# Chapter 6
# Management of Asthma: The Current US and European Guidelines

**Ashwini P. Reddy and Meera R. Gupta**

**Abstract** Asthma management guidelines aim to improve the implementation of current knowledge into daily clinical practice by establishing a consensus of scientific practices for the management of asthma. Initial guidelines were based on consensus of expert opinion in order to employ a severity-based classification system as a guide to treatment. However, advances in asthma research led to the development of evidence-based guidelines and a major paradigm shift to control-based asthma management. Control-based management is central to the published guidelines developed by The National Heart, Lung, and Blood Institute (NHLBI), The Global Initiative for Asthma (GINA), and The British Thoracic Society (BTS), each one using the same volume of evidence but emphasizing aspects particular to their specific patient populations and socioeconomic needs. This chapter summarizes the evolution of these guidelines and summarizes the key points and evidence used in the recommendations for the assessment, monitoring, and management of asthma in all ages, with particular emphasis on the NHLBI guidelines.

**Keywords** Asthma • Asthma: management • NHLBI guidelines • Asthma: drug therapy • Humans • Practice guidelines as topic • GINA guidelines • BTS guidelines • Asthma: pediatric guidelines • Asthma: diagnosis • Asthma: treatment

A.P. Reddy, M.D.
Department of Pediatrics, University of Texas Medical Branch, 301 University Blvd, Galveston, TX, USA
e-mail: apreddy@UTMB.EDU

M.R. Gupta, M.D. (✉)
Department of Internal Medicine, University of Texas Medical Branch, 301 University Blvd, Route 0561, Galveston, TX, USA
e-mail: megupta@UTMB.EDU

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## 6.1 The Need for Guidelines

In the early 1980s, asthma prevalence, morbidity, and mortality were increasing in all age groups worldwide. Findings that with optimal treatment many of these asthma deaths were preventable, led to the development of guidelines for the optimal management of asthma by countries worldwide (Bousquet et al. 2007). To address the growing problem of asthma in the USA, in 1989 the National Heart, Lung, and Blood Institute (NHLBI) initiated the National Asthma Education and Prevention Program (NAEPP), and in 1991, the NAEPP Expert Panel published the first comprehensive "Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma" (EPR 1) based on expert opinions. These guidelines aimed to improve the implementation of current knowledge into daily clinical practice by helping healthcare professionals bridge the gap between current knowledge and treatment (Sheffer and Taggart 1991).

## 6.2 History of the NHLBI Guidelines

### *6.2.1 Adults*

*1991: Expert Panel Report 1*

The first EPR guidelines focused on the recent discovery that asthma was an inflammatory disease, and transitioned clinical management to a treatment approach focused on controlling inflammation rather than managing bronchospasm (NHLBI 1991). A concept of asthma management consisting of a multifaceted approach was introduced where recommendations for the treatment of asthma were organized around four components of effective management (1) assessment of asthma severity and regular monitoring of the effectiveness of therapy, (2) control of environment factors and comorbid conditions affecting asthma, (3) comprehensive pharmacologic therapy for long-term management and acute exacerbations, and (4) patient education to foster a partnership of care between the patients, families, and clinicians. Patients were classified by the level of disease severity based on a composite analysis of symptom frequency, activity limitation, need for rescue medications, and pulmonary function test results, and treatment recommendations for the type and amount of medications for were outlined at each level. An improved understanding of the pathophysiology of asthma and the addition of new medications, such as long-acting β-adrenergic agonists (LABAs) and leukotriene modifiers, led to the first of continuing updates in 1997 (Myers 2008).

*1997: Expert Panel Report 2*

The Expert Panel Report 2 (EPR 2) put forth a number of new ideas. Firstly, the increasing scientific base of published articles on asthma allowed for the evolution of guideline development from opinion based to one based on a systemic review of

scientific evidence. Secondly, due to accumulating scientific evidence leading to the definition of asthma as a chronic inflammatory disorder of the airways and identification of ongoing inflammation as the cause for recurrent episodes of bronchospasm, bronchial hyperresponsiveness, and persistent airflow obstruction from airway remodeling (Laitinen and Laitinen 1994a, b), the EPR 2 sought to emphasize the importance of early recognition and treatment to prevent irreversible airway injury by early intervention with anti-inflammatory therapy (Djukanovic et al. 1992; Jeffery et al. 1992; Laitinen et al. 1992; Levy 1995). As a result, the classification of asthma severity was changed from mild, moderate, and severe to mild intermittent, mild persistent, moderate persistent, and severe persistent in an attempt to more accurately reflect the clinical manifestations of asthma (NHLBI 1997). Furthermore, to emphasize that persistent asthma requires daily long-term therapy (Busse 1993; Duddridge et al. 1993), medications were categorized as being either controller or rescue medications (NHLBI 1997). Although an EPR 2 update on selected topics was published in 2002 (NHLBI 2002), the first major revision of the asthma guidelines occurred in 2007 with the Expert Panel Report 3 (EPR 3).

*2007: Expert Panel Report 3*

Previous guidelines were constructed on the idea of assessing and grading asthma severity to guide management and identify people at risk for severe exacerbations. However, recognition that severity can vary over time and that the responsiveness to treatment is heterogeneous even among patients with asthma of similar severity, raised concerns about classifying asthma by severity alone (Wolfenden et al. 2003; Graham 2006). Furthermore, the use of severity as a single outcome measure had limited value in predicting the treatment required and the patient's response to that treatment (Bateman et al. 2004). As it became recognized that categorizing asthma involved both severity of the disease and its responsiveness to treatment, guideline committees began to propose that asthma severity no longer be used as the basis for treatment decisions and instead focused on assessing and using asthma control (NHLBI 2007).

