



Contents lists available at SciVerse ScienceDirect



Terminology, close-calls, and bracketology for allergy, asthma, and immunology

Paul A. Greenberger, MD *

* Division of Allergy-Immunology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois

ARTICLE INFO

Article history:

Received for publication August 29, 2012.

Received in revised form October 24, 2012.

Accepted for publication November 1, 2012.

Introduction

The subspecialty of allergy-immunology is very broad and encompasses many terms. Diagnosing and treating patients with the various immunologic conditions and diseases and assessing the subtleties that arise require knowledge, effective decision making, and professional expertise to prioritize choices of and responses to avoidance measures and lifestyle interventions, pharmacotherapy, immunotherapy, immune replacement, and immune reconstitution. It has been my impression that allergist-immunologists are very passionate about the level of care they provide to their patients and take pride in the good outcomes that benefit their patients. They also share enthusiasm for improved understanding stemming from advances in clinical immunology and basic science. Some of the choices, decisions, interactions, and “close-calls” that the allergist-immunologist must make or be knowledgeable of are presented in Figure 1.

Specific Examples

Filaggrin vs Tight Junction

Filaggrin is a critical structural protein of the stratum corneum, the outer layer of the epidermis, that contributes to the integrity of the skin as a barrier. Loss of function mutations of filaggrin are associated with atopic dermatitis and ichthyosis vulgaris.¹ The deficiency of filaggrin is associated with a reduction of the tight junction in the stratum corneum that could allow for excessive entry of and “percutaneous” sensitization by allergens.

Cathelicidin vs Vitamin D₃

Cathelicidin is an antimicrobial peptide that is reduced in skin from patients with atopic dermatitis. T-cell–derived interferon γ helps support production of cathelicidin via a vitamin D–dependent pathway.² Thus, there is interest in (and conflicting evidence for the effectiveness of) administering vitamin D₃ to

increase this important antimicrobial peptide and reduce the morbidity of atopic dermatitis.

Bleach vs *Staphylococcus aureus*

In a randomized controlled study of children with atopic dermatitis with evidence of bacterial infection of their skin, after receiving 2 weeks of cephalexin to clear the infection, the use of 0.5 c of 6% bleach (or water) in a 40-gal bath for 5 to 10 minutes twice a week for 3 months and topical nasal mupirocin (or petrolatum) to the children and household members twice daily for 5 days each month reduced the severity of atopic dermatitis.³ At the beginning of the study, *Staphylococcus aureus* was detected in lesional skin in 87% and in the nose from 81% of children.³ *S aureus* was detected at 1 and 3 months and was not eradicated despite clinical improvement. There was little evidence for new colonization of skin with methicillin-resistant *S aureus* in the children who initially were colonized with methicillin-sensitive *S aureus*.³

Double-Blind vs Open Challenge

There are different strengths and limitations for each method of challenge. The double-blind (and placebo-controlled) challenge is performed to clarify whether there is a cause-and-effect relationship between the incriminated material, such as a food or food additive, and response and an absence of symptoms or response with placebo. The double-blind challenge requires effective blinding, such as putting the test food in apple sauce and flavoring the apple sauce with cinnamon or placing the test chemical (such as aspartame, which is 150–200 times as potent as sucrose) in a capsule and then inserting the capsule in a second, larger capsule and “washing” the outside of the capsule so the test capsule is not recognized as sweet. An open challenge can be used when the goal is to learn whether the patient or research subject responds to a test material. In the setting of a report of food allergy, the open challenge is performed to demonstrate the lack of clinical response, such as when the result of a skin test to a food is negative or with a 3-mm wheal with erythema. In both double-blind and open challenge formats, it is important that the observing physician or

Reprints: Paul A. Greenberger, MD, Division of Allergy-Immunology, 676 N St Clair St, #14018, Chicago, IL 60611; E-mail: p-greenberger@northwestern.edu.

