



IgE antibodies in occupational asthma: are they causative or an associated phenomenon?

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Purpose of review

To evaluate recent data on the causative role of specific IgE antibodies, as well as the performance of IgE diagnostic tests, in allergic occupational asthma induced by high (HMW) or low-molecular-weight (LMW) agents.

Recent findings

Skin prick testing (SPT) and specific IgE assays are useful to document allergy to most HMW allergens and some LMW agents. These tests, however, are limited by the lack of standardized and commercially available reagents. There is a wide variability among the quality of occupational allergen extracts used for SPT and the sensitivity of several SPT solutions is low. In addition, many individuals with allergen-specific serum IgE and/or positive SPT to specific HMW allergens do not have clinical symptoms. Sensitization or allergenic cross-reactivity to allergens or epitopes from unrelated sources may interfere in the diagnosis of IgE-mediated allergy, giving rise to false-positive results, particularly when cross-reactive carbohydrate determinants (CCDs) are involved. The immune responses to these ubiquitous structures may interfere with the diagnosis of occupational allergy. Component-resolved diagnosis of IgE-mediated allergic diseases (occupational and nonoccupational) using panels of native or recombinant allergens, or micro-arrayed allergens, have been proposed to identify specific molecules responsible for these disorders and to overcome false-positive in-vitro test results.

Summary

Improvement and standardization of SPT solutions for occupational allergens are highly recommended. More refined diagnostic tools than specific IgE measurements are being developed, such as inhibition assays of IgE binding to CCDs with specific carbohydrate molecules, and component-resolved diagnosis.

Keywords

component-resolved diagnosis, cross-reactive carbohydrate determinants, occupational asthma, skin prick tests, specific IgE determinations

INTRODUCTION

Allergic occupational asthma is caused by sensitizers present at work. It encompasses occupational asthma caused by most high-molecular-weight (HMW) and some low-molecular-weight (LMW) agents for which an IgE-mediated mechanism has been proven, and occupational asthma induced by some specific LMW agents in which the allergic mechanisms responsible have not yet been fully characterized [1[•]]. The first steps of the diagnostic work-up of occupational asthma include, prior to any specific inhalation challenge (SIC), the performance of skin prick testing (SPT) and/or IgE determinations to occupational allergens [1[•],2^{••}]. These tests, however, are limited by the lack of standardized and commercially available reagents. In addition, the presence of either cosensitization or allergenic cross-reactivity to allergens or epitopes

from unrelated sources may complicate further the diagnosis [3]. The pitfalls of currently available IgE tests for the in-vivo and in-vitro diagnosis of allergic diseases have been underlined [4[•]].

PATHOGENESIS AND CAUSATIVE AGENTS

The pathophysiology of allergic occupational asthma usually involves an IgE-dependent mechanism.

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KEY POINTS

- A reliable diagnosis is of utmost importance for the management of patients with occupational allergy because the treatment is essentially based on the avoidance of the allergy source.
- The quality of commercially available occupational extracts for SPT shows a wide variability, and the sensitivity of several SPT extracts is low.
- The immune responses to ubiquitous CCDs may interfere with the diagnosis of occupational allergy.
- Component-resolved diagnosis using microarray technology has recently been introduced in clinical allergology, and its applicability in the occupational allergy field is promising.

Occupational asthma induced by IgE-mediated mechanisms is similar to allergic asthma that is unrelated to work [5], and thus, IgE is the central player in the allergic response [6].

HMW agents act as complete antigens, whereas LMW sensitizers must first react with autologous or heterologous proteins to act as a complete and functional allergen. For some LMW agents (acid anhydrides, chlorinated platinum salts, sulfone chloramide), the development of occupational asthma is associated with the production of specific IgE antibodies. For most other LMW agents, the presence of specific IgE has been documented in only a small number of affected workers without showing a consistent correlation with clinical symptoms [5].