The EPR 3 proposes that concepts of asthma severity and control are linked by common therapeutic goals that are identical for all levels of baseline asthma severity and the specific measures used to assess these domains (frequency of symptoms, need for rescue medications, limitations to normal activities, pulmonary function tests, and frequency of exacerbations). Both concepts are brought into the guidelines of care by initiating pharmacologic therapy based on asthma severity and adjusting therapy based on the level of asthma control (Colice et al. 1999; Strunk et al. 2002; Bacharier et al. 2004). To emphasize the need to consider asthma's effects on quality of life and functional capacity and the risks for future adverse events, severity and control are defined in two domains: impairment and risk. Impairment is an assessment of the frequency and intensity of symptoms and functional limitations, whereas risk is an estimate of the likelihood of either asthma exacerbations or of progressive loss of pulmonary function over time (NHLBI 2007). Although linked, these distinct domains represent different manifestations of asthma that may respond to differently to treatment (Colice et al. 1999; Fuhlbrigge et al. 2002; Bacharier et al. 2004; Schatz et al. 2005).

### *6.2.2 Children*

Pediatric-specific recommendations for asthma management were first introduced in the 1997 EPR 2 guidelines. The availability of an increasing number of studies on wheezing in children led to the formulation of separate recommendations for asthma management in children 5 years of age and under (NHLBI 1997). Similar to adults, children were classified into four groups based on disease severity: mild intermittent, mild persistent, moderate persistent, and severe persistent, with additional recommendations to initiate daily therapy in infants and children consistently requiring symptomatic treatment more than two times per week and in those with episodes of severe exacerbations occurring <6 weeks apart. The lack of evidence on the safety of ICS use in this age group led to recommendations for the preferred use of nedocromil or cromolyn as first-line treatment for mild persistent asthma, and low-dose ICS as alternative therapy (Silverman et al. 1972; Geller-Bernstein and Sneh 1980; Glass et al. 1981; Bertelsen et al. 1986).

*2002: Update to the Expert Panel Report 2*

The availability of nebulized ICS and montelukast for children as young as 2 years of age and new studies on the effectiveness and safety of ICS in children (CAMP 2000) led to an update of the pediatric guidelines in 2002 (NHLBI 2002). Initiation of treatment with long-term controller therapy was extended to infants and children who had more than three episodes of wheezing in the past year and a high risk of developing persistent asthma as indicated by a history of atopy or a parental history of asthma (Martinez 1995; Martinez et al. 1995; Castro-Rodriguez et al. 2000). Results from the Childhood Asthma Management Program (CAMP) trial demonstrating no differences between nedocromil and placebo in lung function or symptom outcome led to its removal from treatment recommendations (CAMP 2000). Low-dose ICS became the preferred therapy for mild persistent asthma, with cromolyn (Petty et al. 1989; Konig 1997) or leukotriene receptor antagonists (LTRA) as alternative therapy (Israel et al. 1996; DuBuske et al. 1997; Altman et al. 1998; Kemp et al. 1998; Knorr et al. 1998, 2001; Nathan et al. 1998; Tashkin et al. 1999; Bleecker et al. 2000; Pearlman et al. 2000; Busse et al. 2001). Comparative studies in older children and adults consistently favoring combination therapy over increasing doses of ICS (Greening et al. 1994; Woolcock et al. 1996) led to the preferred approach of adding LABAs to lower doses of inhaled corticosteroids for moderate persistent asthma in children 5 years of age and older. However, due to the lack of data on LABAs in children under 4 years of age (Verberne et al. 1997), monotherapy with medium-dose ICS was recommended as the preferred treatment option (Anhoj et al. 2002), with the addition of LTRA or theophylline to low-dose ICS as a nonpreferred alternative.

*2007: Expert Panel Report 3*

The EPR 3 divides treatment recommendations into three age groups: 0–4 years of age, 5–11 years of age, and ≥12 years of age. These groupings were chosen based on age-related issues of drug delivery and medication approval, relevance of the

different measures of impairment, potential short- and long-term impact of medications, and the variable levels of scientific evidence available for each age group with limited data on the safety and efficacy of treatments for young children (Baker et al. 1999; Kemp et al. 1999). Additionally, it was recognized that the course of disease changes over time. In children 5 years of age and younger, two general patterns in the progression of asthma symptoms appear: remission of symptoms in the preschool years and persistence throughout childhood (Martinez et al. 1995). Although no absolute markers exist to predict the prognosis of each individual child, longitudinal data from the Tucson Children's Respiratory Study was used to generate an asthma predictive index to identify risk factors for the development of persistent asthma (Castro-Rodriguez et al. 2000; Guilbert et al. 2006); children under 3 years of age with 4 or more episodes of wheezing in the past year that lasted more than 1 day and affected sleep are likely to have persistent asthma at 5 years of age if they also have a positive predictive index, either one of the following: parental history of asthma, atopic dermatitis or aeroallergen sensitization, or two of the following: food allergy, >4 % peripheral eosinophillia or wheezing apart from colds.