Funding Sources: This study was supported by the Ernest S. Bazley Grant to Northwestern Memorial Hospital and Northwestern University.

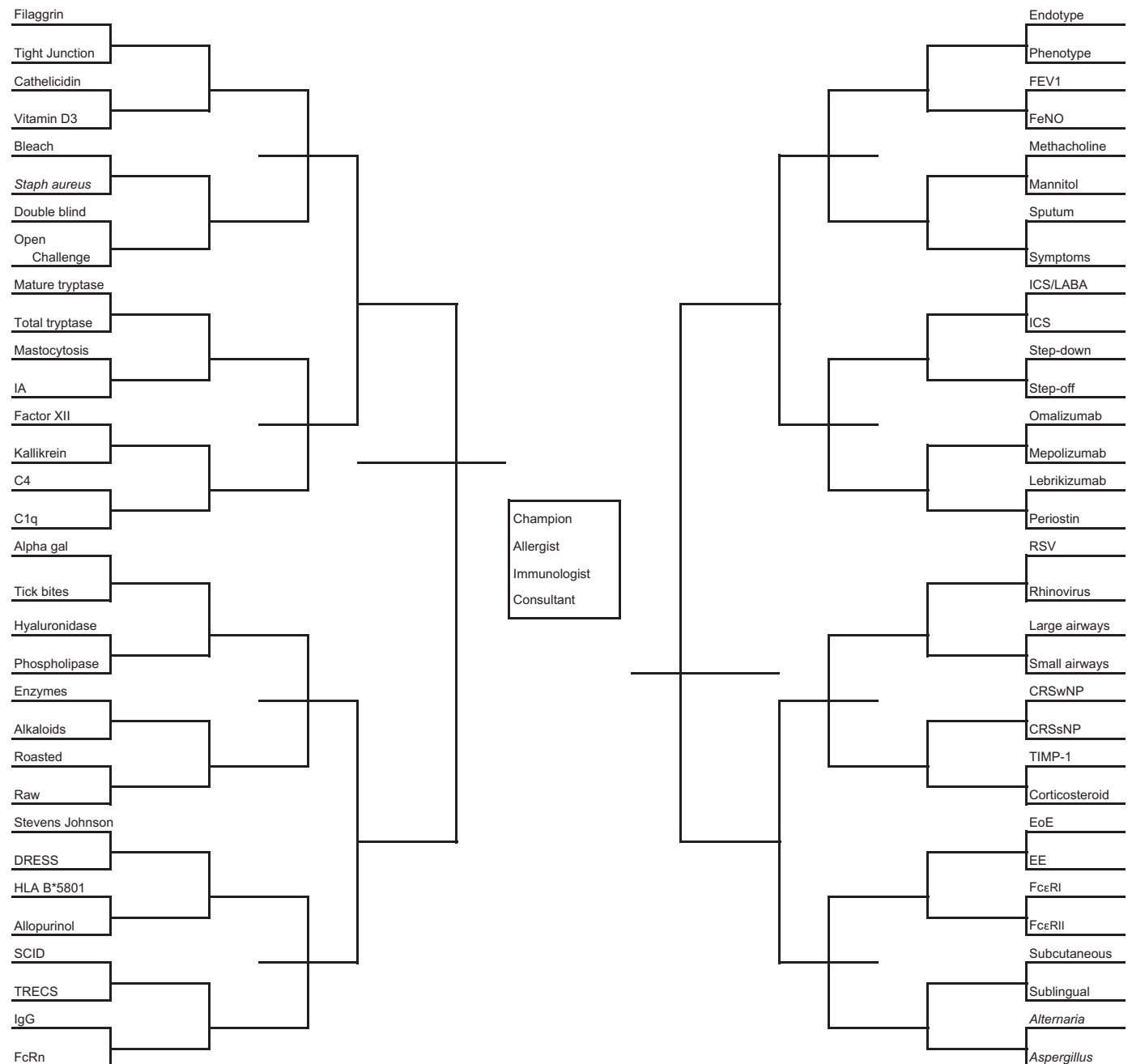


Figure 1. Examples of the some of the specific issues, terms, laboratory tests, and interventions requiring incisive thinking, effective decision making, and “close calls” in the field of allergy-immunology.

health care professional be unbiased in interpreting the symptoms and signs.