Baur [7^{***}] has evaluated the agents and worksites causing allergic or irritant occupational asthma in an evidence-based manner. Approximately, 372 different causes of allergic and 184 different causes of irritant occupational asthma were identified. Using the modified Royal College of General Practitioners three-star grading system, the strongest evidence of association with an individual agent or worksite (***) was found for exposure to laboratory animals. Associations with moderate evidence level (**) were obtained for the following: alpha-amylase, various enzymes from *Bacillus subtilis*, papain, bakeries, western red cedar, latex, psyllium, storage mites, rat, carmine, egg proteins, Atlantic salmon, fish meal, Norway lobster, prawn, snow crab, seafood, trout and turbot, reactive dyes. Agents or worksites causing allergic as well as irritant occupational asthma, included farming, poultry confinement, various isocyanates, and platinum salts. Evidence for causing occupational asthma was found for 78 allergens and for 71 irritants,

respectively, with eight eliciting an allergic as well as an irritative pathomechanism, establishing 141 in total [7^{***}].

Notwithstanding, the list of causative agents of allergic occupational asthma is continuously growing, and new agents and professions are described each year [8,9].

IgE TESTS IN THE DIAGNOSIS OF ALLERGIC OCCUPATIONAL ASTHMA

SPT or specific immunoglobulin E assays are useful to document allergy to most HMW allergens and some LMW agents. A systematic review of the diagnosis of occupational asthma [10] showed that, for HMW agents, nonspecific bronchial hyperresponsiveness (NSBH), SPT, and serum-specific IgE had sensitivities more than 73% when compared with SIC, and specificity was highest for specific IgE vs. SIC [79.0%; 95% confidence interval, CI (50.5–93.3)]. The highest sensitivity among LMW agents occurred between combined NSBH and SPT vs. SIC [100%; 95% CI (74.1–100)]. For HMW agents, high specificity was demonstrated for positive NSBH tests and SPTs alone [82.5%; 95% CI (54.0–95.0)] or when combined with specific IgE [74.3%; 95% CI (45.0–91.0)] vs. SIC. It was concluded that, when SIC is not available, the combination of a NSBH test with a specific SPT or specific IgE may be an appropriate alternative to SIC in diagnosing occupational asthma.

This has been demonstrated for several HMW agents, particularly wheat flour and other bakery allergens [11,12]. Hannu *et al.* [13[•]] investigated whether the SPT result to obeche wood can be used as a predictor for the outcome of SIC tests performed on 34 symptomatic workers. Of these, 27 workers had a positive SIC test result and were diagnosed as having occupational asthma. They found that all workers with a wheal size of at least 3.5 mm from obeche wood had a positive SIC, and they suggest that SIC with obeche wood may be unnecessary in strongly sensitized workers.

An IgE-mediated response is the major pathogenic mechanism for the induction of work-related respiratory symptoms in cereal-exposed workers [14[•]]. Among employees at a soy processing plant, workers with soy-specific IgE (21%) had a six-fold greater odds of work-related asthma [15]. In South Africa, workers from three soy-processing plants were studied with a respiratory questionnaire and estimation of atopy and specific soy IgE [16[•]]. There was a significant association between work-related bronchial and nasal respiratory symptoms and soy sensitization.

In a study [17] in 88 hazelnut processing workers, however, although serum-specific IgE against hazelnut allergens was positive in 17.1% of them, no association was found between being sensitized to hazelnut and work-related respiratory symptoms.

For LMW agents, IgE-mediated allergy is relatively uncommon, with few exceptions. In occupational asthma caused by acid anhydrides, the pathogenesis is thought to involve specific IgE antibodies to these compounds. Bernstein *et al.* [18] investigated the ability of trimellitic anhydride (TMA) skin testing to identify workers with TMA serum-specific IgE antibodies. They found that SPT was positive in eight of 11 workers with TMA serum-specific IgE antibodies, and intradermal testing was positive in two additional workers with TMA serum-specific IgE antibodies, which reinforces the role of skin testing with these compounds.

