

Section F



SPECIAL CONSIDERATIONS

- * Primary immunodeficiency diseases
- * Allergic disease in the elderly
- * Allergic diseases in pregnancy
- * Allergic diseases and sports
- * Allergic diseases in adolescents
- * Adherence to the management plan
- * Allergic diseases and quality of life
- * Allergic diseases in animals

1

PRIMARY IMMUNODEFICIENCY DISEASES

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Primary immune deficiencies (PID) are a group of inherited disorders of the immune system that increase the susceptibility of the individual to severe and often difficult to treat infections, auto-immunity and in some patients malignancy. Over 200 genetic abnormalities that lead to a variety of PID have been identified. Approximately 250,000 people in the United States are diagnosed with PID, but according to estimates of the National Institutes of Health over 250,000 people are under diagnosed. In order to estimate the prevalence of PID in Europe as well as to establish and evaluate harmonized guidelines for the diagnosis and treatment of PID, the European Society for Immunodeficiencies (ESID) has developed an internet-based database for clinical and research data on patients with PID (Table 1).

About 55% of the PID are humoral or B-cell abnormalities, 25% are T-cell or combined T and B-cell immune deficiencies, 25% are phagocytic disorders, 25% are immune dysregulation syndromes, and <10% are complement deficiencies (Figure 1).

The most severe type of PID is lack of immune system at birth,

KEY MESSAGES

- The estimated prevalence of primary immune deficiency is underestimated
- Newborn screening for severe combined immunodeficiency (an immune deficiency that is uniformly fatal if not diagnosed and treated) has led to early diagnosis and treatment of these infants
- Hematopoietic stem cell transplantation has been a major advance in the cure for many primary immune deficiency disorders
- Immunoglobulin replacement therapy has led to improved outcomes in patients with antibody deficiency disorders
- More research is needed to reduce and identify comorbid conditions in patients with primary immune deficiency to improve outcomes and life expectancy

e.g. absent T and B-cells (Severe combined immunodeficiency or SCID). SCID infants often die in the first year of life. Intervention with a bone marrow hematopoietic stem cell transplant is curative. Recent data shows that the prognosis of these infants is better if the diagnosis is made before 3 months of age for stem cell transplantation. Towards this goal in the United States newborn screening using quantification of T-cell receptor excision circles (TRECs) has been initiated in 15 states. This initiative has resulted in the early diagnosis and treatment of SCID infants, and has changed the incidence from 1:100,000 from older

epidemiologic studies to a more recent estimate of <1:50,000 live births. Another approach to the treatment of SCID patients has been gene therapy.

27% of PID are diagnosed before age 6, but 51% are diagnosed after age 30. This latter group is mainly patients with B-cell immune deficiency, the most common of which is the Common Variable Immunodeficiency (CVID). The delay in diagnosis of these adult patients is 9-12 years and contributes to chronic lung disease and other comorbid conditions (Figure 2). Likewise, it is important to identify CVID patients early in order to start them on replacement im-

TABLE 1

| Primary immunodeficiency prevalence based on reported cases in the European Society for Immunodeficiencies (ESID) database* | | | |
|---|-------------------------------|-----------------------------------|---|
| Country | Alive PID patients documented | Population (millions inhabitants) | Documented PID patients per 100 000 inhabitants |
| France | 2399 | 64 • 47 | 3 • 72 |
| Ireland | 76 | 4 • 24 | 1 • 79 |
| Turkey | 1083 | 70 • 59 | 1 • 53 |
| United Kingdom | 878 | 60 • 59 | 1 • 45 |
| Estonia | 15 | 1 • 34 | 1 • 12 |
| Italy | 655 | 59 • 13 | 1 • 11 |
| Belgium | 98 | 10 • 53 | 0 • 93 |
| Poland | 352 | 38 • 12 | 0 • 92 |
| Czech Republic | 88 | 10 • 31 | 0 • 85 |
| Greece | 89 | 11 • 17 | 0 • 8 |
| Germany | 552 | 82 • 24 | 0 • 67 |
| Serbia | 47 | 7 • 27 | 0 • 65 |
| Switzerland | 38 | 7 • 59 | 0 • 5 |
| Slovakia | 22 | 5 • 43 | 0 • 41 |
| Sweden | 32 | 9 • 18 | 0 • 35 |
| Slovenia | 6 | 2 • 02 | 0 • 3 |
| Portugal | 27 | 10 • 95 | 0 • 25 |

Total populations source: Wikipedia.

* Only countries with a prevalence >0.2 are displayed. Reproduced from Gathmann B, Grimbacher B, Beauté J, et al; The European internet-based patient and research database for primary immunodeficiencies results 2006-2008. Clin Exp Immunol. 2009;157(suppl 1):3-11 with permission from John Willey and Sons, Inc.

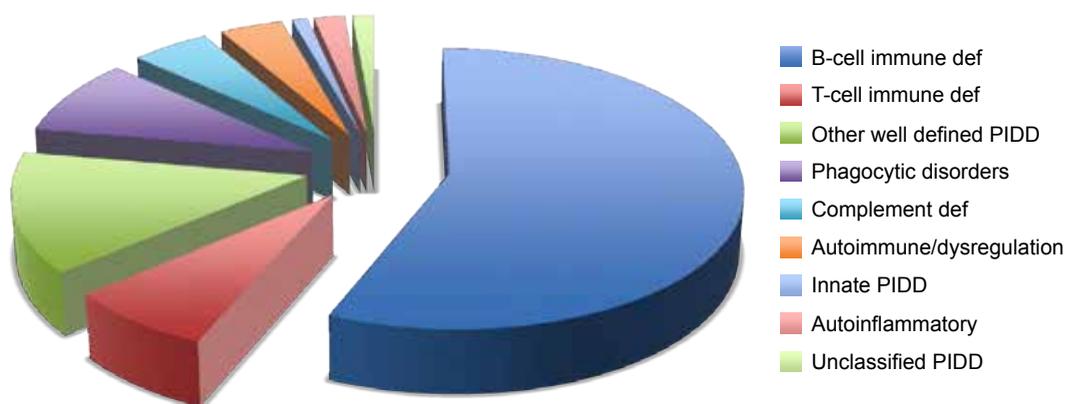


Figure 1 Distribution of Primary Immune Deficiency Diseases in the ESID registry database. (Reproduced from Gathmann B, Grimbacher B, Beauté J, et al; The European internet-based patient and research database for primary immunodeficiencies results 2006-2008. Clin Exp Immunol. 2009;157(suppl 1):3-11 with permission from John Willey and Sons, Inc. Updated 2013 - 119 centers and 18,720 total patients. <http://esid.org/Working-Parties/Registry/ESID-Database-Statistics> accessed Jan 19, 2014.)

