REVIEW

DAVID M. LANG, MD*
Head, Section of Allergy/Immunology, and Co-Director, Asthma Center, Respiratory Institute, Cleveland Clinic

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),[1] that differ substantially from those in EPR2,[2] issued in 1997 and updated in 2002.[3] 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[2] 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-

*Dr. Lang has disclosed that he has received honoraria and consulting fees from AstraZeneca, Genentech/Novartis, GlaxoSmithKline, Merck, Sanofi-Aventis, and Schering/Key companies for teaching, speaking, and consulting.

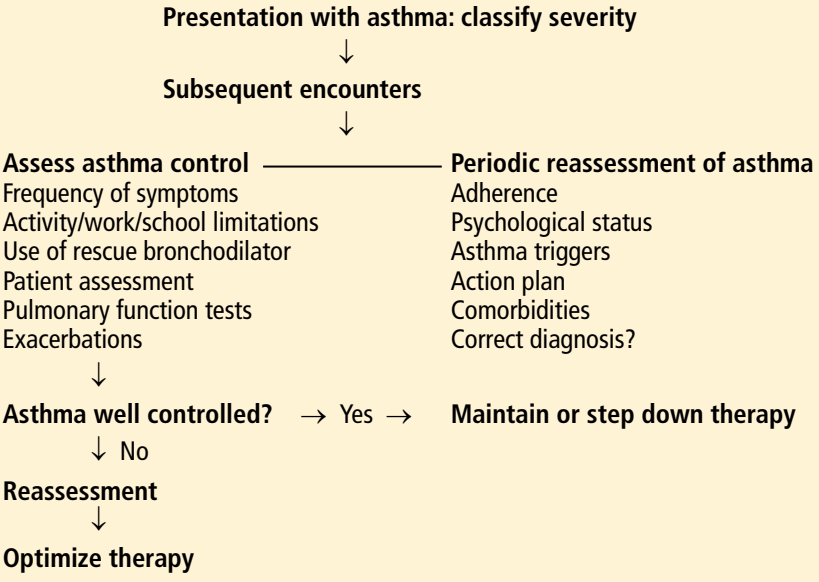

FIGURE 1. The revised paradigm for asthma management recommends that asthma be categorized initially on the basis of severity, with management assigned in an evidence-based manner, but that subsequently, asthma control should be assessed at every clinical encounter, with management decisions based on the level of asthma control.

LI JT, OPPENHEIMER J, BERNSTEIN IL, NICKLAS RA, ET AL. ATTAINING OPTIMAL ASTHMA CONTROL: A PRACTICE PARAMETER. J ALLERGY CLIN IMMUNOL 2005; 116:S3–S11.

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

timate asthma severity,[4,5] 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.[1]

Severity and control are not synonymous

More than a decade ago, Cockroft and Swystun[6] 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.[7–9] 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 [a]		CLASSIFICATION OF ASTHMA SEVERITY			
		INTERMITTENT	PERSISTENT		
			MILD	MODERATE	SEVERE
Impairment	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_1 between exacerbations	FEV_1 > 80% predicted	FEV_1 > 60% but < 80% predicted	FEV_1 < 60% predicted
		FEV_1 > 80% predicted	FEV_1/FVC normal	FEV_1/FVC reduced ≤ 5%	FEV_1/FVC reduced > 5%
		FEV_1/FVC normal			
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year	≥ 2/year [b]		
		Consider severity and interval since last exacerbation.			
		Frequency and severity may fluctuate over time for patients in any severity category.			
		Relative annual risk of exacerbations may be related to FEV_1.			
Recommended step for initiating treatment		Step 1	Step 2	Step 3 And consider short course of oral systemic corticosteroids	Step 4 or 5

FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity

[a] 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.

[b] 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.

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE, NATIONAL ASTHMA EDUCATION AND PREVENTION PROGRAM. EXPERT PANEL REPORT 3: GUIDELINES FOR THE DIAGNOSIS AND MANAGEMENT OF ASTHMA. WWW.NHLBI.NIH.GOV/GUIDELINES/ASTHMA/.