## 6.3 Summary of Recommendations from the 2007 NHLBI Guidelines

### *6.3.1 Assessing and Monitoring Asthma Control*

*Initial Assessment of Severity*

The EPR 3 links the functions of assessment and monitoring to the concepts of severity, control, and responsiveness to treatment. Although severity of disease is best assessed in patients before long-term controller medications are initiated, severity can also be inferred from the least amount of treatment required to maintain control in the domains of current impairment and future risk. Clinical studies confirm that parameters used for the impairment domain reflect increasing gradients of severity in adults (Schatz et al. 2003, 2005; Antonicelli et al. 2004; Diette et al. 2004). However, regardless of their asthma severity as classified on the basis of symptoms, the majority of children 5–18 years of age have normal $FEV_1$ values, and $FEV_1$/FVC appears to be a more sensitive measure of severity (Bacharier et al. 2004; Spahn et al. 2004; Paull et al. 2005). In the risk domain, the frequency of exacerbations requiring intervention with oral systemic steroids has been correlated in observational studies with the designation of persistent asthma; in general, the more frequent and intense the exacerbations, the greater the degree of underlying disease severity (Fuhlbrigge et al. 2001, 2006). Thus, based on specific measures (symptoms, use of rescue medications, frequency of exacerbations, and pulmonary function tests), asthma severity is categorized as either intermittent or persistent, with further classification of persistent asthma as either mild, moderate, or severe. To further emphasize the risk domain, an additional classification for the intensity of exacerbations was added and the designation of mild intermittent asthma was

**Table 6.1** NHLBI 2007 guidelines for classifying asthma severity and initiation of treatment by age

| Components of severity | | | Intermittent | | | Persistent | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Mild | | | Moderate | | | Severe | | | | | |
| Age in years | | | 0–4 | 5–11 | >12 | 0–4 | 5–11 | >12 | 0–4 | 5–11 | >12 | 0–4 | 5–11 | >12 | | | |
| Impairment | Symptoms | | ≤ 2 days/week | | | ≤ 2 days/week but not daily | | | Daily | | | Throughout the day | | | | | |
| | Nocturnal symptoms | | 0 | ≤ 2x/month | | 1-2x/month | 3-4x/month | | 3-4x/ month | ≥ 1x/week | | ≥ 2x/week | Often 7x/week | | | | |
| | SABA use | | ≤ 2 days/week | | | ≥ 2 days/week | | | Daily | | | Several times/day | | | | | |
| | Interferes with normal activity | | None | | | Minor | | | Some | | | Extremely | | | | | |
| | PFT | $FEV_1$ | n/a | > 80% | | n/a | 80% | | n/a | 60–80% | | n/a | < 60% | | | | |
| | | $FEV_1/FVC$ | | > 85% | Normal ratio | | > 80% | Normal ratio | | 75-80% | Reduced by > 5% | | < 75% | Reduced by > 5% | | | |
| Risk | Exacerbations requiring systemic corticosteroids | | 0–1x/year | | | ≥2x/6 months **OR** > 4x/year + risk factors | > 2x/year → | | | | | | | | | | |
| Recommended step for initiating treatment | | | Step 1 | | | Step 2 | | | Step 3 | | | Step 3 | | | Step 4 or Step 5 | | |

modified to intermittent asthma to emphasize that patients at any level of severity can have severe exacerbations (NHLBI 2007). Table 6.1 summarizes the classification of asthma for each age group.

*Assessment of Control*

After treatment is established, periodic monitoring and assessment is used to determine whether the goals of asthma therapy are being achieved, asthma is controlled, and if adjustments in therapy are needed (NHLBI 2007). Similar to the assessment of asthma severity, asthma control is also defined in the domains of impairment and risk in the different age groups, refer Table 6.2. The use of validated questionnaires [Asthma Control Test (Nathan et al. 2004), Childhood Asthma Control Test (Liu et al. 2007), Asthma Control Questionnaire (Juniper et al. 1999), and Asthma Therapy Assessment Questionnaire (Vollmer et al. 1999)] in addition to pulmonary function testing was included to better quantify asthma control (Katz et al. 2002). Once asthma control is obtained, reassessment of asthma severity is recommended, with reclassification by the lowest level of treatment required to maintain control (Lemanske et al. 2001; Hawkins et al. 2003). Recommended intervals for monitoring are 2–6 weeks for new or uncontrolled patients, 1–6 months for those who are controlled, or every 3 months if a change in therapy is anticipated (NHLBI 2007).

### *6.3.2 Stepwise Approach for Asthma Management*

The EPR 3 recommendations for long-term asthma management integrate the four components of therapy into a stepwise therapeutic approach in which medications are increased as necessary and decreased if possible to achieve and maintain

