of life, decreased use of “rescue” medication, and reduced rate of exacerbations and severe exacerbations, compared with higher-dose inhaled corticosteroid monotherapy. This management recommendation was categorized as level A, on the basis of data from multiple randomized, controlled, double-blinded trials.<sup>27–29</sup> Additional evidence<sup>14,30</sup> and data from two meta-analyses<sup>31,32</sup> have provided further support for this recommendation, while no evidence linking LABA exposure to risk for fatal or near-fatal asthma has been found in cohort or case-control studies.<sup>33–38</sup>

Based on safety concerns, the EPR3 guidelines<sup>1</sup> recommend that medium-dose inhaled corticosteroids be regarded as equivalent to adding LABAs to low-dose inhaled corticosteroids, and state: “the established, beneficial effects of LABA for the great majority of patients whose asthma is not well controlled with [inhaled corticosteroids] alone should be weighed against the increased risk for severe exacerbations, although uncommon, associated with daily use of LABA.”<sup>1</sup>

There is currently an honest difference of opinion<sup>39,40</sup> among asthma specialists as to how this management recommendation for moderate persistent asthma—now depicted at “step 3” in the EPR3 guidelines (TABLE 4)—should be implemented. The LABA controversy was reviewed previously in the *Cleveland Clinic Journal of Medicine*.<sup>41</sup>

### ■ THE ROLE OF OMALIZUMAB: WEIGHING COST VS BENEFIT

The 2002 update to the EPR2 guidelines<sup>3</sup> was issued before omalizumab (Xolair) was approved in June 2003.

Patients with severe persistent asthma are categorized in steps 5 or 6 in the EPR3 guidelines (TABLE 5).<sup>1</sup> Preferred management for these patients includes inhaled corticosteroids in high doses combined with long-acting beta agonists and, for step 6 patients, oral corticosteroids.

Omalizumab was approved for management of patients with moderate or severe persistent asthma who are not achieving the goals of asthma management on inhaled corticosteroids, who exhibit a wheal-flare reaction

to a perennial allergen, and whose immunoglobulin E (IgE) level is in the range of 30 to 700 IU/mL.<sup>42</sup> Omalizumab dosing is based on the serum IgE level and on body weight.

### Omalizumab, an anti-IgE monoclonal antibody

Omalizumab is a recombinant, humanized, monoclonal anti-IgE antibody that binds to IgE at the same Fc site as the high-affinity IgE receptor. Its primary mechanism of action is the binding of free IgE in the circulation, forming biologically inert, small complexes that do not activate complement and are cleared by the reticuloendothelial system.<sup>42</sup> Its secondary mechanism of action entails a reduction in the number of high-affinity receptors on basophils, from approximately 220,000 to 8,300 receptors per cell. The latter effect was associated with a 90% reduction in histamine release from basophils in response to ex vivo challenge with dust mite allergen.<sup>43</sup>

### Benefit in randomized trials

Omalizumab has been associated with statistically and clinically significant benefit in randomized, double-blind, placebo-controlled trials.<sup>44,45</sup>

Humbert et al<sup>46</sup> randomized 419 patients whose asthma was not adequately controlled on high-dose inhaled corticosteroids and long-acting beta agonists, who were 12 to 75 years old, with reduced lung function and a history of recent asthma exacerbation, to treatment with omalizumab or placebo. Omalizumab was associated with a statistically significant reduction in the rate of asthma exacerbations and severe asthma exacerbations, as well as statistically significant improvements in asthma-related quality of life, morning peak expiratory flow rate, and asthma symptom scores.

These data support the recommendation in EPR3 to consider a trial of omalizumab in properly selected patients with severe, persistent allergic asthma.

### Omalizumab is cost-beneficial in properly selected patients

The current wholesale acquisition cost of omalizumab is \$532 for one 150-mg vial (David Zito, personal communication). The cost of treatment varies based on body weight and

**Costs are about four times higher in severe than in mild asthma**

**The benefit of allergen immunotherapy observed in randomized controlled trials includes reduced symptoms and medication reliance**

IgE level but may range from a wholesale cost of \$6,388 to \$38,326 per year.

However, as asthma severity increases, both direct and indirect medical expenditures increase substantially.<sup>47,48</sup> Annual costs are approximately four times higher for severe asthma compared with mild asthma<sup>49</sup>; not only are treatment and exacerbation costs higher, but indirect costs are also disproportionately greater. Annual costs for severe asthma are significantly greater if the disease is inadequately controlled.<sup>50</sup> For these reasons, an intervention that leads to improved outcomes for severe, poorly controlled asthma carries the potential for the greatest cost-utility for society, as it can lower direct costs by reducing the frequency and severity of exacerbations, in addition to reducing indirect medical expenditures on the basis of increased productivity and fewer days of missed work or school. The cost of omalizumab in quality-adjusted life years compares favorably with that of biologicals used in managing rheumatoid arthritis, Crohn disease, and multiple sclerosis.<sup>50</sup>

### Adverse effects of omalizumab

In pivotal trials,<sup>43,44</sup> omalizumab was associated with a substantial rate of local reactions. The rate of anaphylaxis was slightly less than 1 in 1,000, and this has been confirmed by surveillance data recorded since approval of the drug in 2003. Based on the observed risk of anaphylaxis, in July 2007, the US Food and Drug Administration added a black-box warning to the omalizumab label and stipulated that a medication guide should be provided for patients.<sup>51</sup> The warning indicates that health care providers administering omalizumab should be prepared to manage anaphylaxis and that patients should be closely observed for an appropriate period after omalizumab administration.

