SECTION 3, COMPONENT 3: CONTROL OF ENVIRONMENTAL FACTORS AND COMORBID CONDITIONS THAT AFFECT ASTHMA

KEY POINTS: CONTROL OF ENVIRONMENTAL FACTORS AND COMORBID CONDITIONS THAT AFFECT ASTHMA

- Exposure of patients who have asthma to allergens (Evidence A) or irritants (EPR—2 1997) to which they are sensitive has been shown to increase asthma symptoms and precipitate asthma exacerbations.
- For at least those patients who have persistent asthma, the clinician should evaluate the potential role of allergens, particularly indoor inhalant allergens (Evidence A):
  - — Use the patient's medical history to identify allergen exposures that may worsen the patient's asthma.
  - — Use skin testing or in vitro testing to reliably determine sensitivity to perennial indoor inhalant allergens to which the patient is exposed.
  - — Assess the significance of positive tests in the context of the patient's medical history.
  - — Use the patient's history to assess sensitivity to seasonal allergens.
- Patients who have asthma at any level of severity should:
  - — Reduce, if possible, exposure to allergens to which the patient is sensitized and exposed.
  - — Know that effective allergen avoidance requires a multifaceted, comprehensive approach; individual steps alone are generally ineffective (Evidence A).
  - — Avoid exposure to environmental tobacco smoke and other respiratory irritants, including smoke from wood-burning stoves and fireplaces and, if possible, substances with strong odors (Evidence C).
  - — Avoid exertion outdoors when levels of air pollution are high (Evidence C).
  - — Avoid use of nonselective beta-blockers (Evidence C).
  - — Avoid sulfite-containing and other foods to which they are sensitive (Evidence C).
  - — Consider allergen immunotherapy when there is clear evidence of a relationship between symptoms and exposure to an allergen to which the patient is sensitive (Evidence B). If use of allergen immunotherapy is elected, it should be administered only in a physician's office where facilities and trained personnel are available to treat any life-threatening reaction that can, but rarely does, occur.

- Adult patients who have severe persistent asthma, nasal polyps, or a history of sensitivity to aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) should be counseled regarding the risk of severe and even fatal exacerbations from using these drugs (Evidence C).

- Clinicians should evaluate a patient for the presence of a chronic comorbid condition when the patient's asthma cannot be well controlled. Treating the conditions may improve asthma management: ABPA (Evidence A), gastroesophageal reflux (Evidence B), obesity (Evidence B, limited studies), OSA (Evidence D), rhinitis/sinusitis (Evidence B), chronic stress/depression (Evidence D).

- Consider inactivated influenza vaccination for patients who have asthma. It is safe for administration to children more than 6 months of age and adults (Evidence A). The Advisory Committee on Immunization Practices of the CDC recommends vaccination for persons who have asthma, because they are considered to be at risk for complications from influenza. However, the vaccine should not be given with the expectation that it will reduce either the frequency or severity of asthma exacerbations during the influenza season (Evidence B).

- Use of humidifiers and evaporative (swamp) coolers is not generally recommended in homes of patients who have asthma and are sensitive to house-dust mites or mold (Evidence C).

- Employed persons who have asthma should be queried about possible occupational exposures, particularly those who have new-onset disease (EPR—2 1997).

- There is insufficient evidence to recommend any specific environmental strategies to prevent the development of asthma.

KEY DIFFERENCES FROM 1997 EXPERT PANEL REPORT

- Evidence strengthens recommendations that reducing exposure to inhalant indoor allergens can improve asthma control and notes that a multifaceted approach is required; single steps to reduce exposure are generally ineffective.

- Formaldehyde and volatile organic compounds (VOCs) have been implicated as potential risk factors for asthma and wheezing.

- Evidence shows that influenza vaccine, while having other benefits, does not appear to reduce either the frequency or severity of asthma exacerbations during the influenza season.

- The section has been expanded to include discussion of ABPA, obesity, OSA, and stress as chronic comorbid conditions, in addition to rhinitis, sinusitis, and gastroesophageal reflux, that may interfere with asthma management.

Introduction

See section 1, "Overall Methods Used To Develop This Report," for literature search strategy and tally of results for the EPR—3: Full Report 2007 on this component, "Control of Environmental Factors and Comorbid Conditions That Affect Asthma." Two Evidence Tables were prepared: 9, Allergen Avoidance; and 10, Immunotherapy.

For successful long-term management of asthma, it is essential to identify and reduce exposures to relevant allergens and irritants and to control other factors that have been shown to increase asthma symptoms and/or precipitate asthma exacerbations. These factors are in five categories: inhalant allergens, occupational exposures, irritants, comorbid conditions, and other factors. Ways to reduce the effects of these factors on asthma are discussed in this component of asthma management.

Inhalant Allergens

The Expert Panel recommends that patients who have asthma at any level of severity should be queried about exposures to inhalant allergens, particularly indoor inhalant allergens, and their potential effect on the patient's asthma (Evidence A). Exposure of a person who has asthma to inhalant allergens to which the person is sensitive increases airway inflammation and symptoms. Substantially reducing such exposure may significantly reduce inflammation, symptoms, and need for medication (See a summary of the evidence in box 3–5.).

DIAGNOSIS—DETERMINE RELEVANT INHALANT SENSITIVITY

Demonstrating a patient's relevant sensitivity to inhalant allergens will enable the clinician to recommend specific environmental controls to reduce exposures. It will also help the patient understand the pathogenesis of asthma and the value of allergen avoidance.

The Expert Panel recommends that, given the importance of allergens and their control to asthma morbidity and asthma management, patients who have persistent asthma should be evaluated for the role of allergens as possible contributing factors as follows (EPR—2 1997):

- **Determine the patient's exposure to allergens, especially indoor inhalant allergens. (See relevant questions in figure 3–17.)**
- **Assess sensitivity to the allergens to which the patient is exposed.**
  - **Use the patient's medical history, which is usually sufficient, to determine sensitivity to seasonal allergens.**
  - **Use skin testing or in vitro testing to determine the presence of specific IgE antibodies to the indoor allergens to which the patient is exposed year round. (See figure 3–18 for a comparison of skin and in vitro tests.) Allergy testing is the only reliable way to determine sensitivity to perennial indoor allergens (See box 3–6 for further explanation.).**
  - **For selected patients who have asthma at any level of severity, detection of specific IgE sensitivity to seasonal or perennial allergens may be indicated as a basis for education about the role of allergens for avoidance and for immunotherapy.**
- **Assess the clinical significance of positive allergy tests in the context of the patient's medical history (See figure 3–19.).**

BOX 3–5. THE STRONG ASSOCIATION BETWEEN SENSITIZATION TO ALLERGENS AND ASTHMA: A SUMMARY OF THE EVIDENCE

The association of asthma and allergy has long been recognized. Recent studies confirm that sensitization among genetically susceptible populations to certain indoor allergens such as house-dust mite, animal dander, and cockroach or to the outdoor fungus Alternaria is a risk for developing asthma in children (Halonen et al. 1997; Sears et al. 1993; Sporik et al. 1990). Sensitization to outdoor pollens carries less risk for asthma (Sears et al. 1989), although exposure to grass (Reid et al. 1986) and ragweed (Creticos et al. 1996) pollen has been associated with seasonal asthma. It is widely accepted that the importance of inhalant sensitivity as a cause of asthma declines with advancing age (Pollart et al. 1989).

An allergic reaction in the airways, caused by natural exposure to allergens, has been shown to lead to an increase in inflammatory reaction, increased airway hyperresponsiveness (Boulet et al. 1983; Peroni et al. 1994; Piacentini et al. 1993), and increased eosinophils in bronchoalveolar lavage (Rak et al. 1991). Other research has demonstrated that asthma symptoms, pulmonary function, and need for medication in mite-sensitive asthma patients correlate with the level of house-dust mite exposure (Custovic et al. 1998; Huss et al. 2001; Sporik et al. 1990; Vervloet et al. 1991) and that reducing house-dust mite exposure reduces asthma symptoms, nonspecific bronchial hyperresponsiveness, and evidence of active inflammation (Morgan et al. 2004; Peroni et al. 2002; Piacentini et al. 1993; Simon et al. 1994). Inhalant allergen exposure to seasonal outdoor fungal spores (O'Hollaren et al. 1991; Targonski et al. 1995) and to indoor allergens (Call et al. 1994) has also been implicated in fatal exacerbations of asthma. These reports emphasize that allergen exposure must be considered in the treatment of asthma.