**Table 6.2** NHLBI 2007 guidelines for assessing asthma control and adjusting therapy by age

| Components of control | | | Well controlled | | | Not well controlled | | | Poorly controlled | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Age in years | | | 0–4 | 5–11 | >12 | 0–4 | 5–11 | >12 | 0–4 | 5–11 | >12 |
| Impairment | Symptoms | | ≤ 2days/week but not daily | | | ≥ 2 days/week **OR** Multiple times per day on ≤ 2 days/week | | | Throughout the day | | |
| | Nocturnal symptoms | | ≤ 1x/mo | | < 2x/mo | > 1x/mo | ≥ 2x/mo | 1-3x/week | > 1x/week | ≥ 2x /week | 4x/week |
| | SABA use | | ≤ 2days/week | | | ≥ 2days/week | | | Several times/day | | |
| | Limitations in activity | | None | | | Some | | | Extremely | | |
| | Questionnaire | ATAQ<br>ACQ<br>ACT/CACT | 0<br>≤ 0.75<br>> 20 | | | 1–2<br>1.5<br>16–19 | | | 3–4<br>N/A<br>≤15 | | |
| | PFTs | $FEV_1$<br>$FEV_1/FVC$ | n/a | 80%<br>> 80% | n/a | n/a | 60–80%<br>75–80% | n/a | n/a | < 60%<br>< 75% | n/a |
| Risk | Exacerbations requiring systemic steroids | | 0–1x/year | | | 2–3x/yr | > 2x/year | | > 3x/year | > 2x/year | |
| | Reduction in lung growth | | n/a | Long-term Follow-up | | n/a | Long-term Follow-up | | n/a | Long-term Follow-up | |
| | Side effects of treatment | | Side effects can vary. Consider in assessment of risk. | | | | | | | | |
| Recommended action for treatment | | | Maintain step down if control at least 3 months | | | Step up 1 step | | | Systemic corticosteroids Step up 1–2 steps | | |

long-term control of asthma. The type, amount, and scheduling of mediation is determined by the level of asthma severity (Table 6.1) or control (Table 6.2), and therapy is stepped up as needed for more severe or uncontrolled asthma, and stepped down, when possible (Table 6.3). To simplify previous guidelines where each step had several progressive actions, the EPR 3 expands the stepwise approach to six treatment steps for all age groups. The two new steps sharpen the focus of recommendations at each progressively higher level of treatment (NHLBI 2007).

The general stepwise approach is applicable to all patients who have asthma, with modifications to meet the needs of different patient age groups. Although medications were repositioned within the six steps of care, ICS therapy remained at the heart of the treatment for persistent asthma for all ages to emphasize the inflammatory nature of asthma, and the use of daily therapy only during specific periods of previously documented risk was added to the step 1 recommendations (Rafferty et al. 1985; Haahtela et al. 1991; Jeffery et al. 1992; van Essen-Zandvliet et al. 1992; Dahl et al. 1993; Kamada et al. 1996; Suissa et al. 2000; Pauwels et al. 2003). Due to the FDA black box warning on all medications containing LABA over concerns regarding its safety, step 3 recommendations were modified from the 2002 guidelines, and increasing the dose of ICS is presented as an equally preferred option to adding an LABA to low-dose ICS in all patients ≥5 years of age (Bateman et al. 2004; O'Byrne et al. 2005). Specific recommendations for each age group are presented below.

### Treatment Recommendations for Children 0–4 Years of Age

Although administration of ICS early in the disease process does not alter the underlying progression, achieving adequate asthma control does reduce impairment from

**Table 6.3** 2007 NHLBI Stepwise treatment recommendations by age

| | | Step1 | Step 2 | Step 3 | Step 4 | Step 5 | Step 6 |
|---|---|---|---|---|---|---|---|
| | | **Intermittent asthma** | | **Persistent asthma: daily medications** | | | |
| 0–4 years of age | Preferred | SABA as needed | Low-dose ICS | Medium-dose ICS | Medium-dose ICS + LABA or montelukast | High-dose ICS + LABA or montelukast | High-dose ICS + LABA or montelukast + Oral steroids |
| | Alternative | | Cromolyn or montelukast | | | | |
| 5–11 years of age | Preferred | | Low-dose ICS | Low-dose ICS + LABA, LTRA, theophylline **OR** Medium-dose ICS | Medium-dose ICS + LABA | High-dose ICS + LABA | High-dose ICS + LABA + Oral steroids |
| | Alternative | | Cromolyn, LTRA, nedocromil, or theophylline | | Medium-dose ICS + LTRA or theophylline | High-doseICS + LTRA or theophylline | High-dose ICS + LTRA or theophylline + Oral steroids |
| ≥12 years of age-Adults | Preferred | | Low-dose ICS | Low-dose ICS + LABA **OR** medium-dose ICS | Medium-dose ICS + LABA | High-dose ICS + LABA **AND** Consider omalizumab | High-dose ICS + LABA + Oral steroids **AND** Consider omalizumab |
| | Alternative | | Cromolyn, LTRA, nedocromil, or theophylline | Low-dose ICS + LABA, LTRA, zileuton, or theophylline | Medium-dose ICS + LTRA,zileuton, or theophylline | | |
| | | For all ages at each step: patient education, environmental control, management of comorbidities | | | | | |
| | | For 5–11 years of age and ≥12 years of age-adults groups: Consider subcutaneous immunotherapy for patients with persistent allergic asthma | | | | | |

symptom burden and the risk for severe exacerbations (Guilbert et al. 2006). Based on the long-term clinical efficacy of ICS in controlling asthma (O'Byrne et al. 2005; Guilbert et al. 2006) in this age group, ICS continue to be the preferred treatment for persistent asthma, although for step 2, montelukast in children 2 years of age or older can be considered if inhaled medication delivery is suboptimal due to either technique or adherence. Studies addressing step 3 care in children from 0 to 4 years of age are limited. Although some studies suggest a dose-dependent decrease in exacerbations, symptoms, and short-acting β-agonist (SABA) use with daily ICS