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 [a]	CLASSIFICATION OF ASTHMA CONTROL		
	WELL CONTROLLED	NOT WELL CONTROLLED	VERY POORLY CONTROLLED
Impairment			
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_1 or peak flow	> 80% predicted or personal best	60%–80% predicted or personal best	< 60% predicted or personal best
Validated questionnaires [b]			
ATAQ	0	1–2	3–4
ACQ	≤ 0.75 [b]	≥ 1.5	NA
ACT	≥ 20	16–19	≤ 15
Risk			
Exacerbations requiring oral systemic corticosteroids	0–1/year	2–3/year [c]	> 3/year
	Consider severity and interval since last exacerbation.		
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_1 = forced expiratory volume in 1 second.

[a] 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.

[b] ACQ values of 0.76–1.4 are indeterminate regarding well-controlled asthma.

[c] 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.

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE, NATIONAL ASTHMA EDUCATION AND PREVENTION PROGRAM. EXPERT PANEL REPORT 3: GUIDELINES FOR THE DIAGNOSIS AND MANAGEMENT OF ASTHMA. WWW.NHLBI.NIH.GOV/GUIDELINES/ASTHMA/.

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,[1] 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).[1]

Validated tests are available to assess control

Asthma control is multidimensional[9] 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.[9–13]

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%) and specificity (71%) for classifying asthma as well controlled or not well controlled.[13]

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

Serial testing as a quality indicator

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

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.[15]

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)

		POINTS			YOUR SCORE
1	2	3	4	5	
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?					
All of the time	Most of the time	Some of the time	A little of the time	None of the time	_____
During the past 4 weeks, how often have you had shortness of breath?					
More than once a day	Once a day	3 to 6 times a week	Once or twice	Not at all a week	_____
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?					
4 or more nights a week	2 or 3 nights a week	Once a week	Once	Not at all or twice	_____
During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication such as albuterol (Proventil)?					
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	_____
How would you rate your asthma control during the past 4 weeks?					
Not controlled at all	Poorly controlled	Somewhat controlled	Well controlled	Completely controlled	_____
Total score					_____

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,"[16] ie, they may have little or no subjective awareness of moderate or even severe ventilatory impairment. A number of studies[17,18] 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 "stepping 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).[9] If asthma is poorly controlled, the patient is at risk of exacerbation of asthma and on this basis is clearly a candidate for intervention.[11–13,19]

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.[20]

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 inhaled corticosteroid use cannot be determined from these data.

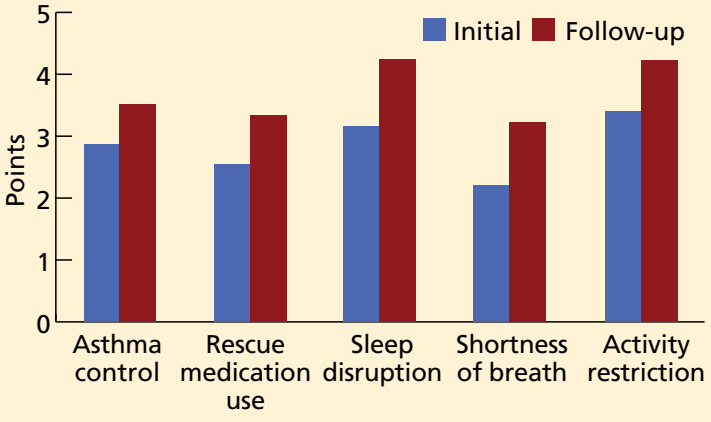

FIGURE 2. Mean scores on the Asthma Control Test (ACT) from patients seen in the Section of Allergy/Immunology at Cleveland Clinic in 2005. Among patients who accomplished initial and follow-up ACT measurements, mean scores reflecting self-reported asthma control increased from 14.54 to 19.06.