Mature Tryptase vs Total Tryptase

Total tryptase in the peripheral blood consists of protryptases (α and β) and mature (nearly all β) tryptases. An increase in mature tryptase represents mast cell degranulation, whereas total tryptase characterizes the mast cell burden.⁴ In a patient with idiopathic anaphylaxis, the baseline serum (total) tryptase is in the normal range. When anaphylaxis occurs, the total tryptase concentration can increase substantially as would mature tryptase. In patients with indolent systemic mastocytosis, the baseline total tryptase concentration is elevated, and when anaphylaxis occurs in such patients, such as after a Hymenoptera sting, the

total tryptase level increases further and the mature tryptase increases.

Mastocytosis vs Idiopathic Anaphylaxis

Mastocytosis (indolent systemic) is in the differential diagnosis of idiopathic anaphylaxis and vice versa. Nearly all patients with indolent systemic mastocytosis have an upregulating mutation (D816V) of c-Kit, a mast cell receptor for stem cell factor.⁵ The tyrosine kinase activity of D816V is a therapeutic target. Idiopathic anaphylaxis is a prednisone-responsive condition that is not life-long for many patients.⁶ The D816V upregulating mutation is not identified during bone marrow examination in patients with true idiopathic anaphylaxis. Perhaps other mutations will be identified in the future. In nearly all patients with indolent systemic

mastocytosis, the total serum tryptase at baseline is greater than 20 ng/mL, whereas in idiopathic anaphylaxis the baseline total serum tryptase would be less than 13 ng/mL.

Factor XII vs kallikrein

There is positive feedback in the contact system. Once factor XII is converted to factor XIIa, it helps convert prekallikrein to kallikrein. Then kallikrein stimulates generation of more factor XII, which leads to a major increase in conversion of more factor XII to factor XIIa, supporting the generation of more kallikrein.⁷ The kallikrein converts high-molecular-weight kininogen to bradykinin.

C4 vs C1q

In screening patients for either hereditary angioedema or acquired C1 esterase inhibitor deficiency, the initial test is C4. If the C4 level is below the normal range, the use of the result for C1q protein helps to differentiate hereditary (normal C1q) from acquired C1 esterase inhibitor deficiency (low C1q).

α -Gal vs Tick Bites

Galactose- $\alpha_{1,3}$ -galactose (α -gal) is the oligosaccharide that is present on the antibody cetuximab because, in the production of this antibody, the cell line contains the enzyme galactosyl-transferase. (This enzyme is not present in hamster ovary cells that often are used for generation of monoclonal antibodies.) Coincidentally, some tick bites can lead to synthesis of IgE antibodies to α -gal. Because α -gal can be present on beef, pork, and lamb, some patients who then eat these foods can experience urticaria or anaphylaxis on a nonimmediate basis, within 3 to 6 hours.⁸

Hyaluronidase vs Phospholipase

Two of the major allergens in honeybee venom are hyaluronidase and phospholipase A2. Hyaluronidases from vespid venom are similar to that of honeybee venom; this is not the case for phospholipases from vespid venoms, where the characteristics differ from honeybee venom.

Enzymes vs Alkaloids

Whereas Hymenoptera venom consists of proteins, fire ant venom consists primarily of alkaloids. The IgE antibodies to fire ant venom are directed against allergenic proteins.