Regarding diisocyanate-induced asthma, specific IgE to toluene diisocyanate (TDI) in a range of 0–40% of workers has been reported [5]. It is widely admitted that the presence of specific IgE is highly diagnostic, but it has low sensitivity in detecting occupational asthma caused by diisocyanates. Budnik *et al.* [19^{***}] have investigated whether specific IgE determination is feasible in methylenediphenyl diisocyanate (MDI)-induced occupational asthma. Specific IgE and IgG binding was measured with fluorescence enzyme immunoassay in 43 study participants. The presumed occupational asthma diagnoses were confirmed in 84% (45% cases having demonstrable specific IgE), whereas specific IgG antibodies were not clinically relevant for occupational asthma diagnosis. The authors stated that isocyanate-specific IgE antibodies are not always detectable, but their presence is strongly predictive of occupational asthma and supportive for the diagnosis.

SKIN PRICK TESTING: STRENGTHS AND WEAKNESSES

SPT performance is related to the quality of allergen extracts. van Kampen *et al.* [20^{***}] assessed different commercially available SPT solutions for selected occupational allergens. The SPT solutions from different manufacturers for wheat flour, rye flour, soy, cow hair/dander, storage mites, and latex were analyzed with respect to their protein and antigen contents. Specific IgE values were used as the gold standard. It was found that protein and antigen contents and patterns of the SPT solutions varied remarkably depending on the manufacturer. Whereas SPT solutions for wheat flour and soy reached overall low sensitivities, sensitivities of

other tested SPT solutions depended on the manufacturer. It was found that solutions with higher protein and antigen content showed higher sensitivities and test efficiencies.

An European Academy of Allergy and Clinical Immunology (EAACI) Task Force assessed the quality of commercially available SPT solutions for selected occupational allergens under standardized procedure conditions in different European centers [21]. In keeping with the aforementioned results, the data evaluation showed a wide variability among SPT solutions and also indicates that the sensitivity of several SPT solutions is low. Therefore, improvement and standardization of SPT solutions for occupational allergens is highly recommended. Clinicians should be aware that commercial SPT solutions are not fully reliable. The key messages of this document are shown below. Main findings of EAACI position paper on SPT in the diagnosis of occupational IgE-mediated respiratory allergy are as follows [21]:

- (1) A high variability in protein and even higher variability in antigen content were detected in all SPT solutions for all tested occupational allergens from different manufacturers.
- (2) Although SPT with higher protein content seems to have a higher potency *in vivo*, determination of protein content alone is not a feasible predictive marker for the quality of a SPT solution.
- (3) Increasing the antigen content of SPT solutions is recommended to those manufacturers whose solutions showed low sensitivities.
- (4) SPTs should always be performed with a metal lancet and, if practicable, in duplicate.
- (5) Depending on the case, small wheal sizes could be relevant. After additional replication, they should be supported by serological IgE tests.
- (6) Until further notice, it is highly recommended to use SPT solutions from different manufacturers in parallel.
- (7) Standardization of SPT for occupational allergens is highly recommended.

ALLERGEN-SPECIFIC SERUM IgE MEASUREMENTS: SHORTCOMINGS AND DEVELOPMENTS

Measurement of circulating specific IgE is an important step in the diagnosis of allergic occupational asthma. Serologic IgE tests, however, also have limitations [4^{*}]. One major drawback is that IgE tests detect sensitization, but this does not imply clinical relevance or a causal relationship. More than 20% of individuals with allergen-specific serum IgE and/or

positive SPT to common allergens do not have clinical symptoms [22], which is also observed with different HMW occupational allergens. Another shortcoming is that sensitization or allergenic cross-reactivity to allergens or epitopes from unrelated sources may interfere in the diagnosis of IgE-mediated allergy, giving rise to false-positive results, and this is particularly true when carbohydrate determinants are involved.

CROSS-REACTIVE CARBOHYDRATE DETERMINANTS

Carbohydrate determinants are one of the most common epitopes for IgE [23], and consequently they have been named cross-reactive carbohydrate determinants (CCDs). These glycoepitopes have been shown to interfere in IgE-specific assays, and it has been suggested that the discrepancies between negative SPT responses and positive IgE determinations (false positive) can be associated with the presence of IgE to CCDs [3]. Specific IgE to CCDs can be highly cross-reactive and it is frequently found in patients polysensitized to common aeroallergens. It is considered that IgE antibodies against CCDs have poor biological activity and lack of clinical relevance [24].