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

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

LABAs: Risks and benefits

Two studies[21,22] 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[23–25] 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[24] or salmeterol combined with fluticasone[25] according to genotype. A prospective study[26] 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,[3]

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.

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE, NATIONAL ASTHMA EDUCATION AND PREVENTION PROGRAM. EXPERT PANEL REPORT 3: GUIDELINES FOR THE DIAGNOSIS AND MANAGEMENT OF ASTHMA. WWW.NHLBI.NIH.GOV/GUIDELINES/ASTHMA/.

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.[27–29] Additional evidence[14,30] and data from two meta-analyses[31,32] 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.[33–38]

Based on safety concerns, the EPR3 guidelines[1] 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."[1]

There is currently an honest difference of opinion[39,40] 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*.[41]

THE ROLE OF OMALIZUMAB: WEIGHING COST VS BENEFIT

The 2002 update to the EPR2 guidelines[3] 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).[1] 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.[42] 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.[42] 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.[43]

Benefit in randomized trials

Omalizumab has been associated with statistically and clinically significant benefit in randomized, double-blind, placebo-controlled trials.[44,45]

Humbert et al[46] 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

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.[47,48] Annual costs are approximately four times higher for severe asthma compared with mild asthma[49]; 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.[50] 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.[50]

Adverse effects of omalizumab

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

In pivotal trials,[43,44] 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.[51] 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.[42] 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[1] 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[1] 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.[1] 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.[52]

The EPR3 guidelines[1] 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 inhalant 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.[53]

The immunologic changes that develop with allergen immunotherapy are complex.[53,54] 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.[54]

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.[53] 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,[55] 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.[56]

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.[57–63]

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.[64] 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.[53]

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

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.[70] 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.[5]

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

REFERENCES

1. **National Heart, Lung, and Blood institute, National Asthma education and Prevention Program**. Expert Panel Report 3: guidelines for the diagnosis and management of asthma. www.nhlbi.nih.gov/guidelines/asthma/. Accessed 8/7/08.
2. **Expert Panel Report 2: Guidelines for the diagnosis and management of asthma**. U.S. Department of Health and Human Services. Publication No. 97-4051; 1997.
3. **Expert Panel Report: Guidelines for the diagnosis and management of**