The important allergens for children and adults appear to be those that are inhaled. Food allergens are not a common precipitant of asthma symptoms. Foods are an important cause of anaphylaxis in adults and children (Golbert et al. 1969; Sampson et al. 1992), but significant lower respiratory tract symptoms are uncommon even with positive double-blind food challenges (James et al. 1994). However, asthma is a risk factor for fatal anaphylactic reactions to food or immunotherapy (Bernstein et al. 2004; Reid et al. 1993).

BOX 3–6. RATIONALE FOR ALLERGY TESTING FOR PERENNIAL INDOOR ALLERGENS

Determination of sensitivity to a perennial indoor allergen is usually not possible with a patient's medical history alone (Murray and Milner 1995). Increased symptoms during vacuuming or bed making and decreased symptoms when away from home on a business trip or vacation are suggestive but not sufficient. Allergy skin or in vitro tests are reliable in determining the presence of specific IgE (Dolen 2001; Yunginger et al. 2000), but these tests do not determine whether the specific IgE is responsible for the patient's symptoms. That is why patients should be tested only for sensitivity to the allergens to which they may be exposed, and why the third step in evaluating patients for allergen sensitivity calls for assessing the clinical relevance of the sensitivity.

The recommendation to do skin or in vitro tests for patients who have persistent asthma and are exposed to perennial indoor allergens will result in a limited number of allergy tests for about half of all asthma patients. This estimate is based on the prevalence of persistent asthma and the level of exposure to indoor allergens. Based on data on children in the United States, it is estimated that at least 70 percent of all patients who have asthma have persistent asthma (Squillace et al. 1997; Taylor and Newacheck 1992). About 80 percent of the U.S. population is exposed to house-dust mites (Arbes et al. 2003; Nelson and Fernandez-Caldas 1995), 60 percent to cat or dog, and a much smaller percentage to both animals (Ingram et al. 1995). Cockroaches are a consideration primarily in the inner-city and southern parts of the United States.

Skin or in vitro tests are necessary to educate patients about the role of allergens in their disease. Education is an essential prerequisite for convincing patients about the need for specific allergen avoidance. Current recommendations for avoidance measures for dust-mite, cat, or cockroach allergens are allergen specific, and it is only possible to convince patients to undertake the measures once they know to what they are allergic.

MANAGEMENT—REDUCE EXPOSURE

The Expert Panel recommends that patients should reduce exposure, as much as possible, to allergens to which the patient is sensitized and exposed:

- **The first and most important step in controlling allergen-induced asthma is to advise patients to reduce exposure to relevant indoor and outdoor allergens to which the patient is sensitive (Evidence A) (See Evidence Table 9, Allergen Avoidance.).**
- **Effective allergen avoidance requires a multifaceted, comprehensive approach; individual steps alone are generally ineffective (Evidence A).**
- **Consider multifaceted allergen-control education interventions provided in the home setting that have been proven effective for reducing exposures to cockroach, dust-mite, and rodent allergens for patients sensitive to those allergens (Evidence A). Further research to evaluate the feasibility of widespread implementation of such programs will be helpful (see "Component 2: Education for a Partnership in Asthma Care.").**

Effective ways patients can reduce their exposures to indoor and outdoor allergens are discussed below and summarized in figure 3–20, which also addresses irritants. Although these recommendations focus on the home environment, reductions in exposures to allergens and irritants are also appropriate in other environments where the patient spends extended periods of time, such as school, work, or daycare. For information about companies that distribute products to help reduce allergen exposure, contact the Asthma and Allergy Foundation of America toll-free hotline at 800–727–8462 or the Allergy and Asthma Network/Mothers of Asthmatics at 800–878–4403.

See "Component 2: Education for a Partnership in Asthma Care" for a description of allergen-control education programs that are delivered in patients' homes. Multifaceted programs that focus on educating patients and providing tools for reducing exposure to cockroach, dust-mite, and rodent allergens have demonstrated success in reducing exposure and reducing asthma morbidity. Further evaluation is needed of the cost-effectiveness and feasibility for widespread implementation of these interventions; however, the efficacy of the interventions warrants their consideration, if available, for patients sensitive to these allergens.

Animal allergens. The Expert Panel recommends the following actions to control animal antigens (Evidence D):

- **If the patient is sensitive to an animal, the treatment of choice is removal of the exposure from the home.**
- **If removal of the animal is not acceptable:**
  - **Keep the pet out of the patient's bedroom.**
  - **Keep the patient's bedroom door closed.**
  - **Remove upholstered furniture and carpets from the home, or isolate the pet from these items to the extent possible.**
  - **Mouse allergen exposure can be reduced by a combination of blocking access, low-toxicity pesticides, traps, and vacuuming and cleaning.**

All warm-blooded animals, including pets and rodents, produce dander, urine, feces, and saliva that can cause allergic reactions (de Blay et al. 1991b; Swanson et al. 1985). Given recent evidence that exposure to cat allergens can be significant in homes, schools, and offices without animals, the issue of allergen avoidance in sites without animals has become more relevant. Successful controlled trials of animal dander avoidance have now been reported for schools and for homes without an animal (Popplewell et al. 2000). Studies suggest that mouse and rat allergen exposure and sensitization are common in urban children who have asthma (Phipatanakul et al. 2004).

High-efficiency particulate air (HEPA) cleaners reduce airborne Can f 1 in homes with dogs. Furthermore, preventing the dog from having access to the bedroom, and possibly the living room, may reduce the total allergen load inhaled (Green et al. 1999). Weekly washing of the pet will remove large quantities of dander and dried saliva that will otherwise accumulate in the house; however, the role of washing in allergen avoidance is not established (Avner et al. 1997, de Blay et al. 1991a, Klucka et al. 1995).

House-dust mite allergen. The Expert Panel recommends the following mite-control measures; effective allergen avoidance requires a multifaceted approach (Evidence A).

- **Recommended actions to control mites include:**
  - **Encase the mattress in an allergen-impermeable cover.**
  - **Encase the pillow in an allergen-impermeable cover or wash it weekly.**
  - **Wash the sheets and blankets on the patient's bed weekly in hot water.**
  - **A temperature of >130 °F is necessary for killing house-dust mites. Prolonged exposure to dry heat or freezing can also kill mites but does not remove allergen. If high temperature water is not available, a considerable reduction in live mites and mite allergens can still be achieved with cooler water and using detergent and bleach.**
- **Actions to *consider* to control mites include:**
  - **Reduce indoor humidity to or below 60 percent, ideally between 30 and 50 percent.**
  - **Remove carpets from the bedroom.**
  - **Avoid sleeping or lying on upholstered furniture.**
  - **Remove from the home carpets that are laid on concrete.**
  - **In children's beds, minimize the number of stuffed toys, and wash them weekly.**

House-dust mites are universal in areas of high humidity (most areas of the United States) but are usually not present at high altitudes or in arid areas unless moisture is added to the indoor air (Platts-Mills et al. 1997). Mites depend on atmospheric moisture and human dander for survival. High levels of mites can be found in dust from mattresses, pillows, carpets, upholstered furniture, bed covers, clothes, and soft toys. The patient's bed is the most important source of dust mites to control. Washing bedding is advised, preferably in hot water, but cold water, detergent, and bleach can also be effective (Arlian et al. 2003; McDonald and Tovey 1992). Several recent studies support the efficacy of allergen avoidance in the treatment of asthma (Carter et al. 2001; Halken et al. 2003; Htut et al. 2001; Morgan et al. 2004; Peroni et al. 2002; Rijssenbeek-Nouwens et al. 2003; van der Heide et al. 1997). Other studies provide important insight into the details of allergen avoidance. For example, three studies reported that mattress covers without other measures were not effective (Luczynska et al. 2003; Terreehorst et al. 2003; Woodcock et al. 2003). Likewise, two well-conducted studies failed to show an effect of HEPA filters alone (Francis et al. 2003; Wood et al. 1998). Thus, the conclusion remains that effective allergen avoidance requires a comprehensive approach, and that individual steps alone are generally ineffective (Platts-Mills et al. 2000).

Chemical agents are available for killing mites and denaturing the antigen; however, the effects are not dramatic and do not appear to be maintained for long periods. Therefore, use of these agents in the homes of persons who have asthma and are sensitive to house-dust mites should not be recommended routinely (Woodfolk et al. 1995). Vacuuming removes mite allergen from carpets but is inefficient at removing live mites.

Room air-filtering devices are not recommended for control of mite allergens, because the allergens are associated with large particles which remain airborne for only a few minutes after disturbance. They are, therefore, not susceptible to removal by air filtration.