therapy, findings are mixed (Bisgaard 1999; Szefler 2002). Moreover, studies looking at the addition of an LABA to low-dose ICS in children ≥4 years of age demonstrated improved lung function and decreased symptoms (Russell et al. 1995; Zimmerman et al. 2004) but did not show a reduction in asthma exacerbations (Bisgaard 2003a). Due to the lack of studies with LABAs in young children combined with lack of evidence of demonstrating improvement in the risk domain, for step 3 the EPR 3 guidelines recommend increasing the dose of ICS prior to adding on adjunctive therapy. No data were found on add-on therapy in children 0–4 years of age whose asthma was not well controlled on medium-dose ICS; thus, recommendations for step 4 of asthma management are extrapolated from studies in older children and adults. In step 4, the EPR-3 recommends adding a noncorticosteroid medication to medium-dose ICS to avoid the risk of side effects associated with high-dose ICS (Van den Berg et al. 2000; Malone et al. 2005).

### Treatment Recommendations for Children 5–11 Years of Age

Long-term studies in children ages 5–12 years of age indicate that daily ICS improves health outcomes for children who have mild or moderate persistent asthma, and that the effectiveness outweighs the potential risk for delayed growth (CAMP 2000). Therefore, similar to the 0–4 years of age category, daily ICS continue to be recommended for the treatment of persistent asthma in step 2. However, in this age group, monotherapy with montelukast has not been found to be as efficacious as ICS on a range of asthma outcomes and is not recommended as an equally preferred alternative in at this treatment step (Garcia Garcia et al. 2005; Ostrom et al. 2005; Sorkness et al. 2007). For step 3, two equally preferred treatment options are available. Data from two trials demonstrated that children 4–11 years of age whose asthma was not completely controlled by low-dose ICS alone achieved improved lung function and symptom control with the addition of an LABA as compared to placebo (Russell et al. 1995; Zimmerman et al. 2004). In another trial, the addition of montelukast to low-dose ICS resulted in a slight increase in lung function and reduction in as-needed SABA use (Simons et al. 2001). Additionally, a systemic review in children 4–16 years of age reported a dose response to ICS for improvement in lung function and symptom control (Masoli et al. 2004). Thus, due to the lack of comparison studies for these various long-term control medications in children <11 years of age, the use of low-dose ICS plus adjunctive therapy with an LABA or LTRA, or increasing to a medium-dose ICS are presented as equally preferred treatment options for step 3. The decision between these options may be made on which domain is affected. Children with low lung function and >2 days per week impairment may be better served by adding an LABA to a low-dose ICS, whereas for the risk domain studies have not demonstrated that adding either LABA or LTRA reduces exacerbations in children (Bisgaard 2003a, b). Based on comparative studies in older children and adults, in step 4 the addition of an LABA is preferred (Greenstone et al. 2005; Masoli et al. 2005), with the use of LTRA or theophylline as a secondary alternative (NHLBI 2007; Peters et al. 2007).

### *6.3.3 Treatment for Youths ≥12 Years of Age and Adults*

As many of the treatment recommendations for the 5–11 years of age group were extrapolated from studies in older children and adults, the stepwise recommendations for patients in the >12 years of age to adult group are identical for steps 1 and 2 (Table 6.3). The recommendations for step 3 are derived from studies demonstrating that the addition of an LABA to medications in patients whose asthma is not well controlled on low- to medium-dose ICS improves lung function, decreases symptoms, and reduces exacerbations and the use of SABAs (Bateman et al. 2004; Greenstone et al. 2005; Masoli et al. 2005). However, although less effective than adding an LABA (Ind et al. 2003), escalating the dose of ICS in patients with uncontrolled asthma was able to improve the status of control to well controlled or totally controlled. Furthermore, additional studies show similar rates of exacerbations and nighttime awakenings among patients treated with medium-dose ICS or combination low-dose ICS/salmeterol (O'Byrne et al. 2005). This evidence combined with the increased risk for potentially deleterious side effects with the daily use of LABAs (Mann et al. 2003; Nelson et al. 2006) led to recommendations of two equally acceptable options for step 3 treatments: the addition of an LABA to low-dose ICS or increasing to medium-dose ICS (Table 6.3). As in children, the decision between these options may be made on which domain is affected. For the impairment domain, adding an LABA rather than increasing the dose of ICS has shown to more consistently result in improvements (NHLBI 2002). However, in the risk domain, the balance of potential risks need to be considered; the increased benefit of adding LABA to low-dose ICS with the risk of rare life-threatening or fatal exacerbations from LABA use versus the reduced risk of exacerbations at high-dose ICS with the risk of systemic effects at those doses (Pauwels et al. 1997; Masoli et al. 2005). As an alternative but not preferred treatment option, leukotriene modifiers or theophylline may be added to low-dose ICS, although these have not been found to be as effective in controlling asthma at all outcome measures (Evans et al. 1997; Ukena et al. 1997; Dahlen et al. 1998; Laviolette et al. 1999). The recommendations for steps 4–6 are identical to those in children aged 5–11, with the exceptions of the addition of zileuton as a choice for adjunctive therapy in step 4, and the use of omalizumab for steps 5 and 6 in patients who have sensitivity to perennial allergens (Bousquet et al. 2004; Humbert et al. 2005).