There are scarce data on the prevalence and clinical relevance of IgE binding to CCDs among individuals with occupational respiratory allergy. Kespohl *et al.* [25] determined the prevalence of specific IgE sensitization to extracts from beech and pine wood among woodworkers and controls from several Danish factories. IgE binding to wood extracts was analyzed in competitive inhibition assays with the glycoprotein horseradish peroxidase as inhibitor. In a significant percentage of individuals with positive IgE to beech wood or pine wood, IgE binding was reduced by more than 80% by horseradish peroxidase, suggesting that IgE binding was mostly directed to carbohydrate structures.

In a Spanish study [26] on patients with baker's asthma, a high prevalence (35%) of allergy to kiwifruit was reported. Bakers sensitized to both kiwifruit and wheat flour showed strong IgE binding to CCDs. CCDs and thiol-proteases homologous to Act d 1 were found to be responsible for wheat–kiwi cross-reactivity [26]. Interestingly, relevant wheat flour allergens associated with baker's asthma, such as some subunits of α -amylase inhibitors and peroxidase, are glycoproteins with N-linked complex glycans [27].

The potential relationship of latex allergy and CCDs has also been investigated [3]. In a group of 104 healthcare workers allergic to latex, only 11.5%

of the sera showed specific IgE response to CCDs [28]. By contrast, Coutinho *et al.* [29] determined the levels of IgE to CCD markers and latex in 270 adults without a history of latex allergy. It was found that the presence of CCD-specific IgE was closely associated with latex IgE reactivity. Inhibition studies and the absence of reactivity to nonglycosylated recombinant latex allergens indicated CCD interference in latex IgE determinations. Moreover, alcohol consumption seemed to be associated with an increased prevalence of IgE reactivity to latex due to higher reactivity to CCDs [29].

Wiszniewska *et al.* [30] investigated the role of IgE reactivity to CCDs in a group of 81 Polish workers (bakers, farmers, carpenters, and healthcare workers) with suspected occupational respiratory allergy. Occupational rhinitis and/or asthma was confirmed in 60% of these individuals by SIC, and MUXF3 was tested as a CCD marker. The authors suggested that the presence of circulating specific IgE to CCDs does not preclude that patients may have true occupational asthma, and that the concomitant sensitization to common allergens was more likely to be due to independent sensitization than to cross-reactivity.

As long as the role of glycan structures in clinical allergic reactions is unclear, the significance of CCDs in the diagnosis of occupational allergy will remain uncertain. However, at present, it seems clear that the immune responses to these ubiquitous structures may interfere with the diagnosis of both occupational and nonoccupational allergy.

To overcome these problems, some strategies are already available or in early phases of development, such as inhibition assays of IgE binding to CCDs with specific carbohydrate molecules [31[■]], the use of nonglycosylated recombinant allergens, and raising monoclonal antibodies against specific carbohydrate epitopes [3].

COMPONENT-RESOLVED DIAGNOSIS

Improvements in component-resolved diagnosis (CRD) of allergic diseases using panels of native or recombinant allergens [28,32] or micro-arrayed allergens [33] have been proposed to identify specific molecules responsible for these disorders and to overcome false-positive in-vitro test results. CRD is being increasingly used in the diagnosis of allergic occupational asthma caused by HMW agents, such as wheat flour [32,34[■],35[■]], soy [36], latex [37,38,39[■]], and laboratory animal allergens [40[■]].

Pahr *et al.* [34[■]] reported the molecular characterization, recombinant expression, and purification of five wheat allergens, a thioredoxin h

isoform, glutathione transferase, 1-Cys-peroxiredoxin, profilin, and dehydrin. 1-Cys-peroxiredoxin, glutathione transferase, and dehydrin were mainly recognized by patients with baker's asthma, but not wheat-induced food allergy. Therefore, the characterized recombinant wheat allergens may be useful for the development of serological tests, which allow the discrimination of different clinical manifestations of wheat allergy.