Cockroach allergen. The Expert Panel recommends that cockroach control measures should be instituted if the patient is sensitive to cockroaches and infestation is present in the home (Evidence B).

Cockroach sensitivity and exposure are common among patients who have asthma and live in inner cities (Call et al. 1992; Gelber et al. 1993; Huss et al. 2001; Kang et al. 1993). In a study of asthma in an inner-city area, asthma severity increased with increasing levels of cockroach antigen in the bedrooms of children who were sensitized (Rosenstreich et al. 1997). Another major study demonstrated efficacy of cockroach avoidance as part of an overall plan for allergen avoidance (Morgan et al. 2004). Patients should not leave food or garbage exposed. Poison baits, boric acid, and traps are preferred to other chemical agents, because the latter can be irritating when inhaled by persons who have asthma. If volatile chemical agents are used, the home should be well ventilated, and the person who has asthma should not return to the home until the odor has dissipated. Care should be taken so that young children do not have access to cockroach baits and poisons.

Indoor fungi (molds). The Expert Panel recommends consideration of measures to control indoor mold (Evidence C). Indoor fungi are particularly prominent in humid environments and homes that have problems with dampness. Children who live in homes with dampness problems have increased respiratory symptoms (Institute of Medicine 2004; Verhoeff et al. 1995), but the relative contribution of fungi, house-dust mites, or irritants is not clear. Because an association between indoor fungi and respiratory and allergic disease is suggested by some studies (Bjornsson et al. 1995; Smedje et al. 1996; Strachan 1988), measures to control dampness or fungal growth in the home may be beneficial.

Outdoor allergens (tree, grass, and weed pollen; seasonal mold spores). The Expert Panel recommends that patients who are sensitive to seasonal outdoor allergens consider staying indoors, if possible, during peak pollen times—particularly midday and afternoon (EPR—2 1997). The strongest associations between mold-spore exposure and asthma have been with the outdoor fungi, such as *Alternaria* (Halonen et al. 1997; O'Hollaren et al. 1991; Targonski et al. 1995). Patients can reduce exposure during peak pollen season by staying indoors with windows closed in an air-conditioned environment (Solomon et al. 1980), particularly during the midday and afternoon when pollen and some spore counts are highest (Long and Kramer 1972; Mullins et al. 1986; Smith and Rooks 1954). Conducting outdoor activities shortly after sunrise will result in less exposure to pollen. These actions may not be realistic for some patients, especially children.

IMMUNOTHERAPY

The Expert Panel recommends that allergen immunotherapy be considered for patients who have persistent asthma if evidence is clear of a relationship between symptoms and exposure to an allergen to which the patient is sensitive (Evidence B) (see Evidence Table 10, Immunotherapy).

Immunotherapy is usually reserved for patients whose symptoms occur all year or during a major portion of the year and in whom controlling symptoms with pharmacologic management is difficult because the medication is ineffective, multiple medications are required, or the patient is

not accepting the use of medication. Reports, however, that immunotherapy can prevent the development of new sensitivities in monosensitized children and adults (Des Roches et al. 1997; Pajno et al. 2001; Purello-D'Ambrosio et al. 2001) and that immunotherapy with birch and timothy pollen extracts can prevent the development of asthma in children who have allergic rhinitis (Moller et al. 2002), along with evidence of persisting effect for at least 3 years after discontinuation (Durham et al. 1999), suggest that immunotherapy should be considered when there is a significant allergic contribution to the patient's symptoms. Specific immunotherapy has been shown to induce a wide range of immunologic responses that include the modulation of T- and B-cell responses by the generation of allergen-specific Treg cells; increases in allergen-specific IgG4, IgG1, and IgA; decrease in IgE and decreased tissue infiltration of mast cells and eosinophils. The relevance of these immunologic changes to the clinical efficacy of specific immunotherapy has yet to be established (Akdis and Akdis 2007).

Controlled studies of immunotherapy, usually conducted with single allergens, have demonstrated reduction in asthma symptoms caused by exposure to grass, cat, house-dust mite, ragweed, *Cladosporium,* and *Alternaria* (Creticos et al. 1996; Horst et al. 1990; Malling et al. 1986; Olsen et al. 1997; Reid et al. 1986; Varney et al. 1997). A meta-analysis of 75 randomized, placebo-controlled studies has confirmed the effectiveness of immunotherapy in asthma, with a significant reduction in asthma symptoms and medication and with improvement in bronchial hyperreactivity (Abramson et al. 2003). This meta-analysis included 36 trials for allergy to house dust mites, 20 for pollen allergy, and 10 for animal dander. On the other hand, only three trials for mold allergy and only six trials with multiple allergen therapy were included. In the United States, standardized extracts are available for house-dust mites, grasses, short ragweed, and cat, and there are unstandardized extracts of other pollens and for dog that appear to have similar potency (Nelson 2007). Available extracts for cockroach and mold, on the other hand, are of very variable allergen content and allergenic potency, and their effectiveness in specific immunotherapy has not been demonstrated (Nelson 2007). Few studies have been reported on multiple-allergen mixes that are commonly used in clinical practice. One, which included high doses of all allergens to which the children were sensitive (Johnstone and Dutton 1968), demonstrated reduction in asthma symptoms compared to lower doses of the same allergens or placebo. Another study, in which the children were given optimal medical therapy and in which the only perennial allergen administered was house-dust mite, demonstrated no improvement in asthma symptoms between active and placebo therapy (Adkinson et al. 1997).

The course of allergen immunotherapy is typically of 3–5 years' duration. Severe and sometimes fatal reactions to immunotherapy, especially severe bronchoconstriction, are more frequent among patients who have asthma, particularly those who have poorly controlled asthma, compared with those who have allergic rhinitis (Bernstein et al. 2004; Reid et al. 1993). If use of allergen immunotherapy is elected, it should be administered only in a physician's office where facilities and trained personnel are available to treat any life-threatening reaction that can, but rarely does, occur (AAAI Board of Directors 1994). For this reason, enthusiasm for the use of immunotherapy in asthma differs considerably among experts (Abramson et al. 2003; Canadian Society of Allergy and Clinical Immunology 1995; Frew 1993).

In Europe, interest has increased in high-dose sublingual immunotherapy (Canonica and Passalacqua 2003). It has been reported to be effective in asthma, with benefit persisting 4–5 years after its discontinuation (Di Rienzo et al. 2003), and to be free of systemic reactions, thus allowing home administration. Comparative studies suggest it is less effective, however, than immunotherapy administered by subcutaneous injection (Khinchi et al. 2004; Lima et al. 2002).

ASSESSMENT OF DEVICES THAT MAY MODIFY INDOOR AIR

The Expert Panel recommends the following actions to modify indoor air:

- **Vacuuming carpets once or twice a week to reduce accumulation of house dust. Patients sensitive to components of house dust should avoid using conventional vacuum cleaners, and these patients should stay out of rooms where a vacuum cleaner is being or has just been used (EPR—2 1997;** Murray et al. 1983**).** If patients vacuum, they can use a dust mask, a central cleaner with the collecting bag outside the home, or a cleaner fitted with a HEPA filter or with a double bag (Popplewell et al. 2000; Woodfolk et al. 1993).

- **Air conditioning during warm weather, if possible, for patients who have asthma and are allergic to outdoor allergens (Evidence C),** because air conditioning allows windows and doors to stay closed, thus preventing entry of outdoor allergens (Solomon et al. 1980). Regular use of central air conditioning also will usually control humidity sufficiently to reduce house-dust mite growth during periods of high humidity (Arlian et al. 2001). Reducing relative humidity is a practical way to control house-dust mites and their allergens in homes in temperate climates (Arlian et al. 2001).

- **Use of a dehumidifier to reduce house-dust mite levels in areas where the humidity of the outside air remains high for most of the year (EPR—2 1997).** House-dust mite levels can be reduced by use of dehumidifiers to maintain levels to or below 60 percent, ideally 30–50 percent, relative humidity (Cabrera et al. 1995).

- **There is insufficient evidence to recommend indoor air cleaning devices. They may reduce some, but not all airborne allergens, but evidence is limited regarding their impact on asthma control.** Indoor air-cleaning devices cannot substitute for the more effective dust-mite and cockroach control measures described previously, because these heavy particles do not remain airborne (Custis et al. 2003). However, air-cleaning devices (i.e., HEPA and electrostatic precipitating filters) have been shown to reduce airborne dog allergen (Green et al. 1999), cat dander (de Blay et al. 1991a; Francis et al. 2003; Wood et al. 1998), mold spores (Maloney et al. 1987), and particulate tobacco smoke (EPA 1990). Use of an air cleaning device containing a HEPA filter may reduce exposure, especially if added to other avoidance measures (Green et al. 1999). However, most studies of air cleaners have failed to demonstrate an effect on asthma symptoms or pulmonary function (Nelson et al. 1988; Reisman et al. 1990; Warburton et al. 1994; Warner et al. 1993; Wood et al. 1998). Air cleaners that are designed to work by the generation of ozone and that emit ozone into the air should be avoided by persons who have asthma.