## 6.4 Other International Guidelines

In addition to the NHLBI guidelines, other international guidelines emphasizing specific patient populations have been published. The Global Initiative for Asthma (GINA) guidelines were first published in 1995 in order to have asthma guidelines that emphasized issues facing developing nations (Bateman et al. 2008). At approximately the same time, the British Thoracic Society (BTS) published their guidelines

in the British medical journal with diagnosis and treatment plans directed towards primary care physicians in their country (Morgan and Higgins 2003). Both the GINA and BTS guidelines have had several revisions since their inception with major changes in classification and treatment.

### *6.4.1 The BTS Guidelines*

The BTS guidelines were initially published in 1990, before the US guidelines were developed. Due to a need for a methodic evidence-based guideline for asthma management, in 1999 the BTS and the Scottish Intercollegiate Guidelines Network (SIGN) partnered together to jointly create the next set of comprehensive asthma guidelines for the UK using explicitly evidence-based methodology. Although guidelines are updated yearly, the last major revision was published in 2008 (BTS/SIGN 2008b). Similar to the NHBLI and GINA guidelines, the goal of these guidelines is to provide recommendations based on current evidence for best practice in the management of asthma and is aimed for healthcare professionals, as well as, others outside the healthcare system actively involved in the care of asthmatic patients.

The BTS/SIGN guidelines are centered on three main concepts (1) the initial diagnosis and monitoring of asthma, (2) pharmacologic and nonpharmacologic management, and (3) the organization and delivery of care, and patient education and self-management. Like the NHLBI guidelines, the BTS/SIGN guidelines provide information on specific medications and recommended doses. The recommendations for the management of patients are divided by age into three groups: <5 years of age, 5–12 years of age, and those greater than 12 years of age, although the guidelines note that many of the recommendations in the 5–12 years of age and greater than 12 years of age groups are the same.

#### Initial Assessment and Monitoring

The focus of the initial assessment of patients with asthma is making an accurate clinical diagnosis. As there are no standardized diagnostic tests to diagnose asthma, the BTS/SIGN guidelines encourage clinicians to determine the "probability" of someone having asthma when they present with symptoms. The approach to diagnosis is based on the primary care model that uses an integrated approach centered on the patients presenting symptoms and acquisition of additional details (personal or family history of atopic disease or asthma and diagnostic testing) to achieve an accurate diagnosis, and based on the initial clinical assessment, patients are classified as having a high, low, or intermediate probability of having a diagnosis of asthma (BTS/SIGN).

For patients in all age groups with a high probability of asthma, a therapeutic trial with daily anti-inflammatory medications is recommended, whereas in those

with a low probability of asthma, investigations and treatments for other conditions are recommended. In children and adults with an intermediate probability of asthma, watchful waiting with follow-up is advised, with an option to initiate an empiric trial of treatment depending on the severity of symptoms and results of diagnostic tests. Similar to the NHBLI guidelines after the initial assessment, monitoring of asthma symptoms using various tools (validated asthma questionnaires, pulmonary function tests, and peak expiratory flow volumes) to assess and measure asthma control plays a key role in the recommendations for management. The BTS/SIGN guidelines emphasize monitoring to facilitate the diagnostic process by determining the response to treatment and providing clinicians with information to support treatment and referral decisions.

## Pharmacologic Management

Guidance on the pharmacologic management of chronic asthma occupies a central position in the 2008 BTS/SIGN guidelines and emphasizes the need to strive for high levels of asthma control with no breakthrough symptoms or exacerbations and minimal side effects. In addition, identifying patient-set targets for control that balances the patients' needs and personal goals for their asthma management with the idea of perfect control to reduce poor adherence to daily medications and poor outcomes is highlighted. Treatment is organized into a stepwise approach, with the aim of treatment to maintain and achieve control by stepping up or down as appropriate. The level of treatment is dictated by assessment of control rather than by severity.

### *Adults*

In adults, treatment is divided into five steps (Table 6.4). In step 1 (mild intermittent asthma) and all subsequent steps, as needed SABAs are required. For persistent symptoms, step 2 (regular preventer therapy) recommendations are to initiate daily therapy with low- to moderate-dose ICS (Adams et al. 2001). For patients uncontrolled at step 2, the step 3 (initial add-on therapy) recommendations are divided into two parts. As patients using various strengths of combination fluticasone/salmeterol inhaler have been found to achieve guideline-defined control more rapidly and at a lower total dose of ICS than with fluticasone alone, the first choice is the addition of an LABA to low- or moderate-dose ICS (Ringbaek et al. 1996; Crompton et al. 1999; Wallaert et al. 1999). However, in patients with a poor response to LABA, a second option of increasing the dose of ICS along with the LABA, or adding an alternative therapy such as LTRA or theophylline in lieu of an LABA is offered (Evans et al. 1997; Ukena et al. 1997; Ducharme 2003). Additionally, at step 3 and above, the use of combination budesonide/formoterol as a rescue medication instead of an SABA (known as the SMART regimen) has been found to be an effective and cost-saving treatment option (Rabe et al. 2006). At step 4 (persistent poor control), the recommendations are for high-dose ICS and the addition of a fourth drug, such as an LTRA, theophylline, or $\beta_2$-agonist tablet. In the fifth and final step

(continuous or frequent use of oral steroids), the addition of daily systemic steroids along with high-dose ICS and referral to a specialist is recommended.