Roasted vs Raw

Roasted peanuts are more allergenic than boiled peanuts. With roasting, some (Ara h 1) but not all (a mixture of Ara h 2/6) of the well-characterized allergens of peanut cause increased mediator release from basophils, which are used as a surrogate for mast cells.⁹ In the experiments, basophils are sensitized by incubating them with sera from peanut allergic individuals. Then increasing concentrations of peanut allergens are incubated and mediator release is measured. Roasting decreased binding to IgE but increased the capacity to cause degranulation. In contrast, during boiling of peanuts, some peanut allergenic proteins are transferred into the hot, cooking water!

Stevens-Johnson Syndrome vs DRESS

Stevens-Johnson syndrome (and toxic epidermal necrolysis) consists of severe mucocutaneous eruptions with or without visceral organ involvement. Lesions may be erythematous or purpuric macules, blisters, or target lesions. Drugs are identifiable causes of Stevens-Johnson syndrome in approximately 75% of cases, with infections, including viruses or *Mycoplasma pneumoniae*, accounting for most of the rest. Drug reaction with

eosinophilia and systemic symptoms (DRESS) is characterized by peripheral blood eosinophilia, abnormal liver function test results, fever, erythematous papules, tender lymphadenopathy, hepatomegaly, and ulcerations of oral mucosa. Lesions may blister. DRESS has been referred to by other names, including anticonvulsant hypersensitivity syndrome.

*HLA-B*5801 vs Allopurinol*

Genetic analysis has helped to identify at risk populations for hypersensitivity reactions. Another high-risk genotype is HLA-B*1502 for carbamazepine-associated DRESS or Stevens-Johnson syndrome in Southeast Asians.

SCID vs TRECS

Infants with severe combined immunodeficiency (SCID) can be identified by screening for the number of T-cell receptor excision circles (TRECS).¹⁰ TRECS occur when precursor type T cells pass into the thymus, where there is rearrangement of T-cell receptor DNA. The “ends” of DNA rearrange and can be identified as circles in peripheral blood. In bloodspots from infants with SCID, there are very few or no TRECS compared with unaffected infants, resulting in a valuable screening tool.

IgG vs FcRn

FcRn (Fc receptor neonatal) has several functions, including transport of IgG across the placenta and prevention of degradation of IgG by translocating intracellular IgG back to the cell surface or lumen of the bloodstream.¹¹ It is thought that FcRn recycling of intracellular IgG back to the bloodstream allows for the long half-life (approximately 23 days) of IgG.

Endotype vs Phenotype

An endotype is a subtype of a disease with its specific characteristics and pathophysiologic features.¹² Two examples of endotypes of asthma are aspirin-exacerbated respiratory disease and allergic bronchopulmonary aspergillosis. Phenotypes are observable characteristics, such as improvement of at least 12% in forced expiratory volume in 1 second (FEV₁) after albuterol, obesity, or adherence, and some phenotypes will apply to many or even all patients with asthma. In the development of novel pharmacologic treatments, it is anticipated that the use of endotype-driven inclusion criteria will result in identifying the very good responders and improve risk-benefit considerations.

FEV₁ vs FeNO

Measurement of FEV₁ has multiple uses, and it is recommended that new patients suspected of having asthma have a flow volume loop tracing to identify inspiratory or expiratory abnormalities. Some patients with asthma do not perceive reductions of FEV₁ of 50%. Other patients may have experienced excessive loss of FEV₁ from long-term asthma that may have started in childhood or because of incompletely controlled asthma as adolescents or adults. Exhaled nitric oxide (FeNO) measurements identify eosinophilic inflammation. Although it has been reported that FeNO-guided management of asthma can achieve reduced inhaled corticosteroid (ICS) requirements,¹³ some other studies have not confirmed superior value of this biomarker.^{14,15}

Methacholine vs Mannitol

In the diagnosis of bronchial hyperresponsiveness, both methacholine and mannitol have value. Methacholine has high sensitivity for detecting bronchial hyperresponsiveness in helping to diagnose asthma but lower specificity because people without asthma but with other conditions have some degree of bronchial

hyperresponsiveness. A few examples are allergic rhinitis, chronic bronchitis, first-degree relatives of patients with asthma, and for up to 6 weeks in healthy people after an upper respiratory infection. Mannitol, acting as an osmotic stimulus for mast cell mediator release, has lower sensitivity but high specificity. Thus, a negative result with mannitol testing helps exclude bronchial hyperresponsiveness, but a positive result likely is more associated with the bronchial hyperresponsiveness of asthma.