- **There is insufficient evidence to recommend cleaning air ducts of heating/ventilation/air conditioning systems (Evidence D).** Cleaning has been reported to decrease levels of airborne fungi in residences (Garrison et al. 1993). The effect on levels of house-dust mite or animal dander has not been studied. Limited evidence continues to preclude the Expert Panel's making a recommendation in this area.

The Expert Panel does not generally recommend use of humidifiers and evaporative (swamp) coolers for use in the homes of house-dust mite-sensitive patients who have asthma (Evidence C). If use of a humidifier is desired to avoid excessive dryness, the relative humidity in the home should be maintained at or below 60 percent, ideally between 30 and 50 percent. These machines are potentially harmful because increased humidity may

encourage the growth of both mold (Solomon 1976) and house-dust mites (Ellingson et al. 1995; McConnell et al. 2002). In addition, humidifiers may pose a problem because, if not properly cleaned, they can harbor and aerosolize mold spores (Solomon 1974).

Occupational Exposures

The Expert Panel recommends that clinicians query patients who are employed and have asthma about possible occupational exposures, particularly those who have new-onset disease (EPR—2 1997). Early recognition and control of exposures are particularly important in occupationally induced asthma, because the likelihood of complete resolution of symptoms decreases with time (Pisati et al. 1993). Occupational asthma is suggested by a correlation between asthma symptoms and work, as well as with improvement when away from work for several days. Other indications of workplace exposure are listed in figure 3–21. The patient may fail to recognize the relationship with work, because symptoms often begin several hours after exposure. Recently, common jobs—such as domestic cleaner, laboratory technician, and house painter—have been associated with the disease (Moscato et al. 1995). Serial peak flow records at work and away from work can confirm the association between work and asthma (Nicholson et al. 2005).

Workplace exposure to sensitizing chemicals, allergens, or dusts can induce asthma which often persists after the exposures are terminated (Pisati et al. 1993). This effect should be distinguished from allergen- or irritant-induced aggravation of preexisting asthma.

Patient confidentiality issues are particularly important in work-related asthma. Because even general inquiries about the potential adverse health effects of work exposures may occasionally result in reprisals against the patient (e.g., job loss), patients who have asthma need to be informed of this possibility and be full partners in the decision to approach management regarding the effects or control of workplace exposures. This situation may require referral to an occupational asthma specialist.

Irritants

The Expert Panel recommends that clinicians query patients who have asthma at any level of severity about exposures to irritants that may cause their asthma to worsen, and advise them accordingly about reducing relevant exposures (EPR—2 1997). Sample assessment questions are in figure 3–17.

ENVIRONMENTAL TOBACCO SMOKE

The Expert Panel recommends that clinicians advise persons who have asthma not to smoke or be exposed to ETS (Evidence C). Query patients about their smoking status and specifically consider referring to smoking cessation programs adults who smoke and have young children who have asthma in the household (Evidence B).

Exposure to ETS is common in the United States (Gergen et al. 1998). ETS is associated with increased symptoms, decreased lung function, and greater use of health services among those who have asthma (Sippel et al. 1999) in all age groups, although exact negative effects may vary by age (Mannino et al. 2001). Exposure to maternal smoking has been shown to be a risk factor for the development of asthma in infancy and childhood (Henderson et al. 1995; Martinez et al. 1995; Soyseth et al. 1995). Effects of ETS on a child's asthma are greater when the mother smokes than when others in the household smoke (Agabiti et al. 1999; Austin and

Russell 1997; Ehrlich et al. 2001). Heavy smokers may be more unaware than those who smoke less of the effects of ETS exposure on children (Crombie et al. 2001). The primary modes of exposure to ETS for adults who have asthma may be when they are at work (Radon et al. 2002) or traveling (Eisner and Blanc 2002). ETS exposure operates as a cofactor in wheezing, along with other insults such as infections (Gilliland et al. 2001). Smoking out of doors to avoid exposing others may not adequately reduce exposure for children (Bahceciler et al. 1999). See "Component 2: Education for a Partnership in Asthma Care" for discussion of programs to encourage parents of children who have asthma not to smoke.

As a routine part of their asthma care, patients should be counseled concerning the negative effects of smoking and ETS.

INDOOR/OUTDOOR AIR POLLUTION AND IRRITANTS

The Expert Panel recommends that clinicians advise patients to avoid, to the extent possible, exertion or exercise outside when levels of air pollution are high (Evidence C).

Increased pollution levels—especially of particulate matter ≤10 micrometers (PM10) (Abbey et al. 1993; Atkinson et al. 2001; Gent et al. 2003; Koenig et al. 1993; Ostro et al. 1995; Pope et al. 1991; Schwartz et al. 1993; Slaughter et al. 2003; Walters et al. 1994) and ozone (Abbey et al. 1993; Cody et al. 1992; Kesten et al. 1995; Ostro et al. 1995; Ponka 1991; Romieu et al. 1995; Thurston et al. 1992; White et al. 1994), but also of SO_2 (Moseholm et al. 1993) and nitric oxide (NO_2) (Kesten et al. 1995; Moseholm et al. 1993)—have been reported to precipitate symptoms of asthma (Abbey et al. 1993; Koenig et al. 1987; Moseholm et al. 1993; Pope et al. 1991), increase SABA use (Gent et al. 2003), and increase ED visits and hospitalizations for asthma (Cody et al. 1992; Kesten et al. 1995; Ponka 1991; Romieu et al. 1995; Schwartz et al. 1993; Thurston et al. 1992; Walters et al. 1994; White et al. 1994).

High exposure to NO_2 in the week before the start of a respiratory viral infection, at levels within current air quality standards, may increase the severity of virus-induced asthma exacerbations (Chauhan et al. 2003).

Exposure to pollutants may increase airway inflammation (Hiltermann et al. 1999) and enhance the risk of allergic sensitization through simultaneous exposure to aeroallergens (Diaz-Sanchez et al. 1999; Fujieda et al. 1998; Jenkins et al. 1999). The propensity for particulate pollution to enhance allergic sensitization may be genetically regulated (Gilliland et al. 2004; Peden 2005).

Formaldehyde and Volatile Organic Compounds

Formaldehyde and VOCs—which can arise from sources such as new linoleum flooring, synthetic carpeting, particleboard, wall coverings, furniture, and recent painting—have been implicated as potential risk factors for the onset of asthma and wheezing (Garrett et al. 1999; Jaakkola et al. 2004; Rumchev et al. 2004). Clinicians should advise patients to be aware of the potential irritating effects of newly installed furnishings and finishes.

Gas Stoves and Appliances

The Expert Panel recommends that clinicians advise patients to avoid, if possible, exposure to gas stoves and appliances that are not vented to the outside, fumes from wood-burning appliances or fireplaces, sprays, or strong odors (Evidence C).

Use of unvented gas stoves and appliances results in increased indoor levels of NO_2. Use of gas stoves for cooking has been associated with increased respiratory symptoms, including wheezing in school children (Garrett et al. 1998; Withers et al. 1998) and increased prevalence of bronchial hyperresponsiveness in atopic adults (Kerkhof et al. 1999). However, data from the National Health and Nutrition Examination Survey III (NHANES III) did not suggest any impact of gas-stove use on pulmonary function or respiratory symptoms in adults who have asthma (Eisner and Blanc 2003). Infants at high risk for asthma who were exposed to higher levels of NO_2—but levels which currently are not considered to be harmful—had increased days of wheezing and shortness of breath (van Strien et al. 2004). In school-aged children, increased levels of NO_2 were associated with increased bronchitis, wheeze, and asthma in girls but not boys (Shima and Adachi 2000). When unflued gas heaters in schools were replaced, NO_2 levels decreased by two-thirds, accompanied by significant reduction in both daytime and nighttime asthma symptoms (Pilotto et al. 2004). Exposure to gas heaters and appliances in infancy has been found to be a risk for wheezing, asthma, and bronchial hyperresponsiveness as well as sensitization to house-dust mites in school-aged children (Phoa et al. 2004; Ponsonby et al. 2000, 2001). Current use of gas appliances also was found to be a risk for decreased FEV_1 in children sensitized to house-dust mites (Glasgow et al. 2001). Fumes from wood-burning appliances or fireplaces can precipitate symptoms in persons who have asthma (Ostro et al. 1994). Sprays and strong odors, particularly perfumes, can also irritate the lungs and precipitate asthma symptoms.