*Children 5–12 Years of Age*

In children 5–12 years of age, treatment is once again divided into 5 steps (Table 6.4), with recommendations similar to those for adults. Although the routine use of ICS in the treatment of viral induced wheezing is not supported by the BTS/SIGN guidelines, symptoms ≥3 times per week, the use of SABA ≥3 times per week, nocturnal symptoms once a week, or a history of exacerbation requiring oral steroids in the preceding 2 years are indications of poor asthma control and the need for daily ICS therapy (Sporik et al. 1991; Martinez et al. 1995; Dodge et al. 1996). The first major difference occurs at step 3 where 400 mcg per day is defined as the upper limit for moderate-dose ICS along with an LABA and/or adjunctive therapy (BTS/SIGN 2008a). Additionally, due to lack of evidence in patients under 18 years of age, the SMART regimen is not recommended. The step 4 recommendations include increasing the dose of ICS to 800 mcg per day in addition to step 3 treatments, and in step 5, the addition of daily systemic steroids along with referral to a specialist is recommended.

*Children <5 Years of Age*

For children <5 years of age, recommendations are divided into only 4 steps (Table 6.4). In step 2, treatment with daily dose of ICS at 200–400 mcg per day or LTRA are offered as potentially equal options (Ducharme 2003; Kelly et al. 2008). For initial add-on therapy in step 3, LTRA should be added on in children on maximal doses of ICS and vice versa (Spector et al. 1994; Altman et al. 1998; Reiss et al. 1998). In this age group, LABAs and ICS at doses >400 mcg per day are not recommended at any level of treatment. Finally, for children with persistent poor control (step 4) or in children under 2 years of age, referral to a specialist is recommended.

### *6.4.2 The GINA Guidelines*

The GINA was established in 1993 as a collaborative effort between the NHBLI and the World Health Organization (WHO) with the purpose of developing asthma diagnosis and management guidelines that took into consideration the differences in socioeconomic status of different countries and the availability of healthcare resources. There were two phases to GINA; the first phase encompassing the actual report which included sections on epidemiology, pathogenesis and preventions, complementary medicines, and health economics, and the second phase focused on creating educational materials for widespread dissemination to public health officials, healthcare professionals, and patients. Since their inception, the GINA guidelines have undergone four major revisions. The third revision represents the

**Table 6.4** 2008 BTS/SIGN treatment recommendations by age

| | Step1 | Step 2 | Step 3 | Step 4 | Step 5 |
|---|---|---|---|---|---|
| | **Mild intermittent asthma** | **Regular preventer therapy** | **Initial add-on therapy** | **Persistent poor control** | **Continuous or frequent use of oral steroids** |
| >5 years of age | SABA as needed | Daily ICS (200-400 mcg/day) **OR** LTRA | Daily ICS (200-400 mcg/day) **+** LTRA | Referral to specialist | |
| 5–12 years of age | | Daily ICS (200–400 mcg/day) | 1. ICS + LABA<br>2. Assess control<br>–Benefit from LABA but not controlled: ↑ICS to 400 mcg/day **+**LABA<br>–No benefit from LABA: ↑ICS to 400 mcg/day **+** LTRA **OR** theophylline | ↑ICS to 800 mcg/day **+** Step 3 therapies | Daily oral steroids at lowest dose providing control **+** Maintain high-dose ICS **+** Referral to specialist |
| ≥12 years of age | | Daily ICS (200–800 mcg/day) | 1. ICS + LABA<br>2. Assess control<br>–Benefit from LABA but not controlled: ↑ICS to 800 mcg/day **+**LABA<br>–No benefit from LABA: ↑ICS to 800 mcg/day **+** LTRA **OR** Theophylline | Consider trials of:<br>• ↑ICS to 2000 mcg/day<br>• Addition of fourth drug (LTRA, theophylline, β-agonist) | Daily oral steroids at lowest dose providing control **+** Maintain high-dose ICS **+** Alternative treatments **+** Referral to specialist |

transition of guidelines from opinion based to evidence based, and the fourth and most recent GINA guidelines represents the paradigm shift in the way asthma is classified.

## Initial Assessment and Monitoring

Similar to the EPR 3, the 2007 GINA guidelines center the long-term management of asthma on four components of effective care (GINA 2011). However, in the GINA guidelines, classification of asthma is based solely on the level of control (Bateman et al. 2008). Previous guidelines emphasized severity as a major indicator of asthma disease, but the misperception that asthma severity correlated with

control, and results of the GOAL study (Bateman et al. 2004) demonstrating that control could be achieved at all levels of asthma severity led to a paradigm shift for asthma care at the international level. Classification uses several composite measures in both domains of risk and impairment, including history of symptoms, exacerbations, and pulmonary function testing, to categorize asthma status as being controlled, partially controlled, or uncontrolled. To be considered well controlled, all of the following criteria must be met: no daytime symptoms, no limitation of normal activities, no nocturnal symptoms, no need for rescue treatment, and normal pulmonary function tests. If any one of these criteria is abnormal, the patient is classified as partially controlled and if three or more criteria are abnormal, the patient is classified as uncontrolled. The patient's current level of asthma control and current treatment determine the selection of pharmacologic treatment.

**Pharmacologic Management**

Treatment options are organized into five steps reflecting the increasing intensity of treatment required to achieve control, with a step up in therapy for patients who are not controlled and consideration to step-down therapy for those who have been well controlled for at least 3 months (Table 6.4). To maintain adaptability in different socioeconomic regions, treatment recommendations are general with a preferred option and other alternatives identified in each step. Treatment options are divided into two age groups: those ≤5 years of age and >5 years of age to adults.