asthma. Update on Selected Topics—2002. J Allergy Clin Immunol 2002; 110:S141–S207.
4. **FitzGerald JM, Boulet LP, McIvor RA, Zimmerman S, Chapman KR**. Asthma control in Canada remains suboptimal: the Reality of Asthma Control (TRAC) study. Can Respir J 2006; 13:253–259.
5. **Braganza S, Sharif I, Ozuah P**. Documenting asthma severity: do we get it right? J Asthma 2003; 40:661–665.
6. **Cockcroft DW, Swystun VA**. Asthma control versus asthma severity. J Allergy Clin Immunol 1996; 98:1016–1018.
7. **Peters SP, Jones CA, Haselkorn T, Mink DR, Valacer DJ, Weiss ST**. Real-world Evaluation of Asthma Control and Treatment (REACT): findings from a national Web-based survey. J Allergy Clin Immunol. 2007;119:1454–1461.
8. **Osborne ML, Vollmer WM, Pedula KL, Wilkins J, Buist AS, O'Hollaren M**. Lack of correlation of symptoms with specialist-assessed long-term asthma severity. Chest 1999; 115:85–91.
9. **Li JT, Oppenheimer J, Bernstein IL, et al**. Attaining optimal asthma control: a practice parameter. J Allergy Clin Immunol 2005; 116:S3–S11.
10. **Nathan RA, Sorkness C, Kosinski M, et al**. Development of the Asthma Control Test: a survey for assessing asthma control. J Allergy Clin Immunol 2004; 113:59–65.
11. **Schatz M, Zeiger RS, Drane A, et al**. Reliability and predictive validity of the Asthma Control Test administered by telephone calls using speech recognition technology. J Allergy Clin Immunol 2007; 119:336–343.
12. **Peters D, Chen C, Markson LE, Allen-Ramey FC, Vollmer WM**. Using an asthma control questionnaire and administrative data to predict health-care utilization. Chest 2006; 129:918–924.
13. **Schatz M, Sorkness C, Li JT, et al**. Asthma Control Test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. J Allergy Clin Immunol 2006; 117:549–556.
14. **Bateman E, Boushey H, Bousquet J, et al**. Can guideline-defined asthma control be achieved? Am J Respir Crit Care Med 2004; 170:836–844.
15. **Davies TJ, Bunn WB, Fromer L, Gelfand EW, Colice GL**. A focus on the asthma HEDIS measure and its implications for clinical practice. Manag Care Interface 2006; 19:29–36.
16. **Rubinfeld AR, Pain MC**. Perception of asthma. Lancet 1976; 1:882–884.
17. **Teeter J, Bleecker E**. Relationship between airway obstruction and respiratory symptoms in adult asthmatics. Chest 1998; 113:272–277.
18. **Shingo S, Zhang J, Reiss T**. Correlation of airway obstruction and patient reported endpoints in clinical studies. Eur Resp J 2001; 17:220–224.
19. **Juniper EF, Bousquet J, Abetz L, Bateman ED; GOAL Committee**. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. Respir Med 2006; 100:616–621.
20. **Nelson H, Weiss S, Bleecker E, Yancey S, Dorinsky P**. The Salmeterol Multicenter Asthma Research Trial. Chest 2006; 129:15–26.
21. **Wechsler M, Lehman E, Lazarus S, et al**. ß-Adrenergic receptor polymorphisms and response to salmeterol. Am J Respir Crit Care Med 2006; 173:519–526.
22. **Palmer CNA, Lipworth BJ, Lee S, Ismail T, MacGregor DF, Mukhopadhyay S**. Arginine-16 beta-2 adrenoceptor genotype predisposes to exacerbations in young asthmatics taking regular salmeterol. Thorax 2006; 61:940–944.
23. **Taylor DR, Drazen JM, Herbison GP, Yandava CN, Hancox RJ, Town GI**. Asthma exacerbations during long term beta agonist use: influence of beta 2 adrenoceptor polymorphism. Thorax 2000; 55:762–727.
24. **Bleecker E, Postma D, Lawrance R, Meyers D, Ambrose H, Goldman M**. Effect of ADRB2 polymorphisms on response to long-acting beta2-agonist therapy: a pharmacogenetic analysis of two randomized studies. Lancet 2007; 370:2118–2125.
25. **Bleecker E, Yancey S, Baitinger L, et al**. Salmeterol response is not affected by beta-2 adrenergic receptor genotype in subjects with persistent asthma. J Allergy Clin Immunol 2006; 118:809–816.
26. **Nelson H, Bleecker E, Corren J, et al**. Characterization of asthma exacerbations by Arg16Gly genotype in subjects with asthma receiving salmeterol alone or with fluticasone propionate. J Allergy Clin Immunol 2008; 121:S131.
27. **O'Byrne P, Barnes P, Rodriguez-Roisin R, et al**. Low dose Inhaled budesonide and formoterol in mild persistent asthma. The OPTIMA Randomized Trial. Am J Respir Crit Care Med 2001; 164:1392–1397.