Olivieri *et al.* [35[¶]] conducted a study in 81 bakers reporting work-related symptoms using commercial tests (SPT, specific IgE, and ISAC microarray) and six additional dot-blotted wheat allergens (Tri a39, Tri a Trx, Tri a GST, Tri a32, Tri a12, Tri a DH). SPTs to wheat were positive in 29 bakers and were associated with work-related asthma, whereas specific IgE to wheat was detected in 51 workers and was associated with work-related asthma and rhinoconjunctivitis. Wheat dot-blotted allergens were positive in 22 bakers, and some specific allergens (Tri a32 and Tri a GST) were associated with work-related dermatitis.

Soy flake processing workers ($n = 135$) in a USA facility were evaluated for immune reactivity to soy [36]. Immunoblotting of soy flake extracts revealed IgE against multiple soy antigens with reactivity toward 48, 54, and 62 kDa bands being the most common. The prominent proteins that bound IgE were identified to be the HMW soybean storage proteins, β -conglycinin (Gly m5), and glycinin (Gly m6). No specific IgE reactivity could be detected to lower MW soy allergens, Gly m1 and Gly m2, in soybean hull extracts.

Ebo *et al.* [38] investigated CRD of latex allergy by microarray and assessed whether the technique allows discriminating relevant allergy from asymptomatic sensitization. In the patients studied, the diagnosis of latex allergy could be established by the combination of recombinant latex components present on the microarray (Hev b1, Hev b3, Hev b5, and Hev b6.02). Over three-quarters of the patients were sensitized for Hev b5 and/or Hev b6.02. In contrast, none of the asymptomatic individuals sensitized to latex or control individuals demonstrated IgE reactivity for rHev b1, rHev b3, rHev b5, or rHev b6.02. Thus, CRD by microarray can improve the diagnosis of IgE-mediated latex allergy by discriminating between genuine allergy and latent sensitization.

Schuler *et al.* [39[¶]] conducted a retrospective study to discriminate between sensitization and relevant allergy to latex. In 14 patients with clinical symptoms and 27 controls, latex SPT, IgE against latex (CAP), and CRD (Hev b1, b3, b5, b6, b7, b8, b9, b10, b11) based on ISAC microarray were performed. SPT correlated very well with clinically relevant

latex allergy, demonstrating a high specificity (95%). However, IgE levels to latex could not safely discriminate between merely sensitized and latex-allergic patients. The majority of patients monosensitized to the latex profilin Hev b8 did not suffer from any relevant symptoms upon contact with latex.

Caballero *et al.* [40[¶]] carried out a study in 75 workers exposed to laboratory animals aiming to develop a diagnosis system based on a multi-allergen IgE immunoblot. The workers with suspected occupational disease and positive SPT results were further studied to determine specific IgE levels to urine and epithelia allergens (CAP) and with multiallergen IgE immunoblotting to detect specific IgE levels to epithelia allergens and bovine serum albumin. Twenty of the 75 workers were studied with CAP and multiallergen IgE immunoblotting. Nine were polysensitized and three were sensitized to only one animal. On the basis of the results of the study and the clinical history, 16% were diagnosed as having occupational allergy. These results suggest that this system can improve the diagnosis of laboratory animal allergy by obtaining a sensitization profile for each exposed worker.

CONCLUSION

The available diagnostic systems sometimes fail to detect specific IgE antibodies to relevant allergenic structures, thus impairing the correct diagnosis. The development of a new methodology combining the allergenic molecule-based diagnosis with the multiplex microarray technology and allowing the analysis of multiple purified allergens in a single test represents an important improvement in the diagnosis of occupational (and nonoccupational) IgE-mediated allergy. This approach may help to discriminate between genuine allergy and latent sensitization.

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Conflicts of interest

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There are no specific conflicts of interest regarding the content of this article.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Moscato G, Pala G, Barnig C, *et al.*, European Academy of Allergy and Clinical Immunology. EAACI consensus statement for investigation of work-related asthma in nonspecialized centres. *Allergy* 2012; 67:491–501.