Comorbid Conditions

The Expert Panel recommends that clinicians evaluate a patient for presence of a chronic comorbid condition when the patient's asthma cannot be well controlled. Treating the following conditions may improve asthma management: ABPA (Evidence A), gastroesophageal reflux (Evidence B), obesity (Evidence B, limited studies), OSA (Evidence D), rhinitis/sinusitis (Evidence B), chronic stress/depression (Evidence D). Several chronic comorbid conditions have been demonstrated to impede asthma management. Evidence suggests that if the conditions are treated appropriately, asthma control can improve, although clearly some conditions are more readily addressed than others. Clinical judgment is needed to weigh the level of asthma control and patient circumstances to determine the appropriate approach.

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

The Expert Panel recommends that ABPA should be suspected in patients who have asthma and have the presence or a history of pulmonary infiltrates. It should also be specifically considered in patients who have evidence of IgE sensitization to *Aspergillus* (positive prick skin test or in vitro tests) and in corticosteroid-dependent patients who have asthma (Evidence A). ABPA complicates both asthma and cystic fibrosis (Greenberger 2002). The fungus grows saphrophytically in bronchial mucus in the bronchi. Although there is no tissue invasion, a surrounding, predominantly eosinophilic inflammation occurs and often leads to damage to the bronchial wall and development of the typical proximal bronchiectasis, which may be varicose (beaded), cylindrical, or saccular (cystic). The classic clinical presentation includes transient migratory lung shadows on chest x ray or computer tomography (CT), peripheral blood eosinophilia, pyrexia, and sputum containing brown plugs or flecks. Occasionally, the same presentation is produced by another organism, usually another fungus.

Clear diagnostic criteria for ABPA are lacking; minimum criteria for the diagnosis of ABPA complicating asthma include (Greenberger 2002):

- Positive immediate skin test to *Aspergillus*
- Total serum IgE >417 IU (1,000 ng/mL)
- Elevated serum IgE and/or immunoglobulin G (IgG) to *Aspergillus*
- Central bronchiectasis (inner two-thirds of the chest CT fields)

An earlier form of the disease, before it has progressed to produce central bronchiectasis, can be diagnosed based on the first three criteria above in patients who have asthma. Additional supporting findings for a diagnosis of ABPA include a history of pulmonary infiltrates, serum precipitating antibodies to *Aspergillus,* peripheral blood eosinophilia, and production of mucus plugs containing *Aspergillus.*

The standard treatment for ABPA is prednisone, initially 0.5 mg per kilogram, with gradual tapering monitored by repeat chest x rays and measurement of total serum IgE concentrations (Greenberger 2002). Azole antifungal agents have also been tried as adjunctive treatment in patients who are stable and who have ABPA (Wark et al. 2003). Itraconazole administered orally for 16 weeks reduced sputum eosinophilia, serum IgE and IgG levels, and the number of exacerbations requiring oral corticosteroids (Stevens et al. 2000).

GASTROESOPHAGEAL REFLUX DISEASE

The Expert Panel recommends that medical management of GERD be instituted for patients who have asthma and complain of frequent heartburn or pyrosis, particularly those who have frequent episodes of nocturnal asthma (Evidence B).

For patients who have poorly controlled asthma, particularly with a nocturnal component, investigation for GERD may be warranted even in the absence of suggestive symptoms (Irwin et al. 1989; Kiljander et al. 1999).

Medical management of GERD includes:

- Avoiding heavy meals, fried food, caffeine, and alcohol.
- Avoiding food and drink within 3 hours of retiring (Nelson 1984).
- Elevating the head of the bed on 6- to 8-inch blocks (Nelson 1984).
- Using appropriate pharmacologic therapy (Harding 1999).

For patients who have persistent reflux symptoms following optimal therapy, further evaluation is indicated.

The symptoms of GERD are common in both children and adults who have asthma (Harding 1999). Reflux during sleep can contribute to nocturnal asthma (Avidan et al. 2001; Cibella and Cuttitta 2001; Davis et al. 1983; Martin et al. 1982). Although a systematic review concluded that there was no overall improvement in asthma following medical treatment for GERD (Gibson et al. 2003), treatment with a proton pump inhibitor was reported to reduce nocturnal symptoms (Kiljander et al. 1999), reduce asthma exacerbations, and improve quality of life related to asthma (Littner et al. 2005). Surgical treatment has been reported to reduce the symptoms of asthma and the requirement for medication (Field et al. 1999; Perrin-Fayolle et al. 1989; Sontag et al. 2003).

OBESITY

The Expert Panel recommends that clinicians consider advising asthma patients who are overweight or obese that weight loss, in addition to improving overall health, might also improve their asthma control (Evidence B, limited studies).

Obesity has been associated with asthma persistence and severity in both children and adults (Camargo et al. 1999; Schaub and von Mutius 2005; Shore and Fredberg 2005; Weiss 2005; Weiss and Shore 2004). Although obesity itself causes alterations in pulmonary physiology that can lead to dyspnea, studies have documented specific increases in asthma among overweight and obese persons.

Increased risk from obesity appears to be greatest in postpubertal women and is associated with more severe symptoms, enhanced airway inflammation, and new-onset or persistent disease (Camargo et al. 1999; Guerra et al. 2004). Presently, the relationship of obesity to allergy is controversial.

The effects of obesity on asthma appear to be independent of diet and physical activity, although these three factors are clearly interrelated. Many epidemiologic studies have controlled for potential effects of diet and physical activity when examining the relationship of obesity to asthma onset (Camargo et al. 1999).

The few RCTs that have been done are small, but they show that weight loss in adults resulted in improvement in pulmonary mechanics, improved FEV_1, reductions in exacerbations and courses of oral corticosteroids, and improved quality of life (Stenius-Aarniala et al. 2000). Weight loss following gastric bypass surgery improved self-reported asthma severity (Simard et al. 2004).

OBSTRUCTIVE SLEEP APNEA

The Expert Panel recommends that clinicians consider evaluating patients who have unstable, not-well-controlled asthma, particularly those who are overweight or obese, to ascertain whether they have symptoms that suggest OSA (Evidence D).

OSA and nocturnal asthma are distinct entities that fall within the broad classification of sleep-disordered breathing. Patients who have OSA and nocturnal asthma may have similar clinical presentations. Both conditions may involve repetitive sleep arousals associated with changes in oronasal airflow, ventilatory effort, and decreases in oxygen saturation (SaO_2) during sleep. Consequently, each of these disorders may be mistaken for the other in some patients. Moreover, asthma and OSA may coexist in a significant number of patients. Congestion of the nasopharynx, with resultant mouth breathing, may heighten the expression of both conditions. OSA-induced hypoxemia may predispose to increased bronchial reactivity, and vagal tone is increased during obstructive apneas (Denjean et al. 1988; Tilkian et al. 1978). On the other hand, sleep disruption secondary to nocturnal asthma could cause periodic breathing and decreased upper airway muscle activity, contributing to upper airway obstruction during sleep. A high prevalence of OSA has been reported in patients who have unstable asthma (Yigla et al. 2003).

Patients who have unstable asthma **and** sleep apnea demonstrated improvement when treated with nasal continuous positive airway pressure (CPAP). Morning and evening PEF before and after SABA significantly improved (Chan et al. 1988). However, nocturnal nasal CPAP in

individuals who have asthma and who do not have apnea is associated with disrupted sleep architecture (Martin and Pak 1991). Thus, confirmation of diagnosis is important.

RHINITIS/SINUSITIS

The Expert Panel recommends that clinicians evaluate patients who have asthma regarding the presence of rhinitis/sinusitis diagnosis or symptoms (Evidence B). It is important for clinicians to appreciate the connection between upper and lower airway conditions and the part the connection plays in asthma management.

There is considerable evidence for the interrelationship of the upper and lower airway and the concept of the airway as a continuum. Varied epidemiologic studies support a substantial association between allergic rhinitis and asthma (Guerra et al. 2002; Leynaert et al. 1999; Linneberg et al. 2002). Those persons who treat asthma need to concern themselves with the best therapy for the upper airway to optimize overall therapy for their patients.