Sputum vs Symptoms

Measurement of sputum eosinophils for prospective management of asthma may provide subclinical yet clinically useful information or be of no major advantage over other markers or physician assessment.¹⁶ As a biomarker, a sputum eosinophil count greater than 2% can help in diagnosis of eosinophilic predominant asthma and identify the corticosteroid-responsive phenotype. However, the test requires induction of sputum for some patients, sample processing, and counting of eosinophils.

Similarly, symptom-based management may or may not¹⁵ be helpful in management. Some patients are hypervigilant in reporting symptoms that can lead to overtreatment. Obese patients may be diagnosed incorrectly as having asthma because they report shortness of breath when they do not have asthma. Alternatively, some patients with severe airways obstruction do not report any symptoms. Both sputum eosinophils and symptoms have value and limitations in diagnosis and management of asthma.

ICS and LABA vs ICS Alone

The debate continues in the literature about next steps if the patient has incomplete control of asthma when a low or moderate dose of ICS is the basis of treatment. Fortunately, nearly all the published literature supports use of a long-acting β -agonist (LABA) combined with an ICS because there are reduced numbers of exacerbations and emergency department visits associated with improved level of control without an increase in risk of harms. Doubling the dose of the ICS is less effective than adding an LABA to the current dose of ICS regarding improvement in FEV₁, symptom-free days, and daytime rescue β_2 -agonists.¹⁷ The use of monotherapy of LABAs without ICSs is associated with uncontrolled asthma and increased likelihood of hospitalization in patients presenting to the emergency department.¹⁸

Step-Down vs Step-Off

When a patient with persistent asthma achieves control of asthma with administration of an ICS-LABA combination product, is the next step step-down of the ICS (guideline position) or discontinuation of the LABA treatment (Food and Drug Administration position)? I favor “stepping down” the ICS first because the patient who has not improved with an ICS alone previously was administered the combination ICS-LABA product and achieved control. Often, such patients are reluctant to return to the previous (ICS) approach because of the risk of loss of control of their asthma. Alternatively, in the setting of an upper respiratory infection and no recent symptoms or use of any controller medication for asthma, some patients present with a barking cough and wheezing dyspnea. Control is achieved with administration of an ICS-LABA combination product during the next 2 months. It is reasonable to considering “stepping off” such patients and attempting to control their asthma with an ICS alone.

Omalizumab vs Mepolizumab

Omalizumab, a monoclonal antibody to IgE, administered subcutaneously, is associated with reductions of exacerbations, oral steroid courses, and number of hospitalizations from asthma.¹⁹

Mepolizumab, an antibody to interleukin 5 that is administered intravenously, reduces exacerbations in patients with severe eosinophilic asthma. It is not commercially available in the United States.

Lebrikizumab vs Periostin

Lebrikizumab, a monoclonal antibody to interleukin 13, administered subcutaneously, improved FEV₁ in patients with asthma ineffectively controlled with ICSs by 9.8% vs 4.3% with placebo.²⁰ One target of lebrikizumab is periostin, a matrix protein that participates in airway remodeling. Patients with higher concentrations of periostin had greater improvement. Lebrikizumab is not commercially available in the United States.

Respiratory Syncytial Virus vs Rhinovirus

Both families of viruses have been associated with early-onset asthma or exacerbations of asthma at any age. In a prospective study of infants (<2 years of age) who presented to the emergency department with acute respiratory illnesses, viruses were identified in nasal swabs in 81.7% by immunofluorescent assays or by extraction of RNA/DNA (respiratory syncytial virus in 34% and rhinovirus in 24%).²¹ Respiratory syncytial virus was associated with more severe respiratory illness, including intensive care hospitalizations and hypoxemia, especially in infants younger than 3 months.²¹

Large Airways vs Small Airways

Asthma affects both large and small airways. When FEV₁ is reduced, it can represent a reduction in the caliber of both the large and small airways.