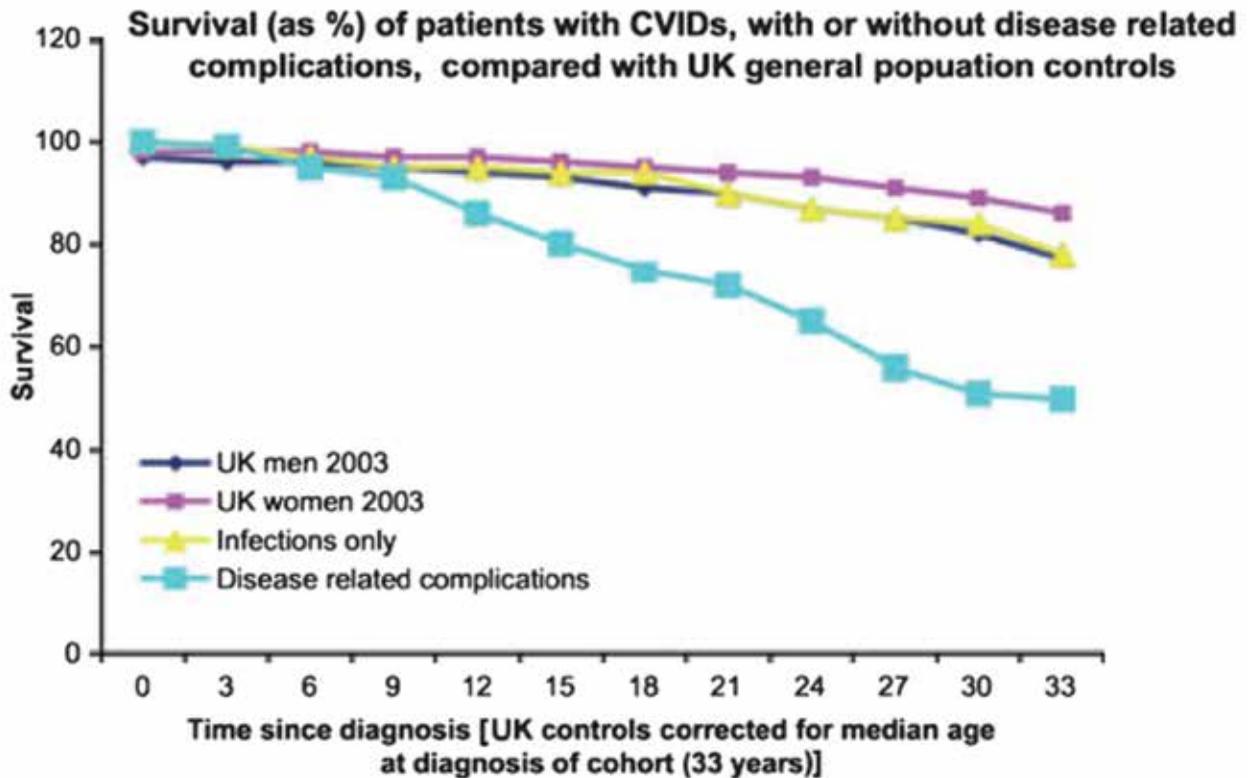


Figure 2 Survival of patients with CVIDs, by years since diagnosis and by clinical phenotype. Yellow line represents those patients without complications; Turquoise line represents those patients with at least one disease related complication. Kaplan-Meier plot of survival. (Republished with permission of *Blood*, from *Common variable immunodeficiency disorders: division into distinct clinical phenotypes*, Chapel H, Lucas M, Lee M, et al, 112,2,2008; permission conveyed through Copyright Clearance Center, Inc.)

munoglobulin (Ig) therapy. Dosage requirements for optimal management of CVID patients have been recently discussed in several publications. The consensus by clinical immunologist is that the optimal dose of Ig therapy is the dose, which minimizes infection and improves patient outcome. Two routes for replacement Ig therapy are recommended either intravenous or subcutaneous. The latter has been utilized in Europe for several decades with advantages over the IV route of less systemic side effects, improved steady state serum IgG levels, home-based self-administration and better quality of life.

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2

ALLERGIC DISEASE IN THE ELDERLY

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EPIDEMIOLOGY

The prevalence of allergic respiratory disease (allergic rhinitis and asthma) in the elderly is difficult to estimate due to differences in cut-off ages (≥ 55 , ≥ 65 , ≥ 75 e.g.). Nonetheless, in vitro assays for specific IgE in adults age ≥ 55 years in the U.S. showed that $\sim 65\%$ were sensitized to at least one allergen. However, a Swiss study found that only 26% of men and 18% of woman aged >60 years were sensitized. Skin prick testing of elderly Koreans found a similar lower rate of allergic sensitization (17-18%). Chronic rhinitis was also fairly common in the elderly Korean population (25%), but allergic sensitization did not show a significant association. The Swiss study found the prevalence of self-reported allergic rhinitis to be 13% for men and 15% for women ages >60 years. The lifetime prevalence of allergic rhinitis in adults (18-79) in Germany was similarly estimated to be 15%.

Of more concern is asthma in the elderly, which is difficult to estimate, because of confusion with COPD, the overlap of asthma with COPD, and confounding conditions like congestive heart failure. Reported incidence of newly diag-

nosed asthma in a U.S. population was 103/100,000 at age 65-74 years, 81/100,000 ages 75-84 years, and 58/100,000 age >85 years. Allergic sensitization does not appear to be a major factor in the development of asthma in the elderly.

The prevalence of asthma in the elderly is variable in different populations (Table 1), but appears to be rising over the past decade. Only 2% of Chinese citizens ages >50 self-reported having asthma. However, physician diagnosed asthma was higher in Hong Kong Chinese aged ≥ 70 years (4-5%). Doctor diagnosed asthma in Swiss citizens aged >60 years was 6.6% in men and 7.6% in women. Current asthma in U.S. citizens ≥ 65 years were similar at 6.3% (Table 1). Asthma death rate increases with age (Figure 1).

KEY MESSAGES

- Asthma and allergic rhinitis are not uncommon in the elderly.
- Asthma in the elderly is heterogeneous in origin and often associated with loss of lung function
- Co-morbid conditions can affect treatment. Smoking adversely affects outcomes
- Additional research into pathophysiology and phenotypes is needed to improve treatment approaches

PROGNOSIS

Some 8-15% of older adults in the U.S. are annually admitted to the hospital. Often elderly adults lack a perception of dyspnea and hospitalized patients used peak-flow meters less often than younger patients and had less self-management knowledge. Women 50-60 years old being non-white and less educated appear to be at risk for hospitalization. Fortunately, when controlled for age, asthma is not associated with all-cause mortality. However, patients with asthma associated with COPD have worsened survival.

FUTURE RESEARCH

Asthma in the elderly presents diagnostic challenges defining the pathophysiologic mechanism, and further characterization of phenotype can lead to better treatments.

TABLE 1

| Reported Prevalence of Asthma in Older Populations | | |
|--|--------------------------------|-------------|
| Prevalence | Population | Age (years) |
| 2% | Chinese, self-reported | >50 |
| 3.9% | Chinese, symptoms | >50 |
| 4-5% | Hong Kong, physician-diagnosed | ≥70 |
| 6.6% males 7.6% females | Swiss, physician-diagnosed | >60 |
| 6.3% | U.S., NHANES study | ≥65 |