In addition to the general similarity of normal nasal and bronchial mucosa, these mucosa may show similar changes when inflamed, including erosion of the epithelium, thickening of the basement membrane, and cellular infiltrate that is often eosinophilic (Ponikau et al. 2003). In patients who have allergic rhinitis, nasal allergen challenge has been shown to induce adhesion molecule expression and inflammatory mediators in bronchial mucosa and sputum (Beeh et al. 2003; Braunstahl et al. 2001). Segmental bronchial allergen challenge causes inflammatory changes in both nasal and bronchial mucosa (Braunstahl et al. 2000, 2001).

Treatment of allergic rhinitis and asthma with intranasal corticosteroids has decreased exhaled NO and H_2O_2, markers of lower airway inflammation (Sandrini et al. 2003). Review of the literature on antihistamine therapy in the treatment of asthma reveals positive results (Nelson 2003). Both intranasal steroids and second-generation antihistamines with or without decongestants have been reported to decrease ED visits for asthma (Adams et al. 2002; Corren et al. 2004; Crystal-Peters et al. 2002). However, the validity of the statistical approach used to arrive at this conclusion, in at least one of these articles, has been questioned (Suissa and Ernst 2005). Immunotherapy may also be considered for the treatment of allergic rhinitis (See previous section “Immunotherapy.”)

A similar manifestation of “the airway as a continuum” exists in patients who have sinusitis and asthma. A direct relationship can be seen between severity of CT of sinus, markers of lower airway inflammation including eosinophils in peripheral blood and sputum, level of exhaled NO, as well as decreases in pulmonary function (ten Brinke et al. 2002). In children who have asthma and are treated with intranasal corticosteroids and antibiotics for rhinosinusitis, improvement in respiratory symptoms has been shown to be accompanied by decreases in inflammatory cells and mediators in the nose (Tosca et al. 2003). Studies of sinus surgery in patients who have chronic rhinosinusitis and asthma have shown mixed results (Dunlop et al. 1999; Uri et al. 2002).

STRESS, DEPRESSION, AND PSYCHOSOCIAL FACTORS IN ASTHMA

The Expert Panel recommends that clinicians consider inquiring about the potential role of chronic stress or depression in complicating asthma management for patients whose asthma is not well controlled (Evidence C); additional patient education may be helpful (Evidence D). Clinical trials are needed to evaluate the effect of stress and stress reduction on asthma control, but observational studies demonstrate an association between increased stress

and worsening asthma. See "Component 2: Education for a Partnership in Asthma Care" for strategies to help improve patients' coping skills and support for asthma management.

The role of stress and psychological factors in asthma is important but not fully defined. Emerging evidence indicates that stress can play an important role in precipitating exacerbations of asthma and possibly act as a risk factor for an increase in prevalence of asthma (Busse et al. 1995; Sandberg et al. 2004; Wright et al. 2002). Chronic stressors increase the risk of asthma exacerbations, especially in children who have severely negative life events and those who have brittle asthma (Miles et al. 1997; Sandberg et al. 2000).

The mechanisms involved in this process have yet to be fully established and may involve enhanced generation of pro-inflammatory cytokines (Friedman et al. 1994). In a prospective study of a birth cohort predisposed to atopy, higher caregiver stress in the first 6 months after birth was significantly associated with an increased atopic immune profile in the children (high total IgE level, increased production of tumor necrosis factor-alpha (TNF-α) and a suggested trend between higher stress and reduced interferon-gamma (IFN-γ production) (Wright et al. 2004a). Equally important are psychosocial factors that are associated with poor outcome (e.g., conflict between patients and family and the medical staff, inappropriate asthma self-care, depressive symptoms, behavioral problems, emotional problems, and disregard of perceived asthma symptoms) (Brush and Mathé 1993; Strunk et al. 1985; Strunk 1993). Asthma severity can be affected by personal or parental factors, and both should be evaluated in cases of poorly controlled asthma. For example, maternal depression is common among inner-city mothers of children who have asthma and has been associated with increased ED visits and poor adherence to therapy by these children (Bartlett et al. 2001, 2004). Furthermore, in a large prospective study of inner-city children who had asthma, increased exposure to violence, as reported by caretakers, predicted a higher number of symptom days in their children, with caregivers' perceived stress mediating some, although not all, of this effect (Wright et al. 2004b). It may also be important to evaluate psychosocial and socioenvironmental factors in children who have repeated hospitalizations; however, it is not clear whether psychosocial factors affect or result from the frequent hospitalizations (Chen et al. 2003).

Other Factors

MEDICATION SENSITIVITIES

Aspirin

The Expert Panel recommends that clinicians query adult patients who have asthma regarding precipitation of bronchoconstriction by aspirin and other NSAIDs (Evidence C). If patients have experienced a reaction to any of these drugs, they should be informed of the potential for all of these drugs to precipitate severe and even fatal exacerbations. Adult patients who have severe persistent asthma or nasal polyps should be counseled regarding the risk of using these drugs (Evidence C). Alternatives to aspirin that usually do not cause acute bronchoconstriction in aspirin-sensitive patients include acetaminophen (7 percent cross-sensitivity) (Jenkins et al. 2004), salsalate (Settipane et al. 1995; Szczeklik et al. 1977), or the COX-2 inhibitor celecoxib (Gyllfors et al. 2003). Aspirin desensitization treatment, followed by daily aspirin, is a potential option to decrease disease activity and reduce corticosteroid requirements (Berges-Gimeno et al. 2003a,b).

As many as 21 percent of adults and 5 percent of children who have asthma have aspirin-induced asthma, especially when identified through oral provocation testing rather than

verbal history (Jenkins et al. 2004). In one study, 39 percent of adults who had asthma and were admitted to an asthma-referral hospital were reported to experience severe and even fatal exacerbations of asthma after taking aspirin or certain other NSAIDs (Spector et al. 1979). The prevalence of aspirin sensitivity increases with increasing age and severity of asthma (Chafee and Settipane 1974; Spector et al. 1979).

Beta-Blockers

The Expert Panel recommends that clinicians advise asthma patients to avoid nonselective beta-blockers, including those in ophthalmological preparations (Evidence B). Nonselective beta-blockers can cause asthma symptoms (Odeh et al. 1991; Schoene et al. 1984), although cardioselective beta-blockers, such as betaxolol, may be tolerated (Dunn et al. 1986). A recent systematic review, primarily of single dose or short-term studies in younger subjects, indicates that patients who have mild to moderate airway obstruction can tolerate cardioselective beta-blockers; therefore, if needed for managing cardiovascular disorders, these agents may be administered after careful evaluation (Salpeter et al. 2002).

SULFITE SENSITIVITY

The Expert Panel recommends that clinicians advise patients who have asthma symptoms associated with eating processed potatoes, shrimp, or dried fruit or with drinking beer or wine to avoid these products (Evidence C). These products contain sulfites, which are used to preserve foods and beverages. Sulfites have caused severe asthma exacerbations, particularly in patients who have severe persistent asthma (Taylor et al. 1988).

INFECTIONS

Viral Respiratory Infections

It is well established that viral respiratory infections can exacerbate asthma, particularly in children under age 10 who have asthma (Busse et al. 1993). Respiratory syncytial virus (RSV), rhinovirus, and influenza virus have been implicated (Busse et al. 1993), with rhinovirus being implicated in the majority of the exacerbations of asthma in children (Johnston et al. 1995). The role of infections causing exacerbations of asthma also appears to be important in adults (Nicholson et al. 1993). Rhinovirus, considered to be mainly an upper airway pathogen, has recently been demonstrated in the lower airways in patients who have asthma (Mosser et al. 2005). Rhinovirus infections in patients who have asthma may induce exacerbations due to abnormalities in epithelial cells' innate immune responses to infection (Wark et al. 2005).

Viral infections are the most frequent precipitants of wheezing during infancy and asthma exacerbations during childhood. Many infants and toddlers who wheeze with viral infections are predisposed to have bronchial obstruction during these illnesses because of very small airway size (Martinez et al. 1995), and they will not have further exacerbations during later childhood.

However, chronic asthma also may start as early as the first year of life among infants who have a family history of asthma, persistent rhinorrhea, atopic dermatitis, or high IgE levels. Early identification of these infants would allow institution of environmental controls to reduce exposure to tobacco smoke, animal dander, and house-dust mites and, thus, potentially reduce symptoms. RSV infections severe enough to require hospitalization during infancy and early childhood may be a risk factor for subsequent chronic asthma (Sigurs et al. 2005).