Consensus document to provide an operative protocol to allergists and physician dealing with asthma useful for identifying the individuals suspected of having work-related asthma to direct them to in-depth investigations in a specialized center.

2. Aasen TB, Burge PS, Henneberger PK, *et al.*, ERS Task Force on the Management of Work-related Asthma; EOM Society. Diagnostic approach in cases with suspected work-related asthma. *J Occup Med Toxicol* 2013; 8:17.

Excellent overview addressing the diagnostic approach of work-related asthma, based on recent studies and systematic literature reviews.

3. Quirce S, Salcedo G. The role of cross-reactive carbohydrate determinants in the diagnosis of occupational allergy. *Clin Exp Allergy* 2010; 40:962–964.
4. Cramer R. The crux with a reliable in vitro and in vivo diagnosis of allergy. *Allergy* 2013; 68:693–694.

Interesting editorial raising the strengths and limitations of available diagnostic tests for IgE-mediated allergy.

5. Maestrelli P, Boschetto P, Fabbri LM, Mapp CE. Mechanisms of occupational asthma. *J Allergy Clin Immunol* 2009; 123:531–542; quiz 543–544.
6. Gould HJ, Sutton BJ. IgE in allergy and asthma today. *Nat Rev Immunol* 2008; 8:205–217.

7. Baur X. A compendium of causative agents of occupational asthma. *J Occup Med Toxicol* 2013; 8:15.

Very useful review study focusing on the identification of causes of occupational asthma to provide an evidence-based compendium of allergenic and irritant etiological agents.

8. Quirce S, Sastre J. New causes of occupational asthma. *Curr Opin Allergy Clin Immunol* 2011; 11:80–85.
9. Lemiere C, Ameille J, Boschetto P, *et al.* Occupational asthma: new deleterious agents at the workplace. *Clin Chest Med* 2012; 33:519–530.

10. Beach J, Russell K, Blitz S, *et al.* A systematic review of the diagnosis of occupational asthma. *Chest* 2007; 131:569–578.

11. Quirce S, Fernández-Nieto M, Escudero C, *et al.* Bronchial responsiveness to bakery-derived allergens is strongly dependent on specific skin sensitivity. *Allergy* 2006; 61:1202–1208.

12. Malo JL, Cardinal S, Ghezzo H, *et al.* Association of bronchial reactivity to occupational agents with methacholine reactivity, sputum cells and immunoglobulin E-mediated reactivity. *Clin Exp Allergy* 2011; 41:497–504.

13. Hannu T, Lindström I, Palmroos P, *et al.* Prediction of obche wood-induced asthma by specific skin prick testing. *Occup Med (Lond)* 2013; 63:429–431.
- This study shows that positive SPT results to obche wood in symptomatic workers were good predictors of a positive SIC, and thus SIC with obche wood may be unnecessary in strongly sensitized workers.

14. Quirce S, Diaz-Perales A. Diagnosis and management of grain-induced asthma. *Allergy Asthma Immunol Res* 2013; 5:348–356.

Comprehensive and up-to-date review dealing with the current diagnosis and treatment of grain-induced asthma, emphasizing the role of cereal allergens as molecular tools to enhance diagnosis and management of this disorder.

15. Cummings KJ, Gaughan DM, Kullman GJ, *et al.* Adverse respiratory outcomes associated with occupational exposures at a soy processing plant. *Eur Respir J* 2010; 36:1007–1015.

16. Harris-Roberts J, Robinson E, Fishwick D, *et al.* Sensitization and symptoms associated with soybean exposure in processing plants in South Africa. *Am J Ind Med* 2012; 55:458–464.

Interesting study documenting the association between work-related bronchial and nasal respiratory symptoms and soy IgE-mediated sensitization.

17. Balbay EG, Karatas N, Arbak P, *et al.* Serum IgE antibodies against hazelnut in hazelnut processing workers. *Sci World J* 2012; 2012:108953.