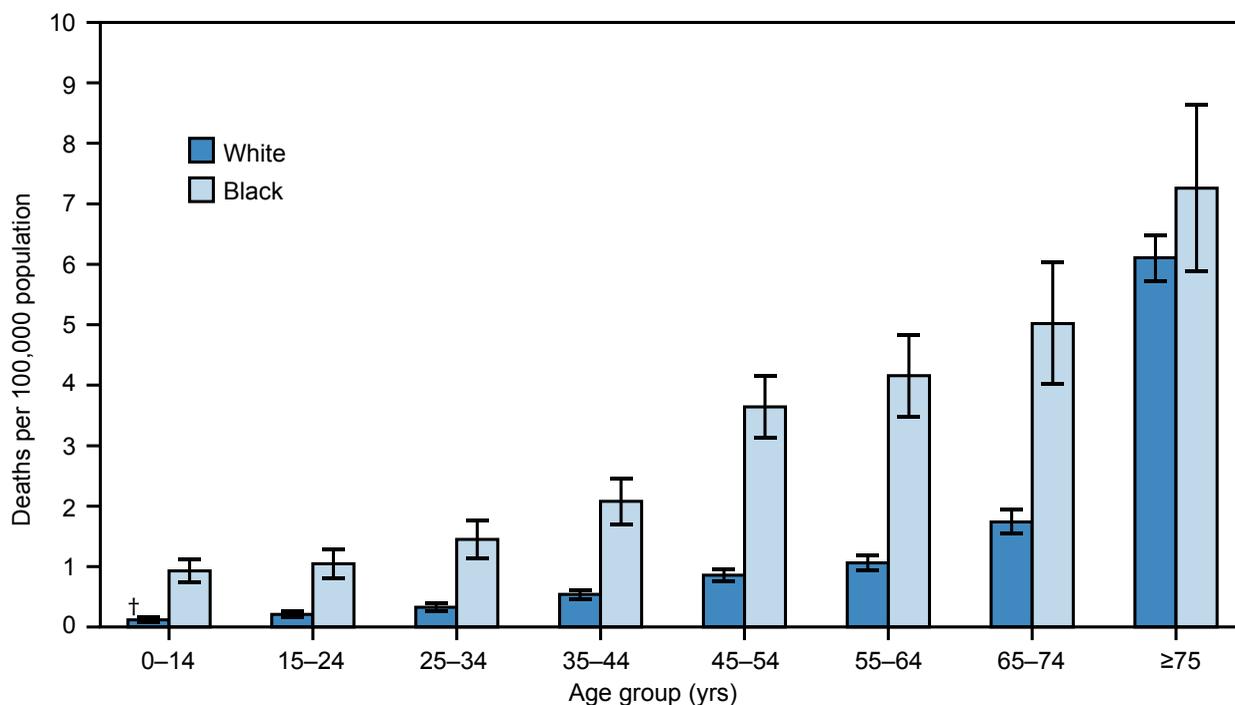


Figure 1 Asthma Death Rates by Race and Age, United States 2007-2009. (From Centers for Disease Control and Prevention, *Morbidity and Mortality Weekly Report*, 2012;61:315.)

Smoking avoidance and cessation can clearly reduce the burden of asthma in the elderly.

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3

ALLERGIC DISEASES IN PREGNANCY

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ASTHMA

A meta-analysis, derived from a substantial body of literature spanning several decades and including very large numbers of pregnant women, (over 1,000,000 for low birth weight and over 250,000 for preterm labor), indicates that pregnant women with asthma are at a significantly increased risk of a range of adverse maternal and fetal outcomes (Table 1). Suboptimal control of asthma or more severe asthma during pregnancy is associated with increased maternal or fetal risk.

Once the diagnosis of asthma is confirmed a decision regarding the need for controller medication versus rescue medication

KEY MESSAGES

- Pregnant asthmatics have a higher risk of adverse perinatal outcomes
- Unlike rhinitis of pregnancy, which presents with predominant nasal congestion symptoms, patients with allergic rhinitis often report prominent sneezing, nasal pruritus, and watery rhinorrhea, and some have concomitant ocular itching and irritation
- Treatment for urticaria during pregnancy may be necessary, if it is affecting quality of life
- Atopic dermatitis is the most common skin disorder observed during pregnancy
- Anaphylaxis is a rare event during pregnancy, but may be associated with severe maternal and neonatal complications

can be made (Table 2). Inhaled corticosteroids are the mainstay of controller therapy during pregnancy, but addition of long-acting beta agonists is appropriate, if required to achieve control. Adherence to therapy can change during pregnancy with a corresponding change in asthma control. Most commonly observed is decreased adherence as a result of a mother's concerns about the safety of medications for the fetus.

ALLERGIC RHINITIS

Allergic rhinitis (AR) is usually pre-existing, although it may develop or be recognized for the first time during pregnancy. Patients with AR

often report prominent sneezing, nasal pruritus, and watery rhinorrhea, and some have concomitant ocular itching and irritation. Common triggers include dust mites, animal danders, molds, and pollens. The mainstays of therapy are avoidance of triggers, oral antihistamines and intranasal glucocorticoids. No important differences in efficacy or safety appear to exist between the various intranasal glucocorticoid preparations. Pregnant women who require antihistamines for AR should generally be treated with a second generation agent such as loratadine (10 mg once daily) or cetirizine (10 mg daily), since these drugs have reassur-

TABLE 1

Adverse fetal outcomes reported to be increased in infants of asthmatic women

| |
|---------------------------|
| Low birth weight |
| Preterm birth |
| Small for gestational age |
| Congenital anomalies |
| Stillbirth |
| Low APGAR scores at birth |

TABLE 2

Safety of commonly used medications for the treatment of asthma during pregnancy

| Drug | FDA | Perinatal Outcome |
|--|---|---|
| Inhaled Bronchodilators | | |
| Short-acting Bronchodilators | Albuterol(C) | Reassuring human data; some associations with specific malformations but may be chance or confounded by severity |
| Long-acting bronchodilators | Formoterol(C) Salmeterol(C) | Small amount of human data has been reassuring |
| Theophylline | | |
| No increase in congenital malformations; toxicity may be an issue | | |
| Systemic Corticosteroids | | |
| Associated with oral clefts, low birth weight, preterm birth, preeclampsia and intrauterine growth retardation. Some of these effects may be confounded by severity. | | |
| Inhaled Corticosteroids | | |
| | Budesonide -B Beclomethasone-C Fluticasone_C Mometasone -C Triamcinolone -C | Substantial reassuring data. Risk of increased malformations with high dose, but may be confounded by severity. Most data for budesonide. |
| Leukotriene Receptor Antagonist | | |
| | Montelukast -B Zafirlukast -B | Moderate amount of reassuring data |
| 5-LO Inhibitor | | |
| | Zileuton -C | Animal studies not reassuring; no human data |
| Anti-IgE | | |
| | Xolair-B | Increased risk of low birth weight and preterm birth, but may be confounded by severity |

Adapted from Schatz M, Zeiger RS, Falkoff R, Chambers C, Macy E, Mellon MH. Asthma and allergic diseases during pregnancy. In: Middleton's Allergy: Principles and Practice, 8th ed, Adkinson, NF, Bochner BS, Burks AW et al (Eds), Mosby, St. Louis, MO 2014, pp. 951-69

ing animal and human data, are less sedating, and have fewer anticholinergic side effects compared with first generation (Table 3).

ATOPIC DERMATITIS

Atopic dermatitis (AD), or eczema is one of the most frequently observed skin diseases in pregnant patients. Most pregnant patients with AD present with lesions on the flexural aspects of the extremities, although truncal involvement is not uncommon. AD can change in severity during pregnancy, but has not been associated with an increased risk of perinatal complications such as congenital malformations. Similar to treatment of AR, the treatment for AD relies on avoidance of triggers and the judicious use of medications such as antihistamines for pruritus and topical corticosteroids (Table 4).

URTICARIA/ANGIOEDEMA

While there is no specific pregnancy-related urticaria, idiopathic urticaria may occur during pregnancy as well as urticaria due to any of the causes known to affect non-pregnant women. There have been no associations between presence of urticaria and adverse fetal outcomes. As in non-pregnant patients with urticaria, the treatment of choice is oral antihistamines, especially loratadine or cetirizine as noted above. Although not studied specifically in pregnancy for this purpose, leukotriene receptor antagonists such as montelukast (FDA Category B) may also be considered for recalcitrant urticaria, and may be continued, if started prior to pregnancy.