28. **Greening AP, Ind PW, Northfield M, Shaw G**. Added salmeterol versus higher dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. Lancet 1994; 344:219–224.
29. **Woolcock A, Lundback B, Ringdal N, Jacques LA**. Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroids. Am J Respir Crit Care Med 1996; 153:1481–1488.
30. **Walters EH, Walters JAE, Gibson MDP**. Long-acting beta2-agonists for stable chronic asthma. Cochrane Database Syst Rev 2003; (3): CD001385. DOI: 10.1002/14651858.CD001385.
31. **Masoli M, Weatherall M, Holt S, Beasley R**. Moderate dose inhaled corticosteroids plus salmeterol versus higher doses of inhaled corticosteroid in symptomatic asthma. Thorax 2005; 60:730–734.
32. **Sin DD, Man J, Sharpe H, Gan WQ, Man SFP**. Pharmacological management to reduce exacerbations in adults with asthma. A systematic review and meta-analysis. JAMA 2004; 292:367–376.
33. **Mann RD, Kubota K, Pearce G, Wilton L**. Salmeterol: a study by prescription event monitoring in a UK cohort of 15,407 patients. J Clin Epidemiol 1996; 49:247–250.
34. **Lanes S, Lanza L, Wentworth C**. Risk of emergency care, hospitalization, and ICU stays for acute asthma among recipients of salmeterol. Am J Respir Crit Care Med 1998; 158:857–861.
35. **Meier CR, Jick H**. Drug use and pulmonary death rates in increasingly symptomatic asthma patients in the UK. Thorax 1997; 52:612–617.
36. **Williams C, Crossland L, Finnerty J, et al**. A case control study of salmeterol and near-fatal attacks of asthma. Thorax 1998; 53:7–13.
37. **Lanes S, Garcia Rodriguez LA, Herta C**. Respiratory medications and risk of asthma death. Thorax 2002; 57:683–686.
38. **Anderson HR, Ayres JG, Sturdy PM, et al**. Bronchodilator treatment and deaths from asthma: case control study. Br Med J 2005; 330:117–124.
39. **Martinez FD**. Safety of long-acting beta agonists—an urgent need to clear the air. N Engl J Med 2005; 353:2637–2639.
40. **Nelson HS**. Long-acting beta-agonists in adult asthma: evidence that these drugs are safe. Prim Care Respir J 2006; 15:271–277.
41. **Lang DM**. The long-acting beta agonist controversy: a critical examination of the evidence. Cleve Clin J Med 2006; 73:973–992.
42. **Rambasek T, Lang DM, Kavuru M**. Omalizumab: where does it fit in current asthma management? Cleve Clin J Med 2004; 71:251–261.
43. **McGlashan D, Bochner B, Adelman D, et al**. Down regulation of Fc(epsilon)RI expression on human basophils during in vivo treatment of atopic patients with anti-IgE antibody. J Immunol 1997; 158:1438–1445.
44. **Busse W, Corren J, Lanier B, et al**. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. J Allergy Clin Immunol 2001; 108:184–190.
45. **Soler M, Matz J, Townley R et al**. The anti-IgE antibody omalizu-mab reduces asthma exacerbations and steroid requirement in allergic asthmatics. Eur Respir J 2001; 18:254–261.
46. **Humbert M, Beasley R, Ayres J, et al**. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. Allergy 2005; 60:309–316.
47. **Van Ganse E, Antonicelli L, Zhang Q, et al**. Asthma-related resource use and cost by GINA classification of severity in three European countries. Respir Med 2006; 100:140–147.
48. **Godard P, Chanez P, Siraudin L, Nicoloyannis N, Duru G**. Costs of asthma are correlated with severity: a 1-yr prospective study. Eur Respir J 2002; 19:61–67.
49. **Cisternas MG, Blanc PH, Yen IH, et al**. A comprehensive study of the direct and indirect costs of adult asthma. J Allergy Clin Immunol 2003; 111:1212–1218.
50. **Sullivan S, Turk F**. An evaluation of the cost effectiveness of omalizumab for the treatment of severe persistent asthma. Allergy 2008; 63: 670–684.
51. **US Food and Drug Administration**. Omalizumab (marketed as Xolair) information. www.fda.gov/cder/drug/infopage/omalizumab/default.htm. Accessed August 31, 2007.
52. **Williams SG, Schmidt DK, Redd SC, Storms W**. Key clinical activities for quality asthma care. Recommendations of the National Asthma Education and Prevention Program. MMWR Recomm Rep 2003; 52(RR-6):1–8.
53. **Cox L, Li J, Nelson H, Lockey R, et al**. Allergy Immunotherapy: a practice parameter second update. J Allergy Clin Immunol 2007; 120:S25–S85.