Bacterial Infections

Recent studies in both children and adults suggest that infections with both *Mycoplasma* and *Chlamydia,* in addition to viral infections, may contribute to exacerbation rates and disease chronicity and severity (Cunningham et al. 1998; Esposito et al. 2000; Kraft et al. 2002). Studies to confirm and expand upon these initial observations have been impeded due to the lack of definitive serologic markers to document current or past infection, as well as the inherent difficulties in obtaining biologic specimens from the lower airway to confirm the presence of these infectious agents (Martin et al. 2001).

Influenza Infection

The Expert Panel recommends that clinicians consider inactivated influenza vaccination for patients who have asthma. It is safe to administer in children over 6 months and adults who have asthma (Evidence A), and the Advisory Committee on Immunization Practices of the CDC recommends the vaccine for persons who have asthma because they may be at increased risk for complications from influenza. However, the vaccine should not be given with the expectation that it will reduce either the frequency or severity of asthma exacerbations during the influenza season (Evidence B).

Recent evaluations in both children and adults have yielded inconsistent and unconvincing results regarding the ability of influenza vaccination to reduce either overall rates of asthma exacerbations or exacerbations specifically related to influenza infection during the influenza season (Abadoglu et al. 2004; Bueving et al. 2004; Cates et al. 2004; Kramarz et al. 2001). The Advisory Committee on Immunization Practices recommends inactivated influenza vaccine for persons who have chronic disorders of the pulmonary systems, including asthma, because they are considered to be at increased risk for complications from influenza, such as hospitalizations and increased requirements for antibiotics (CDC 2006).

Administration of partially inactivated influenza vaccine is safe in both adults and children who have asthma (American Lung Association Asthma Clinical Research Centers 2001). Vaccination with cold-adapted, live, attenuated influenza vaccine has also been demonstrated to be safe in school-aged, adolescent, and adult patients who have asthma (Belshe et al. 2004). However, the observation of an increased risk of asthma/reactive airway disease in children <36 months of age is of potential concern (Bergen et al. 2004). In patients who have documented histories of anaphylactic reactions after ingestion of egg protein and documented evidence of current allergic sensitization to eggs (skin testing or in vitro antigen-specific IgE antibody testing), the risk/benefit ratio of administration of influenza vaccine should be reviewed carefully. If the decision is made to administer the live, attenuated vaccine, a subspecialist familiar with appropriate challenge testing and published safe administration protocols should be consulted prior to administration (Zeiger 2002).

FEMALE HORMONES AND ASTHMA

In the opinion of the Expert Panel, no recommendation can be made at this time regarding female hormones and asthma.

There is considerable interest in the effects of female hormones on asthma severity. Studies are not totally concordant in their findings, but most evidence suggests that some women have worsening of their asthma during the premenstrual and menstrual times of the cycle (Haggerty et al. 2003; Shames et al. 1998). Two ED studies, however, suggest that many women

experience asthma exacerbations during the preovulatory phase (Brenner et al. 2005; Zimmerman et al. 2000). Studies on hormone replacement therapy (HRT) after menopause also demonstrate apparent discordance. A cross-sectional study reported better pulmonary function and less frequent asthma exacerbations (Kos-Kudla et al. 2001), whereas a prospective cohort study found higher risk of adult-onset asthma (Barr et al. 2004).

Although associations between female hormones and asthma severity are not uniform or clear, it may be useful for clinicians, as they develop action plans with their patients, to appreciate the role that female hormone levels may have in the course of asthma.

DIET

In the opinion of the Expert Panel, there is insufficient evidence to make specific recommendations with regard to dietary constituents that should be consumed or avoided to affect asthma.

Patients have great interest in whether dietary factors may influence the onset, persistence, or severity of asthma. Although people who have asthma frequently experience bronchoconstriction as part of an acute IgE-mediated reaction to a food, food allergy is rarely the main aggravating factor in chronic asthma in children and even more rarely in adults (Sampson 2003).

Preliminary evidence suggests that antioxidant vitamins (Currie et al. 2005; Devereux et al. 2002; Kaur et al. 2001; Martindale et al. 2005; McKeever et al. 2004; Pearson et al. 2004; Shaheen et al. 2001) and omega-3 fatty acids (Broadfield et al. 2004; Dunstan et al. 2003; Kompauer et al. 2004; Mihrshahi et al. 2003, 2004; Peat et al. 2004; Woods et al. 2004) reduce asthma development and symptom severity, but no conclusive evidence shows that any dietary factors prevent or exacerbate the disease.

Physicians and patients are encouraged to promote a varied diet consistent with the Dietary Guidelines for Americans (DHHS and USDA 2005). In brief, most Americans need to consume diets with more fruits, vegetables, and whole grains, and eat less solid fats (saturated fat, *trans* fat), salt, and added sugars.

Primary Prevention of Allergic Sensitization and Asthma

In the opinion of the Expert Panel, there is insufficient evidence to recommend any specific strategies to prevent the development of asthma.

Primary prevention of asthma—preventing initial development—is an active area of investigation. Although a number of trials have investigated dietary and environmental manipulations as preventive measures for asthma and allergy, clinical trials have not been uniform in their approaches, making firm conclusions difficult. Also, most of these interventions have been evaluated over a relatively short period of time, thus limiting their weight for any long-term implications.

Evaluations of dust-mite mitigation in homes of children of atopic parents show effectiveness of interventions in decreasing dust-mite levels as well as decreased incidence of wheezing (Custovic et al. 2001; Tsitoura et al. 2002). Prospective assessment of dust-mite reduction and cow's milk avoidance (breastfeeding or hydrolysate) appears to show protective effects at

8-year followup (Arshad et al. 2003), while breastfeeding, dust-mite and pet avoidance, and tobacco smoke avoidance were protective at 7-year followup (Chan-Yeung et al. 2005).

Trials evaluating breastfeeding have generally shown protective benefit (Chandra 1997; Gdalevich et al. 2001; Oddy et al. 1999), although there are conflicting studies (Sears et al. 2003; Wright et al. 2001). Pet exposure as preventive or provocative is controversial (Celedon et al. 2002; Ownby et al. 2002). Although interesting data support the development of tolerance rather than clinical disease after exposure to cat (Platts-Mills et al. 2001), there is also contrary information (Brussee et al. 2005).

Dietary modification or supplementation with antioxidants or omega-3 polyunsaturated fatty acids to reduce the likelihood of asthma and allergic diseases requires further research (Devereux and Seaton 2005). Preliminary studies with probiotics show promise (Kalliomaki et al. 2001; Rautava et al. 2005) but require further study.

Several recent studies have suggested that acetaminophen may contribute to the pathogenesis of asthma and asthma-related symptoms. The effect has been observed in both children and adults in population-based, birth-cohort, and case-control studies. A comprehensive review of this topic has been published (Eneli et al. 2005). However, one potential limitation of many studies on intake of commonly available over-the-counter analgesics, such as acetaminophen, is the potential for confounding by indication (Signorello et al. 2002). In summary, preliminary evidence appears to indicate a possible association between acetaminophen intake and wheeze, but the data are limited and potentially confounded. Although choice of analgesic/antipyretic should always be made carefully, at the current time, it would be premature to recommend avoidance of acetaminophen.

Exposure to daycare in early childhood may be beneficial, while tobacco smoke exposure both in utero and in early childhood is a risk factor for asthma (Becker et al. 2004; Gergen et al. 1998; Gilliland et al. 2001). Larger family size may be preventive, with the incidence of asthma decreasing with an increasing number of siblings (Bodner et al. 1998; Mattes et al. 1999; Rona et al. 1997). The weight of evidence regarding larger family size, daycare exposure with more likelihood of respiratory infection, and country living is in keeping with the hygiene hypothesis of the origin of atopy and asthma. This hypothesis purports that more developed societies are more prone to higher incidence of allergy and asthma because their cleanliness downregulates immune processes for fighting infection in favor of those that cause atopic disease. Rural lifestyle may be protective compared to urban living (Bibi et al. 2002; Kauffmann et al. 2002).

FIGURE 3–17. ASSESSMENT QUESTIONS* FOR ENVIRONMENTAL AND OTHER FACTORS THAT CAN MAKE ASTHMA WORSE

Inhalant Allergens

Does the patient have symptoms year round? (If yes, ask the following questions. If no, see next set of questions.)

- Does the patient keep pets indoors? What type?
- Does the patient have moisture or dampness in any room of his or her home (e.g., basement)? (Suggests house-dust mites, molds.)
- Does the patient have mold visible in any part of his or her home? (Suggests molds.)
- Has the patient seen cockroaches or rodents in his or her home in the past month? (Suggests significant cockroach exposure.)
- Assume exposure to house-dust mites unless patient lives in a semiarid region. However, if a patient living in a semiarid region uses a swamp cooler, exposure to house-dust mites must still be assumed.