ANAPHYLAXIS

Anaphylaxis during pregnancy is

considered a rare condition with an estimated prevalence of 2.7 cases/100,000 deliveries. Antibiotics are the most common trigger. If maternal oxygenation is compromised there may be associated fetal hypoxemia. Epinephrine remains the treatment of choice in pregnant patients. Anaphylactoid Syndrome of Pregnancy (ASP) is a rare complication of delivery in mother and/or infant during the process of birth. The maternal mortality rate worldwide for this complication is between 10 and 16%, while the fetal mortality rate is upwards of 30%. While the majority of infants will survive, the majority will also incur some form of neurologic defect. The pathophysiology is thought to be related to amniotic fluid or fetal cells entering maternal circulation. Mast cell degranulation appears to be a

TABLE 3

Safety of commonly used medications for the treatment of rhinitis during pregnancy

| Drug Class | Drug/FDA Class | Adverse perinatal Outcome |
|---------------------------------|------------------------|---|
| Oral Antihistamines | Azelastine -C | No human data, animal studies show increase in teratogenicity, skeletal abnormalities and fetal death in high doses |
| | Cetirizine -B | No increase in congenital malformation |
| | Chlorpheniramine | No increase in congenital malformation |
| | Dexchlorpheniramine -B | No increase in congenital malformation |
| | Fexofenadine -C | This active metabolite of terfenadine has been associated with dose related weight gain animal studies. |
| | Diphenhydramine | No increase in congenital malformation ;withdrawal syndrome a risk |
| | Hydroxyzine | No increase in congenital malformations; withdrawal syndrome a risk |
| Decongestants | Loratadine -B | No increase in congenital malformations, low birth weight, or small for gestational age |
| | Oxymetazoline | No increase in congenital malformations; possible utero-placental insufficiency with higher doses |
| | Phenylephrine | Associated with club foot, eye/ear malformations |
| | Phenylpropanolamine | Increase in total and specific congenital malformations in one study, association with gastroschisis and VSD in case-control studies |
| Intranasal Antihistamines | Pseudoephedrine | Association with gastroschisis, hemifacial microsmia and small intestinal atresia in some case-control studies |
| | Azelastine | No controlled studies; |
| Intranasal Corticosteroids | Olapatadine | No controlled data; animal studies reassuring |
| | Budesonide -B | Substantial reassuring data for inhaled corticosteroids. Risk of increased malformations with high dose, but may be confounded by severity. Most data for budesonide. |
| | Fluticasone -C | |
| Triamcinolone-C Mometasone-C | | |

Adapted from Schatz M, Zeiger RS, Falkoff R, Chambers C, Macy E, Mellon MH. Asthma and allergic diseases during pregnancy. In: Middleton’s Allergy: Principles and Practice, 8th. Adkinson, NF, Yunginger, JW, Busse, WW et al (Eds), Mosby, St. Louis, MO (in press)

TABLE 4

Treatment options for atopic dermatitis in pregnancy

| | |
|---------------------------|---|
| Safe | Emollients, mild to moderate strength topical corticosteroids, oral antihistamines, ultraviolet B light |
| Relatively safe (caution) | Oral corticosteroids, cyclosporine, azathioprine, topical calcineurin inhibitors |
| Avoid | Methotrexate, mycophenolate mofetil, psoralens plus ultraviolet A light (PUVA) |

prominent part of this syndrome. Symptoms typically include vascular collapse and disseminated intravascular coagulation. Treatment relies on controlling hemorrhage as well as vascular instability.

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4

ALLERGIC DISEASES AND SPORTS

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Physical exercise, although recommended for the general population and for allergic subjects, may represent a trigger of bronchial obstruction (in subjects with or without co-existing clinical asthma), rhino-conjunctivitis symptoms, skin manifestations and even severe anaphylaxis. Atopy has been shown to represent a risk factor for these conditions in both competitive and non-competitive exercisers.

EXERCISE-INDUCED BRONCHOCONSTRICTION

Exercise-Induced Bronchoconstriction (EIB) represents a sign of poor asthma control. However, EIB may also occur in subjects with no evidence of clinical asthma, particularly in children, athletes, patients with atopy or rhinitis and following respiratory infections. The type, duration and intensity of physical exercise and environmental conditions are critical factors for the occurrence of EIB.

EIB recognizes a peculiar patho-physiological pathway. The hyperventilation, particularly of cold and dry air, causes water loss and increased osmolarity of the airways which results in epithelial damage and release of several inflammatory agents. Additional mechanisms have been suggested.

KEY MESSAGES

- Physical activity is highly recommended to maintain health status and prevent chronic inflammatory conditions, including allergic diseases
- Exercise, however, may trigger bronchial, nasal, ocular, skin and even systemic symptoms, particularly in subjects with allergic diseases
- Accordingly, allergic diagnosis should be part of the routine medical examination in both competitive and non-competitive exercisers
- Early diagnosis of exercise-related symptoms and their adequate management may allow allergic subjects not only to practice sports safely, even at competitive level, but also to make physical exercise as a pillar of their therapeutic strategy
- Diagnosis and treatment of allergic diseases in elite athletes require special considerations in order to ensure the best performances, while respecting current anti-doping regulations

Self-reported symptoms after exercise are not sufficient for a diagnosis of EIB, which has to be documented through pulmonary function tests before and after a standardized bronchial provocation. Exercise challenge or its surrogate indirect tests (Eucapnic Voluntary Hyperpnea and Hypertonic Saline or Mannitol) are recommended. Direct bronchial provocation with histamine or methacholine is less accurate to document EIB, particularly in subjects without underlying asthma.

EIB is usually efficiently reversed by beta-2 adrenergic agent inhala-

tion. The best preventive strategy for EIB in asthmatics is represented by achieving complete asthma control, according to GINA guidelines. Prevention of EIB in subjects without clinical asthma includes both pharmacologic and non-pharmacologic measures.

RHINITIS AND CONJUNCTIVITIS

Allergic rhino-conjunctivitis is a very frequent condition in exercisers. The type of sport influences mechanisms and symptoms (swimmer, winter, runner, boxer nose). Exposure to specific sensitizing allergens



Allergic rhinitis in 16/40 (40.0%)
 NARES in 2/40 (5.0%)
 Infective rhinitis 2/40 (5.0%)

“Swimmer’s nose” in 20/40 (50.0%)

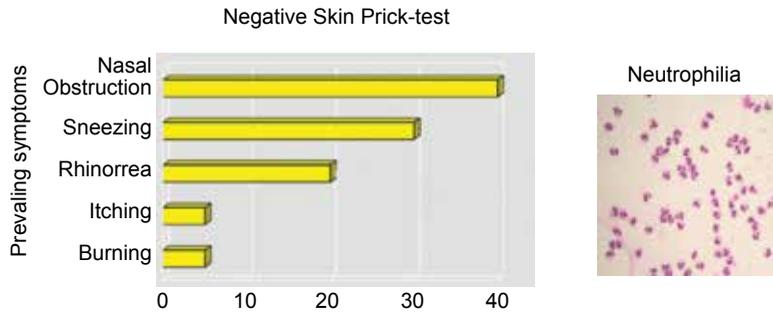


Figure 1 The swimmer nose: incidence, symptoms and inflammatory phenotype.

during in-door or out-door exercising may trigger or exacerbate nasal and ocular symptoms and affect performance. Rhinitis and conjunctivitis may also occur in non-allergic subjects: non-allergic rhinitis with neutrophilia has been reported in swimmers (Figure 1), possibly in relation to chlorine exposure, while cold air exposure may cause vasomotor rhinitis in winter athletes. Diagnosis and treatment do not differ from those recommended by ARIA guidelines in the general population. Particular attention should be placed on the potential negative effects on vigilance and reaction times of anti-histamines, particularly of those of the first-generation.