54. **Akdis M, Akdis CA**. Mechanisms of allergen-specific immunotherapy. J Allergy Clin Immunol 2007; 119:780–789.
55. **Murray AB, Milner RA**. The accuracy of features in the clinical history for predicting atopic sensitization to airborne allergens in children. J Allergy Clin Immunol 1995; 96:588–596.
56. **Bernstein IL, Li JT, Bernstein DI, et al**. Allergy diagnostic testing: an updated practice parameter. Ann Allergy Asthma Immunol 2008; 100(suppl 3):1S–148S.
57. **Walker S, Pajno GB, Lima MT, Wilson DR, Durham SR**. Grass pollen immunotherapy for seasonal rhinitis and asthma: a randomized, controlled trial. J Allergy Clin Immunol 2001; 107:87–93.
58. **Varney VA, Edwards J, Tabbah K, Brewster H, Mavroleon G, Frew AJ**. Clinical efficacy of specific immunotherapy to cat dander: a double-blind placebo-controlled trial. Clin Exp Allergy 1997; 27:860–867.
59. **Cantani A, Arcese G, Lucenti P, Gagliesi D, Bartolucci M**. A three-year prospective study of specific immunotherapy to inhalant allergens: evidence of safety and efficacy in 300 children with allergic asthma. J Investig Allergol Clin Immunol 1997; 7:90–97.
60. **Hedlin G, Wille S, Browaldh L, et al**. Immunotherapy in children with allergic asthma: effect on bronchial hyperreactivity and pharmacotherapy. J Allergy Clin Immunol 1999; 103:609–614.
61. **Arvidsson MB, Löwhagen O, Rak S**. Allergen specific immunotherapy attenuates early and late phase reactions in lower airways of birch pollen asthmatic patients: a double blind placebo-controlled study. Allergy 2004; 59:74–80.
62. **Pichler CE, Helbling A, Pichler WJ**. Three years of specific immunotherapy with house-dust-mite extracts in patients with rhinitis and asthma: significant improvement of allergen-specific parameters and of nonspecific bronchial hyperreactivity. Allergy 2001; 56:301–306.
63. **Mirone C, Albert F, Tosi A, et al**. Efficacy and safety of subcutaneous immunotherapy with a biologically standardized extract of *Ambrosia artemisiifolia* pollen: a double-blind, placebo-controlled study. Clin Exp Allergy 2004; 34:1408–1414.
64. **Abramson MJ, Puy RM, Weiner JM**. Allergen immunotherapy for asthma. Cochrane Database Syst Rev 2003; (4):CD001186.
65. **Jacobsen L**. Preventive aspects of immunotherapy: prevention for children at risk of developing asthma. Ann Allergy Asthma Immunol 2001; 87:43–46.
66. **Moller C, Dreborg S, Ferdousi HA, et al**. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT study). J Allergy Clin Immunol 2002; 109:251–256.
67. **Niggemann B, Jacobsen L, Dreborg S, et al; PAT Investigator Group**. Five year follow-up on the PAT study: specific immunotherapy and long-term prevention of asthma in children. Allergy 2006: 61:855–859.
68. **Des Roches A, Paradis L, Menardo JL, et al**. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract VI: specific immunotherapy prevents the onset of new sensitizations in children. J Allergy Clin Immunol 1997; 99:450–453.
69. **Pajno GB, Barberio G, DeLuca F, et al**. Prevention of new sensitizations in asthmatic children monosensitized to the house dust mite by specific immunotherapy: a six year follow up study. Clin Exp Allergy 2001; 31:1392–1397.
70. **Lang DM**. Do beta blockers really enhance the risk of anaphylaxis during immunotherapy? Curr Allergy Asthma Rep 2008; 8:37–44.

***ADDRESS**: David M. Lang, MD, Head, Section of Allergy/Immunology, Respiratory Institute, C22, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail langd@ccf.org*