Do symptoms get worse at certain times of the year? (If yes, ask when symptoms occur.)

- Early spring? (trees)
- Late spring? (grasses)
- Late summer to autumn? (weeds)
- Summer and fall? (*Alternaria*, *Cladosporium,* mites)
- Cold months in temperate climates? (animal dander)

Tobacco Smoke

- Does the patient smoke?
- Does anyone smoke at home or work?
- Does anyone smoke at the child's daycare?

Indoor/Outdoor Pollutants and Irritants

- Is a wood-burning stove or fireplace used in the patient's home?
- Are there unvented stoves or heaters in the patient's home?
- Does the patient have contact with other smells or fumes from perfumes, cleaning agents, or sprays?
- Have there been recent renovations or painting in the home?

Workplace Exposures

- Does the patient cough or wheeze during the week, but not on weekends when away from work?
- Do the patient's eyes and nasal passages get irritated soon after arriving at work?
- Do coworkers have similar symptoms?
- What substances are used in the patient's worksite? (Assess for sensitizers.)

Rhinitis

- Does the patient have constant or seasonal nasal congestion, runny nose, and/or postnasal drip?

Gastroesophageal Reflux Disease (GERD)

- Does the patient have heartburn?
- Does food sometimes come up into the patient's throat?
- Has the patient had coughing, wheezing, or shortness of breath at night in the past 4 weeks?
- Does the infant vomit, followed by cough, or have wheezy cough at night? Are symptoms worse after feeding?

Sulfite Sensitivity

- Does the patient have wheezing, coughing, or shortness of breath after eating shrimp, dried fruit, or processed potatoes or after drinking beer or wine?

Medication Sensitivities and Contraindications

- What medications does the patient use now (prescription and nonprescription)?
- Does the patient use eyedrops? What type?
- Does the patient use any medications that contain beta-blockers?
- Does the patient ever take aspirin or other nonsteroidal anti-inflammatory drugs?
- Has the patient ever had symptoms of asthma after taking any of these medications?

*These questions are examples and do not represent a standardized assessment or diagnostic instrument. The validity and reliability of these questions have not been assessed.

FIGURE 3–18. COMPARISON OF SKIN TESTS WITH IN VITRO TESTS

Advantages of Skin Tests

- Less expensive than in vitro tests.
- Results are available within 1 hour.
- Equally sensitive as in vitro tests.
- Results are visible to the patient. This may encourage compliance with environmental control measures.

Advantages of RAST and Other In Vitro Tests

- Do not require knowledge of skin testing technique.
- Do not require availability of allergen extracts.
- Can be performed on patients who are taking medications that suppress the immediate skin test (antihistamines, antidepressants).
- No risk of systemic reactions.
- Can be done for patients who have extensive eczema.

FIGURE 3–19. PATIENT INTERVIEW QUESTIONS* FOR ASSESSING THE CLINICAL SIGNIFICANCE OF POSITIVE ALLERGY TESTS

- **Animal dander.** If pets are in the patient's home and the patient is sensitive to dander of that species of animal, the likelihood that animal dander allergy is contributing to asthma symptoms is increased if answers to the following questions are affirmative. However, absence of positive responses does not exclude a contribution of animal dander to the patient's symptoms.
  - — Do nasal, eye, or chest symptoms appear when the patient is in a room where carpets are being or have just been vacuumed?
  - — Do nasal or chest symptoms improve when the patient is away from home for a week or longer?
  - — Do the patient's symptoms become worse during the first 24 hours after returning home?
- **House-dust mites.** Mite allergy is more likely to be a contributing factor to asthma severity if answers to the following questions are affirmative. However, absence of a positive response does not exclude a contribution of mite allergen to the patient's symptoms.
  - — Do nasal, eye, or chest symptoms appear when the patient is in a room where carpets are being or have just been vacuumed?
  - — Does making a bed cause nasal or chest symptoms in the patient?
  - — Does the patient sneeze repeatedly in the morning?
- **Indoor fungi (molds).** Contribution of indoor molds in causing asthma symptoms is suggested by a positive answer to this question:
  - — Do nasal, eye, or chest symptoms appear when the patient is in damp or moldy rooms, such as basements?
- **Outdoor allergens (pollens and outdoor molds).** Contribution of pollens and outdoor molds in causing asthma symptoms is suggested by a positive answer to this question:
  - — Is asthma worse in a specific season or at a time when the patient has hay fever symptoms in spring, summer, fall, or parts of the growing season?
  - — Usually, if pollen or mold spores are causing increased asthma symptoms, the patient will also have symptoms of allergic rhinitis—sneezing, itching nose and eyes, runny and obstructed nose.

*These questions are provided as examples for the clinician. The validity and reliability of these questions have not been assessed.

FIGURE 3–20. SUMMARY OF MEASURES TO CONTROL ENVIRONMENTAL FACTORS THAT CAN MAKE ASTHMA WORSE

Allergens

Reduce or eliminate exposure to the allergen(s) the patient is sensitive to, including:

- **Animal dander:** Remove animal from house or, at a minimum, keep animal out of the patient's bedroom.
- **House-dust mites:**
  - **Recommended:** Encase mattress in an allergen-impermeable cover; encase pillow in an allergen-impermeable cover or wash it weekly; wash sheets and blankets on the patient's bed in hot water weekly (water temperature of >130 °F is necessary for killing mites): cooler water and detergent and bleach will still reduce live mites and allergen level. Prolonged exposure to dry heat or freezing can also kill mites but does not remove allergen.
  - **Desirable:** Reduce indoor humidity to or below 60 percent, ideally 30–50 percent; remove carpets from the bedroom; avoid sleeping or lying on upholstered furniture; remove carpets that are laid on concrete.
- **Cockroaches:** Use poison bait or traps to control insects, but intensive cleaning is necessary to reduce reservoirs. Do not leave food or garbage exposed.
- **Pollens (from trees, grass, or weeds) and outdoor molds:** If possible, adults who have allergies should stay indoors, with windows closed, during periods of peak pollen exposure, which are usually during the midday and afternoon.
- **Indoor mold:** Fix all leaks and eliminate water sources associated with mold growth; clean moldy surfaces. Consider reducing indoor humidity to or below 60 percent, ideally 30–50 percent. Dehumidify basements if possible.
- It is recommended that allergen immunotherapy be considered for patients who have asthma if evidence is clear of a relationship between symptoms and exposure to an allergen to which the patient is sensitive.

Tobacco Smoke

Advise patients and others in the home who smoke to stop smoking or to smoke outside the home. Discuss ways to reduce exposure to other sources of tobacco smoke, such as from daycare providers and the workplace.

Indoor/Outdoor Pollutants and Irritants

Discuss ways to reduce exposures to the following:

- Wood-burning stoves or fireplaces
- Unvented gas stoves or heaters
- Other irritants (e.g., perfumes, cleaning agents, sprays)
- Volatile organic compounds (VOCs) such as new carpeting, particle board, painting

FIGURE 3–21. EVALUATION AND MANAGEMENT OF WORK-AGGRAVATED ASTHMA AND OCCUPATIONAL ASTHMA

Evaluation

Potential for workplace-related symptoms:

- Recognized sensitizers (e.g., isocyanates, plant or animal products).
- Irritants* or physical stimuli (e.g., cold/heat, dust, humidity).
- Coworkers may have similar symptoms.

Patterns of symptoms (in relation to work exposures):

- Improvement occurs during vacations or days off (may take a week or more).
- Symptoms may be immediate (<1 hour), delayed (most commonly, 2–8 hours after exposure), or nocturnal.
- Initial symptoms may occur after high-level exposure (e.g., spill).

Documentation of work-relatedness of airflow limitation:

- Serial charting for 2–3 weeks (2 weeks at work and up to 1 week off work, as needed to identify or exclude work-related changes in PEF):
  - Record when symptoms and exposures occur.
  - Record when a bronchodilator is used.
  - Measure and record peak flow (or FEV_1) every 2 hours while awake.
- Immunologic tests.
- Referral for further confirmatory evaluation (e.g., bronchial challenges).

Management

Work-aggravated asthma:

- Work with onsite health care providers or managers/supervisors.
- Discuss avoidance, ventilation, respiratory protection, tobacco smoke-free environment.

Occupationally induced asthma:

- Recommend complete cessation of exposure to initiating agent.

*Material Safety Data Sheets may be helpful for identifying respiratory irritants, but many sensitizers are not listed.

Key: FEV_1, forced expiratory volume in 1 second; PEF, peak expiratory flow

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