ALLERGIC SKIN DISEASES

Urticaria and angioedema may occur not only in relation to physical activity, but also to other factors connected to the specific sport practiced (pressure by sport instruments; exposure to water, cold, sun, etc.). Sports instruments and vests (often made by rubber) may cause allergic contact dermatitis and eczema in exposed sensitized individuals.

EXERCISE-INDUCED ANAPHYLAXIS

Exercise-Induced anaphylaxis (EIA) is a rare, but unpredictable and severe, syndrome in which anaphylaxis occurs in conjunction with exercise. EIA is often associated with food allergy and may only occur as a combination of exercise and ingestion of the sensitizing food (FDEIA). Therefore, an accurate diagnosis of food allergy (including molecular diagnostics) has to be made in subjects with EIA, and the sensitizing food should be eliminated from the diet (possibly also avoiding any food ingestion in the three hours before exercising).

ALLERGIC DISEASES IN ELITE ATHLETES

Several studies indicate that sensitization and allergic diseases occur in elite athletes with a higher prevalence than in the general population (Figure 2). Suggested mechanism is the combined effect of a strenuous, chronic training and environmental exposure (allergens, pollutants, cold air, etc.) on both the immune system (with

a switch to a Th2 cytokine profile, this also explaining the higher incidence of infections, particularly of the upper respiratory tract) and target organs. Diagnosis and treatment of allergic diseases in elite athletes require special considerations in order to ensure the best performances, while respecting current anti-doping regulations (Table 1).

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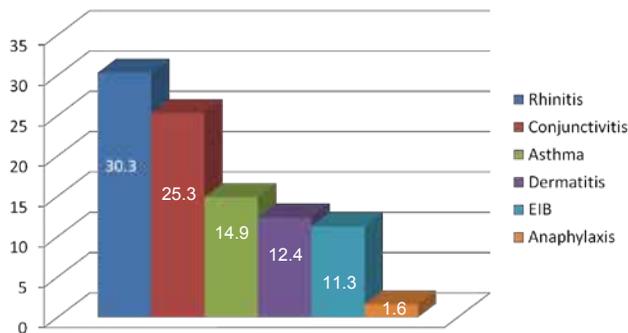
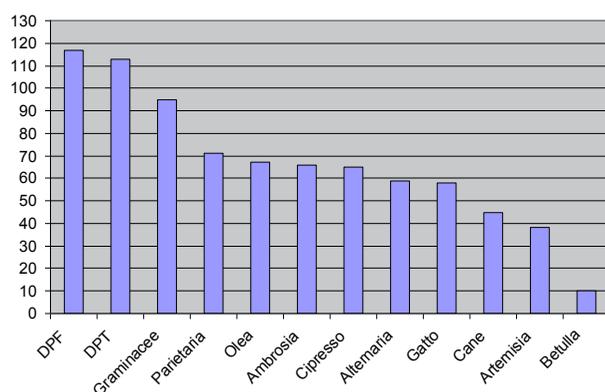
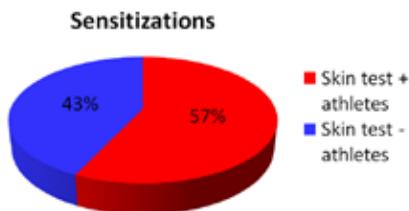


Figure 2 Prevalence of sensitization and allergic diseases in 378 Italian Olympic athletes (Bonini M. et al, 2014 submitted).

SECTION F - Special considerations

TABLE 1

| WADA rules for anti-allergic drugs | | |
|------------------------------------|--|---|
| Treatment | WADA Rules | Notes |
| Antihistamines | Permitted | Second generation molecules should be preferred to avoid side effects |
| Leukotriene modifiers | Permitted | |
| Inhaled steroids | Permitted | |
| Immunotherapy | Permitted | SCIT should not be performed before of after physical exercise |
| β2 agonists | Inhaled <i>Salbutamol</i> (max 1600 mcg/24h) | The presence in urine of salbutamol > 1000 ng/mL or formoterol > 40 ng/mL is presumed not be an intended therapeutic use of the substance and will be considered as an Adverse Analytical Finding |
| | <i>Formoterol</i> (max 54 mcg/24H) and <i>Salmeterol</i> | |
| | All others prohibited in and out competition | |
| Systemic steroids | Prohibited in competition | |
| Ephedrine, methylephedrine | Prohibited in competition | A concentration in urine greater than 10 µg/mL represent an Adverse Analytical Finding |

5

ALLERGIC DISEASES IN ADOLESCENTS

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IMPACT OF ALLERGY IN ADOLESCENCE

Many adolescents are affected by allergies. More than a third have symptoms of rhinoconjunctivitis, about 1 in 7 have asthma and around 1 in 50 have food allergy. This group experiences more morbidity and mortality than would be expected, they are overrepresented in fatal series of food allergy and asthma death registry data. Therefore adolescents deserve special attention in any allergy clinic.

ADOLESCENTS AS PATIENTS

Adolescence is a challenging time for any individual, even if they do not have a chronic medical condition. While coping with the



KEY MESSAGES

- Many adolescents are affected by allergic diseases, and allergies have a major impact on their daily life
- The developmental milestones of adolescence can be challenging for patients, their parents and their clinicians
- Adolescent patients need to be approached in a way that promotes their development as active patients, who are empowered to take ownership of their allergies

physical changes associated with puberty, they have to start taking responsibility for themselves and others, gain independence, develop relationships outside their immediate families and renegotiate the rules at home (Figure 1).

All this may perhaps explain why adolescents are often poorly engaged with their healthcare provider. For example, despite follow up in an allergy clinic, adolescent patients often fail to avoid their triggering food allergens and carry their adrenaline autoinjector. There are similar issues with asthma. Looking at an allergy clinic from the adolescents' perspective, they may see consultations as being dominated by their parents, perhaps do not feel that clinic is relevant for them and may have issues around their confidentiality.

HOW CAN WE IMPROVE THE MANAGEMENT OF ADOLESCENT PATIENTS?

During adolescence, children must develop into independent adults with responsibilities for maintaining health status moving from parents to patient. Parents find this challenging, and adolescent may have limited opportunities to take on responsibility for their health. The management of adolescent patients, therefore needs to promote this transition.

There are a number of generic approaches that may help to engage adolescent patients:

- Ensure that adolescent patients are active participants in clinic using appropriate language, being empathic, respectful, and non-judgmental.
- Taking a patient rather than a