Chronic Rhinosinusitis With vs Without Nasal Polyposis

The presence of chronic rhinosinusitis implies aggressive inflammation of the sinuses with or without major contributions of microbial pathogens or biofilms.

TIMP-1 vs Corticosteroids

Tissue inhibitor of metalloproteinase 1 (TIMP-1) helps control matrix metalloproteinases that participate in lung remodeling in asthma. ICSs increase TIMP-1, one of the many benefits of ICSs.

Eosinophilic Esophagitis vs Erosive Esophagitis

Eosinophilic esophagitis is contrasted with erosive esophagitis.

FcεRI vs FcεRII

The high-affinity (FcεRI) receptor is detectable on mast cells, basophils, activated eosinophils, Langerhans cells (activation favoring T_H2 cells), and the inflammatory dendritic epidermal cells (activation favoring T_H1 cells).²² The lower-affinity (FcεRII) receptor (CD23) is found on B cells and monocytes. B cells serve as antigen-presenting cells by internalizing IgE-allergen complexes and presenting them to T cells. In experiments with sera from patients who have received as few as 5 weeks of subcutaneous allergen immunotherapy with ragweed, the newly formed IgG antibodies can compete with IgE for binding to ragweed and inhibit some of the IgE-ragweed complex presentation to B cells that occurs via FcεRII.²³ The addition of omalizumab to allergen immunotherapy reduced the IgE-ragweed presentation to B cells even more.

Subcutaneous vs Sublingual

Subcutaneous and sublingual are the 2 routes for administration of allergen immunotherapy.²⁴ Efficacy and immunogenicity have

been shown for both routes. There is no product available for sublingual administration in the United States.

Alternaria vs *Aspergillus*

The outdoor mold (*Alternaria*) is contrasted with the perennial indoor and outdoor mold (*Aspergillus*).

Conclusion

In basketball, the good players learn how to “look and see” the real-time, ever-changing movements of their 4 teammates and 5 opposing players. In allergy, asthma, and immunology, we must be mindful of crowd-noise, pseudoscientific advocacy, and scientific information while being wary of our preset favorites in making clinical decisions. Fortunately, the subspecialty of allergy/immunology is fun and exciting. Continued advances in scientific understanding should help us be fortunate when we face the inevitable “close calls.”