The package insert also describes a numerical, but not statistically significant, increase in the rate of malignancy in patients receiving omalizumab.<sup>42</sup> Malignancy developed in 0.5% of patients receiving omalizumab, compared with 0.2% of patients who received placebo. Because these malignancies were diagnosed over a shorter period than the time required for oncogenesis (ie, 6 months in 60% of cases), and because a heterogeneous variety of tumors

was observed, there is reason to doubt these tumors were causally associated with omalizumab.

Postmarketing surveillance studies are in progress that will provide more definitive data on the potential relationship between malignancy and omalizumab exposure.

### Omalizumab: Guideline recommendations

The EPR3 guidelines<sup>1</sup> state that omalizumab is the only adjunctive therapy to demonstrate efficacy when added to high-dose inhaled corticosteroids plus long-acting beta agonists in patients with severe, persistent, allergic asthma and that evidence does not support use of the following agents, which in some cases are approved for managing other conditions and have been advocated for management of severe, refractory asthma: methotrexate, soluble interleukin (IL)-4 receptor, anti-IL-5, anti-IL-12, cyclosporine A, intravenous immune globulin, gold, troleandomycin, and colchicine. The data supporting use of macrolides were characterized as “encouraging but insufficient to support a recommendation.”

The strength of evidence for the use of omalizumab for patients in steps 5 and 6 who fulfill the criteria for its use (see above) was classified in the EPR3 guidelines<sup>1</sup> as category B. The guidelines also say that omalizumab may be considered for adjunctive therapy in properly selected patients in step 4, as a means to avoid higher doses of inhaled corticosteroids, but that additional studies are needed to establish its utility for such patients. This recommendation was classified as category D because of the lack of published comparator trials.

### ■ ALLERGEN IMMUNOTHERAPY FOR PATIENTS WITH ASTHMA

Many patients with asthma have clinically relevant, IgE-mediated (allergic) potential to inhaled allergens.<sup>1</sup> For patients with persistent asthma (steps 2–6 in **FIGURE 3**), allergic reactions can contribute to airway inflammation, provoke symptoms, and lead to more use of medications. For this reason, identification and management of clinically relevant allergy merits consideration.<sup>52</sup>

The EPR3 guidelines<sup>1</sup> recommend considering allergen immunotherapy for patients

with mild or moderate persistent asthma (steps 2–4) who have a clinically relevant component of allergy to inhaled substances.

### Changing the immune response

Allergen immunotherapy entails the incremental administration of inhaled allergens by subcutaneous injection for the purpose of inducing immune system changes in the host response. The goal of immunotherapy is to protect against allergic reactions that can be expected to occur with ongoing exposure to clinically relevant allergens.<sup>33</sup>

The immunologic changes that develop with allergen immunotherapy are complex.<sup>53,54</sup> Successful immunotherapy results in generation of a population of CD4+/CD25+ T lymphocytes producing IL-10, transforming growth factor beta, or both. Allergen immunotherapy has been shown to block the immediate- and late-phase allergic response; to decrease recruitment of mast cells, basophils, and eosinophils on provocation or natural exposure to allergens in the skin, nose, eye, and bronchial mucosa; to blunt the seasonal rise in specific IgE; and to suppress late-phase inflammatory responses in the skin and respiratory tract. However, the efficacy of immunotherapy in relation to these immunologic changes is not completely understood.<sup>54</sup>

### Many patients need skin testing

Allergen immunotherapy may be considered for patients with asthma for whom a clear relationship exists between symptoms and exposure to an allergen to which the patient is sensitive.<sup>53</sup> Because it is often not possible to determine whether a patient is sensitive to a perennial indoor allergen (eg, dust mite) on the basis of the medical history alone,<sup>55</sup> many patients with asthma benefit from immediate hypersensitivity skin testing to objectively assess or rule out allergy to common inhalants. In certain situations, *in vitro* testing may be performed, but skin testing has a higher negative predictive value and is recommended as a better screening test.<sup>56</sup>

### Benefits of allergen immunotherapy

Numerous randomized, double-blind, placebo-controlled trials have shown that allergen immunotherapy is associated with benefit for reducing symptoms and medication reliance.<sup>57–63</sup>

A meta-analysis of 75 randomized, placebo-controlled studies confirmed the effectiveness of immunotherapy in asthma, with a significant reduction in asthma symptoms and medication use and with improvement in bronchial hyperreactivity.<sup>64</sup> This meta-analysis included 36 trials of dust mite allergen, 20 of pollen, and 10 of animal dander. Immunotherapy is efficacious for pollen, mold, dust mite, cockroach, and animal allergens; however, its effectiveness is more established for dust mite, animal dander, and pollen allergens, as fewer studies have been published demonstrating efficacy using mold and cockroach allergens.<sup>53</sup>

In addition, several studies have found that children with allergic rhinitis who receive allergen immunotherapy are significantly less likely to develop asthma.<sup>65–67</sup> Immunotherapy has also been associated with a statistically significant reduction in future sensitization to other aeroallergens.<sup>68,69</sup>

### Risk of systemic reaction from allergen immunotherapy

The decision to begin allergen immunotherapy should be individualized on the basis of symptom severity, relative benefit compared with drug therapy, and whether comorbid conditions such as cardiovascular disease or beta-blocker exposure are present. These comorbid conditions are associated with heightened risk of (more serious) anaphylaxis—the major hazard of allergen immunotherapy.<sup>70</sup> Systemic reactions during allergen immunotherapy occur at a rate of approximately 3 to 5 per 1,000 injections; for this reason, allergen immunotherapy should only be administered in a medical facility where personnel, supplies, and equipment are available to treat anaphylaxis.<sup>5</sup>

**Beta-blockers have been associated with increased risk of more serious anaphylaxis**

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