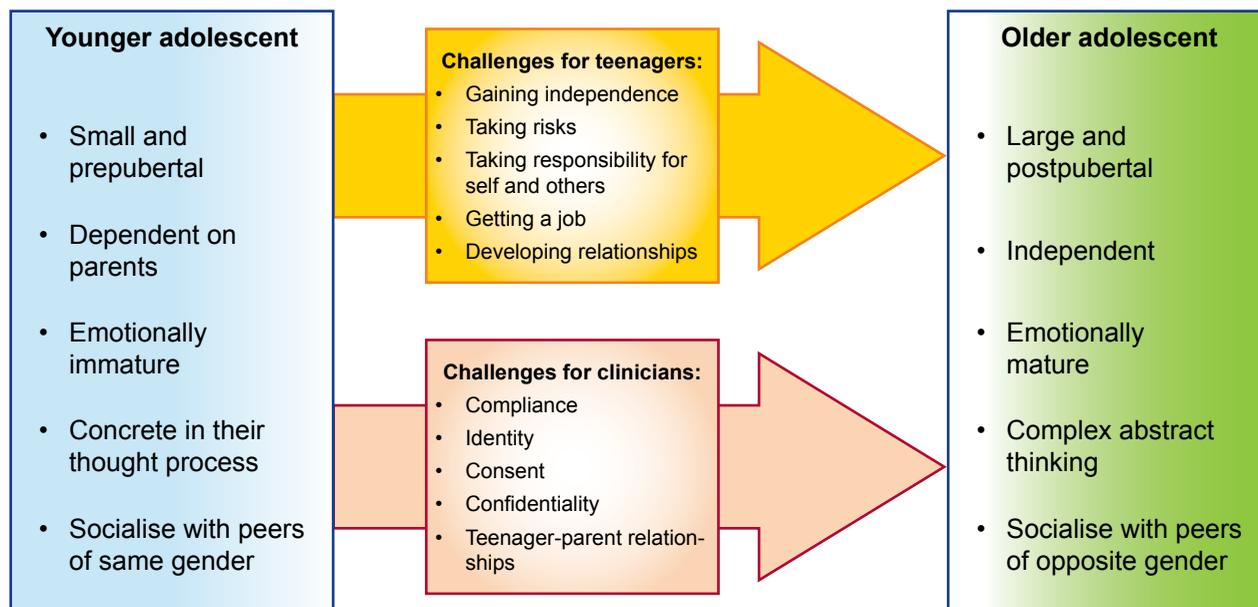


Figure 1 Adolescent development: challenges for patients and clinicians.

diseased centred approach may help adolescents realise the value of a clinic appointment.

- Slowly transition from parents. Seeing adolescent patients on their own for the initial part of the consultation may help to empower them to take ownership of their allergies.

For individual allergic diseases there are additional specific approaches that may be helpful. For asthma, for example, the focus should be on what activities asthma stops them doing and dealing with these by prescribing therapies that fit into their daily schedule. For food allergy, for example, education around the recognition and management of allergic re-

actions should be directed at the adolescent patient using scenario based role playing and adrenaline autoinjector simulators.

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6

ADHERENCE TO THE
MANAGEMENT PLAN*Andrew Nickels**James T. Li**Mayo Clinic
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The global burden of non-adherence in allergic diseases is substantial. Developing an optimal management plan in allergic diseases depends equally on appropriate medication recommendations as well as the patient's ability and desire to adhere to the proposed treatment. Adherence is the extent to which a patient's behavior resembles the "agreed upon" management plan as outlined by their healthcare provider. The qualification of 'agreed upon' emphasizes the importance of shared decision making between patient and their providers. Adherence contrasts the term compliance, which conceptualizes the patient's role as limited to following recommendations, without explicit consideration of patient's preferences and goals. In allergic disease, adherence issues have been most fully explored in asthma care, primarily due to the increased availability of traceable outcome measures, such as exacerbation rates, systemic corticosteroids use, emergency department visits, and hospitalizations.

Patient's adherence to the "agreed upon" management plan can be difficult to assess and sometimes not evident until poor outcomes

KEY MESSAGES

- Adherence is the extent to which a patient's behavior reflects the "agreed upon" the management plan as outlined by their healthcare provider
- Barriers to adherence are numerous and include disease and patient specific concerns, as well as, provider practice pattern, health system constraints, and the larger societal context
- Strategies to improve adherence include written action plans, simplification of treatment regimens, and novel technologies such as social media or text messaging (SMS)
- Shared decision making between patients and provider is crucial in constructing an effective treatment plan and improving adherence

are suffered. Barriers to adherence are numerous and include chronicity of disease, increasingly complex medication regimens, high medication cost, and lack of perceived treatment benefit (Figure 1). Assessing the level of adherence is crucial and can be accomplished by direct patient interviewing, pharmacy fill rate, medication monitoring methods (pill counting, inhaler dose counters, etc) or through biochemical assays. Exhaled nitric oxide is emerging as a potentially powerful bioassay for measuring inhaled corticosteroid adherence in patients with asthma.

Improve adherence is critically

important in the management of allergic diseases. Written Action Plans (WAPs) may be a useful tool for the practicing allergist to enhance patient understanding of the management plan (Figure 2). In the acute care setting, WAP have been shown to significantly increase patient adherence to inhaled corticosteroids, improve asthma control, and medical follow up. WAPs are available for a number of allergic diseases including anaphylaxis and allergic rhinitis. Simplifying the management plan can also improve patient adherence (Figure 3).

The widespread availability and acceptability of technologic inter-

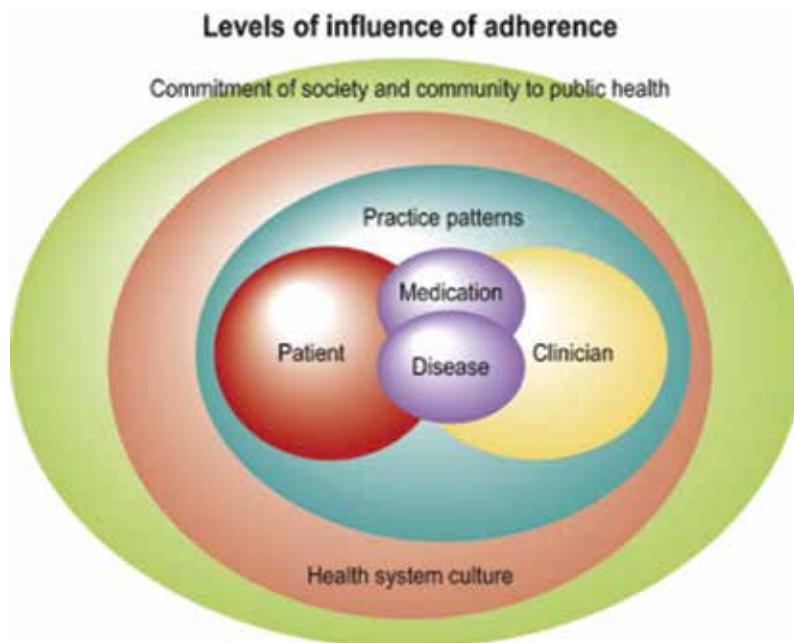


Figure 1 Barriers to adherence are numerous and are influenced by a multitude of levels. Societal concerns and the health system culture set the stage for the patient-provider interaction. On an individual level, a clinician's practice pattern and the patient's individual preferences and goals affect the milieu in which the treatment plan is made. The particulars of the disease and the available medications make up the specific variable of this complex equation. (Reproduced from Middleton's Allergy: Principles and Practice, 8ed, Apter A, Bender B, Rand C, Ed. Adkinson et al, Adherence, 1473, copyright 2013 with permission from Elsevier.)



Figure 3 This patient found herself overwhelmed by a complex treatment plan for her allergic diseases. Simplification of treatment regimens, as well as, understanding patient's treatment preferences and goals lead to improved adherence.

ventions, such as text messaging or social media, may be useful tool in improving adherence rates and evidence on this topic is emerging.

Of all the potential interventions aimed at improving patient adherence, striving to strengthen the provider-patient relationship and focusing on management plans that takes the patient's preference into account may lead to optimal treatment outcomes in allergic diseases.