References

- [1] Kawasaki H, Nagao K, Kubo A, et al. Altered stratum corneum barrier and enhanced percutaneous immune responses in filaggrin-null mice. *J Allergy Clin Immunol*. 2012;129:1538–1546.
- [2] Sandhu MS, Casale TB. The role of vitamin D in asthma. *Ann Allergy Asthma Immunol*. 2010;105:191–199.
- [3] Huang JT, Abrams M, Tlougan B, Rademaker A, Paller AS. Treatment of *Staphylococcus aureus* colonization in atopic dermatitis decreases disease severity. *Pediatrics*. 2009;123:e808–e814.
- [4] Ferrer M, Nunez-Cordoba JM, Luquin E, et al. Serum total tryptase levels are increased in patients with active chronic urticaria. *Clin Exp Allergy*. 2010;40:1760–1766.
- [5] Bains SN, Hsieh FH. Current approaches to the diagnosis and treatment of systemic mastocytosis. *Ann Allergy Asthma Immunol*. 2010;104:1–10.
- [6] Ditto AM, Harris KE, Krasnick J, Miller MA, Patterson R. Idiopathic anaphylaxis: a series of 335 cases. *Ann Allergy Asthma Immunol*. 1996;77:285–291.
- [7] Kaplan AP, Joseph K. The bradykinin-forming cascade and its role in hereditary angioedema. *Ann Allergy Asthma Immunol*. 2010;104:193–204.
- [8] Commins SP, Satinover SM, Hosen J, et al. Delayed anaphylaxis, angioedema, or urticaria after consumption of red meat in patients with IgE antibodies specific for galactose- α -1,3-galactose. *J Allergy Clin Immunol*. 2009;123:426–433.
- [9] Visser YM, Iwan M, Adel-Patient K, et al. Effect of roasting on the allergenicity of major peanut allergens Ara h 1 and Ara h 2/6: the necessity of degranulation assays. *Clin Exp Allergy*. 2011;41:1631–1642.
- [10] Puck JM. Laboratory technology for population-based screening for severe combined immunodeficiency in neonates: the winner is T-cell receptor excision circles. *J Allergy Clin Immunol*. 2012;129:607–616.
- [11] Rath T, Kuo TT, Baker K, et al. The immunologic functions of the neonatal Fc receptor for IgG [published online ahead of print]. *J Clin Immunol*. September 5, 2012.
- [12] Lotvall J, Akdis CA, Bacharier LB, et al. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. *J Allergy Clin Immunol*. 2011;127:355–360.
- [13] Smith AD, Cowan JO, Brassett KP, et al. Use of exhaled nitric oxide measurements to guide treatment of chronic asthma. *N Engl J Med*. 2005;352:2163–2173.
- [14] Szefer SJ, Mitchell H, Sorkness CA, et al. Management of asthma based on exhaled nitric oxide in addition to guideline-based treatment for inner-city adolescents and young adults. *Lancet*. 2008;372:1065–1072.
- [15] Calhoun WJ, Ameredes BT, King TS, et al. Comparison of physician-, biomarker-, and symptom-based strategies for adjustment of inhaled corticosteroid therapy in adults with asthma. *JAMA*. 2012;308:987–997.
- [16] Melosini L, Dente FL, Bacci E, et al. Asthma control test (ACT): comparison with clinical, functional, and biological markers of asthma control. *J Asthma*. 2012;49:317–323.
- [17] Greenstone IR, Ni Chroinin MN, Masse V, et al. Combination of inhaled long-acting β_2 -agonists and inhaled steroids versus higher dose of inhaled steroids in children and adults with persistent asthma. *Cochrane Database Syst Rev*. 2005;4:CD005533.
- [18] Liao MM, Ginde AA, Clark S, Camargo CA. Salmeterol use and risk of hospitalization among emergency department patients with acute asthma. *Ann Allergy Asthma Immunol*. 2010;104:478–484.
- [19] Karpel J, Massanari M, Geba GP, et al. Effectiveness of omalizumab in reducing corticosteroid burden in patients with moderate to severe persistent allergic asthma. *Ann Allergy Asthma Immunol*. 2010;105:465–470.
- [20] Corren J, Lemanske RF Jr, Hanania NA, et al. Lebrikizumab treatment in adults with asthma. *N Engl J Med*. 2011;365:1088–1098.
- [21] Laurent C, Dugue AE, Brouard J, et al. Viral epidemiology and severity of respiratory infections in infants in 2009: a prospective study. *Pediatr Infect Dis J*. 2012;31:827–831.
- [22] Bieber T. The pro- and anti-inflammatory properties of human antigen-presenting cells expressing the high affinity receptor for IgE (Fc ϵ RI). *Immunobiology*. 2007;212:499–503.
- [23] Klunker S, Saggar LR, Seyfert-Margolis V, et al. Combination treatment with omalizumab and rush immunotherapy for ragweed-induced allergic rhinitis: Inhibition of IgE-facilitated allergen binding. *J Allergy Clin Immunol*. 2007;120:688–695.
- [24] Cox L, Esch RE, Corbett M, et al. Allergen immunotherapy practice in the United States: guidelines, measures, and outcomes. *Ann Allergy Asthma Immunol*. 2011;107:289–299.