Step 1 treatment with intermittent use of SABA is reserved for patients with intermittent symptoms. For frequent symptoms or periodic impairment, step 2 or higher level of treatment is recommended. Treatment steps 2–5 combine as-needed SABA with regular controller treatments. At step 2, a low-dose ICS is recommended for all ages, with alternative controller medications including LTRA for patients who are unable or unwilling to use ICS for any reason. Other non-ICS options are not recommended for routine or initial step 2 care due to their comparatively low efficacy. At step 3, the recommended option for adolescents and adults is to combine low-dose ICS with an LABA, whereas increasing the dose of ICS or combining low-dose ICS with leukotriene modifiers are the alternatives. However, for children 5 years of age or younger, increasing the dose of ICS is presented as an equally preferred alternative, as there is no clear evidence in this age group for the use of low-dose ICS with leukotriene modifiers. At step 4 of treatment, two or more controller medications along with a rescue medication are recommended, and for step 5, the addition of oral glucocorticosteroids or anti-IgE therapy in selected patients is added to the therapy.

### *6.4.3 Comparison of Guidelines*

In all of these guidelines, the overriding goal is to establish a consensus of scientific practices for the management of asthma centered on common themes: to assess

asthma symptoms and control, the importance of both nonpharmacologic and pharmacologic treatments to maintain control and manage exacerbations, and to develop a partnership between patients and healthcare providers through patient education and use of self-management plans. Similarly, the evolution of guidelines from opinion based to evidence based and the shift from the classification of asthma by disease severity to symptom control are mirrored by the NHLBI, BT/SIGN, and GINA. As national guidelines, both the NHLBI and the BTS/SIGN guidelines provide specific recommendations for diagnostic modalities, and medications with dosage recommendations commiserate with the availability of resources in those countries. In contrast, the GINA guidelines were established to create a more internationally focused set of guidelines taking into consideration the disparities in the socioeconomic status and access to healthcare resources that exist across the world. As such, the GINA guidelines provide more general treatment strategies for management and diagnosis, sections on acceptable alternatives utilizing affordable medications, and added recommendations for more comprehensive asthma education on a global level. The 2008 GINA treatment recommendations are given in Table 6.5.

The major difference between the guidelines is in the initial assessment of patients with asthma. Whereas in the NHLBI guidelines, an initial assessment of severity to initiate treatment is used, the GINA guidelines solely use markers defining the level of control to both initiate and manage asthma treatment. In contrast, the evaluation of asthma in the BTS/SIGN guidelines focuses on making an accurate diagnosis of asthma which likely reflects the primary care-based medical system in the UK. In the long-term management of asthma, all three guidelines outline a stepwise approach to asthma management utilizing the assessment of control to determine the appropriate level of pharmacologic management. As the GINA guidelines arose from a collaboration with the NHLBI, it is not surprising that the many of the concepts regarding the use of the impairment and risk domains in the assessment of control and how control is defined are similar, as well the number of defined treatment steps. In contrast, whereas the BTS/SIGN guidelines also base management on control, the division into specific domains is not explicitly defined. Additionally, definitions of control are more stringently defined by BTS/SIGN, with no tolerance for exacerbations or breakthrough symptoms, and five steps in asthma management of asthma instead of six. Overall, these differences likely reflect the variations in how healthcare is managed in these nations rather than divergent ideologies or interpretations of the literature.

## 6.5 The Current Status of Asthma Care and Future Directions

Despite the increasing prevalence in asthma, the last decade has seen reductions in death rates and hospitalizations due to asthma (Spahn and Szefler 1996; Szefler 2011a, b). Improved asthma management and new medications have reduced the number of patients receiving systemic steroids, and the number of patients with

**Table 6.5** 2008 GINA treatment recommendations

| | Treatment steps | | | | |
|---|---|---|---|---|---|
| | **Step 1** | **Step 2** | **Step 3** | **Step 4** | **Step 5** |
| | Asthma education | | | | |
| | Environmental control and control of co-morbidities | | | | |
| | As-needed SABA | | | | |
| Controller options | SABA | **Select one** | **Elect one** | **Add one or more** | **Add one or both** |
| | | Low-dose ICS | Low-dose ICS + LABA | Medium- **OR** High-dose ICS + LABA | Oral steroids |
| | | Leukotriene modifier | Medium- **OR** High-dose ICS | Leukotriene modifier | Anti-IgE treatment |
| | | | Low-dose ICS + Leukotriene modifier | Sustained-release theophylline | |
| | | | Low-dose ICS + Sustained-release theophylline | | |

adverse effects due to these drugs. However, racial and gender disparities, and the continued variable response to treatment amongst patients has spurred the growing concept of personalized medicine, which could significantly advance current asthma management. Identification of biomarkers and epigenetic markers could prompt a more effective treatment strategy to prevent exacerbations, halt disease progression, and define asthma phenotypes and specific phenotype related interventions. To date, several biomarkers such as exhaled nitric oxide levels and sputum eosinophil levels have been studied as prototypic markers for disease activity and targets for therapeutic intervention, and exploration of genetic markers continues in relation to clinical application for asthma management. Better understanding of asthma physiology at the individual level and new discoveries on ways to better manage asthma could lead to another revision in asthma guidelines both in the USA and globally.

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