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Asthma Action Plan

DATE: ____ / ____ / ____ PATIENT NAME _____
 WEIGHT: _____ EMERGENCY CONTACT _____ PHONE _____
 HEIGHT: _____ PRIMARY CARE PROVIDER/CLINIC NAME _____ PHONE _____
 DOB: ____ / ____ / ____ WHAT TRIGGERS MY ASTHMA _____

Baseline Severity

Best Peak Flow

Always use a **holding chamber / spacer** **with/without** a mask with your inhaler. (circle choices)

| GREEN ZONE | DOING WELL | GO! | | | | | | | | | | | | | |
|--|---|----------|----------|------|-------|-------|-------|-------|-------|-------|----------|----------|-------|-------|--|
| <p>You have ALL of these:</p> <ul style="list-style-type: none"> ■ Breathing is good ■ No cough or wheeze ■ Can work/exercise easily ■ Sleeping all night <p>Peak Flow is between: <input type="text"/> and <input type="text"/> <i>80-100% of personal best</i></p> | <p>Step 1: Take these controller medicines every day:</p> <table border="0"> <tr> <td style="text-align: center;">MEDICINE</td> <td style="text-align: center;">HOW MUCH</td> <td style="text-align: center;">WHEN</td> </tr> <tr> <td>_____</td> <td>_____</td> <td>_____</td> </tr> <tr> <td>_____</td> <td>_____</td> <td>_____</td> </tr> </table> <p>Step 2: If exercise triggers your asthma, take the following medicine 15 minutes before exercise or sports.</p> <table border="0"> <tr> <td style="text-align: center;">MEDICINE</td> <td style="text-align: center;">HOW MUCH</td> </tr> <tr> <td>_____</td> <td>_____</td> </tr> </table> | MEDICINE | HOW MUCH | WHEN | _____ | _____ | _____ | _____ | _____ | _____ | MEDICINE | HOW MUCH | _____ | _____ | |
| MEDICINE | HOW MUCH | WHEN | | | | | | | | | | | | | |
| _____ | _____ | _____ | | | | | | | | | | | | | |
| _____ | _____ | _____ | | | | | | | | | | | | | |
| MEDICINE | HOW MUCH | | | | | | | | | | | | | | |
| _____ | _____ | | | | | | | | | | | | | | |

| YELLOW ZONE | GETTING WORSE | CAUTION |
|--|--|---------|
| <p>You have ANY of these:</p> <ul style="list-style-type: none"> ■ Difficulty breathing ■ Coughing ■ Wheezing ■ Tightness in chest ■ Difficult to work/exercise ■ Wake at night coughing <p>Peak Flow is between: <input type="text"/> and <input type="text"/> <i>50-79% of personal best</i></p> | <p>Step 1: Keep taking GREEN ZONE medicines and ADD quick-relief medicine: _____ puffs or 1 nebulizer treatment of _____ <i>Repeat after 20 minutes if needed (for a maximum of 2 treatments).</i></p> <p>Step 2: Within 1 hour, if your symptoms aren't better or you don't return to the GREEN ZONE, take your oral steroid medicine _____ and call your health care provider today.</p> <p>Step 3: If you are in the YELLOW ZONE more than 6 hours, or your symptoms are getting worse, follow RED ZONE instructions.</p> | |

| RED ZONE | EMERGENCY | GET HELP NOW! | | | | |
|---|--|---------------|----------|-------|-------|--|
| <p>You have ANY of these:</p> <ul style="list-style-type: none"> ■ It's very hard to breathe ■ Nostrils open wide ■ Medicine is not helping ■ Trouble walking or talking ■ Lips or fingernails are grey or bluish <p>Peak Flow is between: <input type="text"/> and <input type="text"/> <i>Below 50% of personal best</i></p> | <p>Step 1: Take your quick-relief medicine NOW:</p> <table border="0"> <tr> <td style="text-align: center;">MEDICINE</td> <td style="text-align: center;">HOW MUCH</td> </tr> <tr> <td>_____</td> <td>_____</td> </tr> </table> <p>or 1 nebulizer treatment of _____</p> <p>AND</p> <p>Step 2: Call your health care provider NOW AND Go to the emergency room OR CALL 911 immediately.</p> | MEDICINE | HOW MUCH | _____ | _____ | |
| MEDICINE | HOW MUCH | | | | | |
| _____ | _____ | | | | | |

DATE: ____ / ____ / ____ MD/NP/PA SIGNATURE _____
 FOLLOW-UP APPOINTMENT IN _____ AT _____ PHONE _____

Figure 2 Written Action Plans, such as this Asthma Action Plan, may be a useful tool for the practicing allergist to enhance patient understanding of the management plan. Written Action Plans are available for a variety of allergic disease including anaphylaxis, food allergy, asthma, and eczema. Reproduced from the Minnesota (USA) Department of Health with permission. Accessed January 27, 2014. URL: <http://www.health.state.mn.us/divs/hpcd/cdee/asthma/ActionPlan.html>

7

ALLERGIC DISEASES AND QUALITY OF LIFE

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Allergic diseases are rarely fatal. Even the most extreme and severe form of allergy, anaphylaxis, has a low mortality rate. Allergic diseases rarely lead to traditional forms of infirmity, and societal awareness and concern regarding allergic diseases has thus been limited. However, research carried out over the last decades has shown that allergic diseases significantly impact quality of life (QoL) of patients, and this knowledge has dispelled many notions of allergy as being a “trivial” disease. Despite this, misunderstandings about the correct development and use of instruments measuring QoL may give the impression that these outcomes are “soft” and subjective. In fact, proper application of good instruments generates outcomes that are neither.

HEALTH-RELATED QUALITY OF LIFE: WHAT MATTERS TO PATIENTS?

Health-related quality of life (HRQL) is that part of overall QoL, which is affected by health and disease (Figure 1). The most important aspect of questionnaires measuring HRQL is that they are properly validated, as it is this process, which ensures that non-disease-related QoL is-

sues are excluded and that only HRQL is measured. Many instruments have also ascertained the minimal clinically important difference (MCID), which represents the smallest change or difference in HRQL scores, which is clinically meaningful to patients. Thus, HRQL instruments can accurately measure aspects of disease important to patients. In addition, they can show if changes, for example brought about by treatment are relevant from the patient’s point of view.

KEY MESSAGES

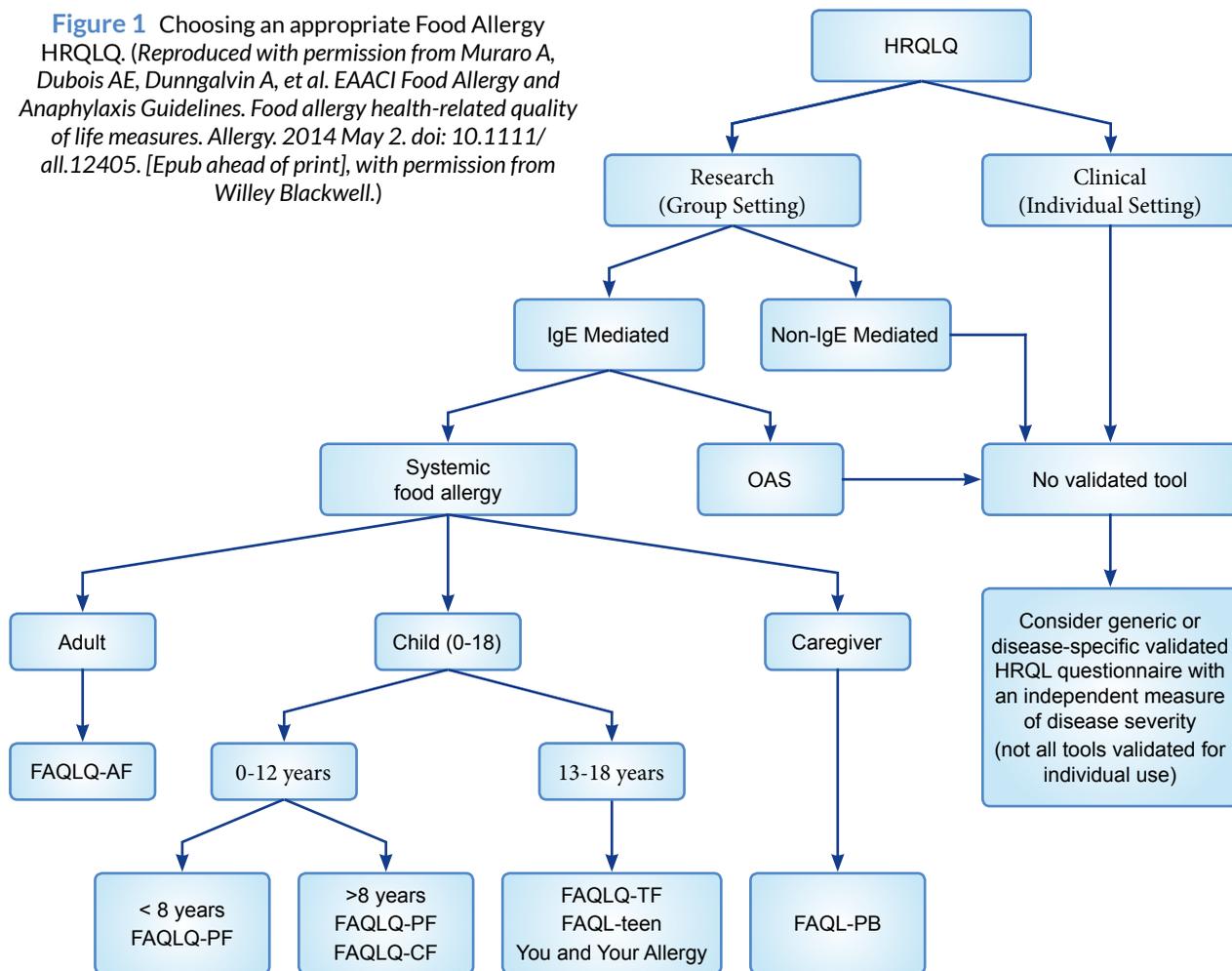
- Health-related quality of life (HRQL) is one of the most important outcomes in studies on allergic diseases
- HRQL may be accurately measured using instruments developed for this purpose
- HRQL is unjustifiably underutilized in clinical studies
- Use of HRQL in clinical practice requires further research

MEASURING HEALTH-RELATED QUALITY OF LIFE IN ALLERGIC DISEASES

Over the past 25 years, instruments for measurement of HRQL have been developed for rhinitis, asthma and atopic dermatitis, allergic diseases which tend to be



Figure 1 Choosing an appropriate Food Allergy HRQLQ. (Reproduced with permission from Muraro A, Dubois AE, Dunngalvin A, et al. EAACI Food Allergy and Anaphylaxis Guidelines. Food allergy health-related quality of life measures. *Allergy*. 2014 May 2. doi: 10.1111/all.12405. [Epub ahead of print], with permission from Wiley Blackwell.)



chronic and where the impact on HRQL is of paramount importance in the assessment of management. More recently, instruments have been developed for measuring HRQL in patients at risk for anaphylaxis, both from vespula venoms and foods, where the expectation of outcome of future episodes and consequent avoidance behavior, rather than chronic symptoms, drives HRQL. The choice of the correct tool to measure HRQL is essential (Figure 2).

Despite the eminent suitability of these measurements for research purposes, HRQL is usually a secondary rather than a primary

outcome in most studies. Ironically, symptom-medication scores, which are frequently used instead, are difficult to interpret, because it is usually unknown what changes are big enough to be important to patients. Application of HRQL measures in clinical practice is limited by the lack of studies formally assessing the contribution of this information to management.

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8

ALLERGIC DISEASES IN ANIMALS

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Hypersensitivity disorders represent a major burden for companion and large animals, especially dogs, cats and horses. The other species are probably also affected even though data are only sparse. Major allergens include insect (flea, flies), environmental (house dust and storage mites, pollens, molds, epithelia) and food allergens. From a clinical point of view, the skin and the gastrointestinal tract are by far the most frequently affected, even though horses and cats may present with clinical signs of allergic asthma.

Insect allergies were the first well characterized allergy disorders in animals and are considered to be type I and type IV hypersensitivity reactions. In dogs and cats, fleas are frequently involved and flea hypersensitivity dermatitis was long considered the first cause of skin disorders in both dogs and cats. In horses numerous flies have been suspected to induce similar disorders. Affected animals present with intense itch usually localized on the dorsal aspect of the body. In contrast, bee and wasp allergies are comparatively rare in domestic animals and are usually associated with urticaria, angioedema and/or anaphylaxis.

KEY MESSAGES

- Hypersensitivity disorders, particularly allergy is frequent in animals and affect all commonly treated species
- The main target organs are the skin and the intestinal tract even though a counterpart of asthma is recognized in cats and horses
- Atopic dermatitis, the most frequent allergy in dogs and cats, affect up to 50% of individuals in some predisposed breeds
- Treatment of allergic disorders in animals is mainly based on allergen avoidance, use of immunomodulatory drugs and allergen-specific immunotherapy

Environmental allergies mostly target the skin in animals. Atopic dermatitis is the most frequent diseases in dogs and in some breeds (French Bulldog, Shar pei, West-Highland-White Terrier more than 50% of individuals are affected. Affected animals present with itch and erythema usually localized to the head, feet and ventral parts of the body (Figure 1). Canine atopic dermatitis is considered the counterpart of human disease and most of the findings observed in humans are applicable to the dog. In fact, canine atopic dermatitis is a Th2 driven disorder in the acute phase of the disease and is mainly Th1 in the more chronic one. The most frequently involved allergens are house dust mites even though similar symptoms have been observed

with pollen and food allergies. AD is less well characterized in cats, horses and other domestic animals but the disease is recognized in all of these species.

Mites and pollen allergens are also involved in the pathogenesis of equine and feline asthma. Equine heaves is a spontaneous occurring asthma-like condition affecting 10–20% of adult horses in the northern hemisphere and other temperate climates. Similarly to asthma, heaves is a chronic disorder of the airways, which is characterized by variable and recurring airflow obstruction, bronchial hyperresponsiveness and airway inflammation. During disease exacerbation, horses present increased respiratory efforts at rest, coughing and exercise intol-



Figure 1 Atopic dermatitis in a dog.

erance. Clinical signs are triggered or exacerbated by inhalation of dust particles present in the stables, especially those associated with hay feeding. Neutrophils and macrophages are present in large numbers in the airways of horses with heaves and may contribute to the disease through the release of several inflammatory mediators. Experimental models of feline asthma have been developed with cats sensitized to various allergens including mites and pollens. Similarities of horse heaves with the human asthma are currently being used to evaluate airway remodelling and its reversibility in ways that are not possible in humans for ethical reasons. Research perspectives that can be relevant to asthma include the role of neutro-

phils in airway inflammation and their response to corticosteroids, systemic response to pulmonary inflammation, and maintaining athletic capacities with early intervention.

Treatment of allergic disorders in animals is mainly based on allergen avoidance (insects: use of antiparasitic treatment avoidance or organic dust for heaves), use of allergen-specific immunomodulatory (AIT) drugs such as glucocorticoids or cyclosporine and desensitization. AIT is mainly used for the treatment of atopic dermatitis in dogs and cats and is successful in about 60-70% of the cases. Bronchodilators and corticosteroids are administered systemically or by inhalation in heaves to provide rapid relief of airway ob-

struction, or when control of the environment is partial or absent.

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