18. Bernstein JA, Ghosh D, Sublett WJ, *et al.* Is trimellitic anhydride skin testing a sufficient screening tool for selectively identifying TMA-exposed workers with TMA-specific serum IgE antibodies? *J Occup Environ Med* 2011; 53:1122–1127.

19. Budnik LT, Preisser AM, Permentier H, Baur X. Is specific IgE antibody analysis feasible for the diagnosis of methylenediphenyl diisocyanate-induced occupational asthma? *Int Arch Occup Environ Health* 2013; 86:417–430.

Very informative study showing that isocyanate-specific IgE antibodies are not always detectable, but their presence can be predictive of isocyanate-induced asthma and supportive for the diagnosis of occupational asthma.

20. van Kampen V, de Blay F, Folletti I, *et al.* Evaluation of commercial skin prick test solutions for selected occupational allergens. *Allergy* 2013; 68:651–658.

Clinically relevant comparative study assessing the quality of selected HMW occupational allergens. High differences in potency and diagnostic performance of studied allergenic extracts were found.

21. van Kampen V, de Blay F, Folletti I, *et al.* EAACI position paper: skin prick testing in the diagnosis of occupational type I allergies. *Allergy* 2013; 68:580–584.

22. Bousquet J, Anto JM, Bachert C, *et al.* Factors responsible for differences between asymptomatic subjects and patients presenting an IgE sensitization to allergens: a GA2LEN project. *Allergy* 2006; 61:671–680.

23. Altmann F. The role of protein glycosylation in allergy. *Int Arch Allergy Immunol* 2007; 142:99–115.

24. Mari A. IgE to cross-reactive carbohydrate determinants: analysis of the distribution and appraisal of the in vivo and in vitro reactivity. *Int Arch Allergy Immunol* 2002; 129:286–295.

25. Kespohl S, Schlünssen V, Jacobsen G, *et al.* Impact of cross-reactive carbohydrate determinants (CCDs) on wood dust sensitization. *Clin Exp Allergy* 2010; 40:1099–1106.

26. Palacin A, Quirce S, Sanchez-Monge R, *et al.* Allergy to kiwi in patients with baker's asthma: identification of potential cross-reactive allergens. *Ann Allergy Asthma Immunol* 2008; 101:200–205.

27. Salcedo G, Quirce S, Diaz-Perales A. Wheat allergens associated with baker's asthma. *J Invest Allergol Clin Immunol* 2011; 21:81–92; quiz 94.
28. Raulf-Heimsoth M, Rihs HP, Rozynek P, *et al.* Quantitative analysis of immunoglobulin E reactivity profiles in patients allergic or sensitized to natural rubber latex (*Hevea brasiliensis*). *Clin Exp Allergy* 2007; 37:1657–1667.

29. Coutinho V, Vidal C, Garrido M, *et al.* Interference of cross-reactive carbohydrates in the determination of specific IgE in alcohol drinkers and strategies to minimize it: the example of latex. *Ann Allergy Asthma Immunol* 2008; 101:394–401.

30. Wiszniewska M, Zgorzelska-Kowalik J, Nowakowska-Swirta E, *et al.* Cross-reactive carbohydrate determinants in diagnostics of occupational allergy: preliminary results. *Allergy* 2010; 65:664–666.

31. Holzweber F, Svehla E, Fellner W, *et al.* Inhibition of IgE binding to cross-reactive carbohydrate determinants enhances diagnostic selectivity. *Allergy* 2013; 68:1269–1277.

This study deals with the important issue of clinically irrelevant IgE to CCDs, and how to eliminate the effect of IgE directed against these structures with a semisynthetic CCD blocker.

32. Sander I, Rozynek P, Rihs HP, *et al.* Multiple wheat flour allergens and cross-reactive carbohydrate determinants bind IgE in baker's asthma. *Allergy* 2011; 66:1208–1215.

33. Giangrieco I, Rafaianni C, Liso M, *et al.* Allergens in allergy diagnosis: a glimpse at emerging new concepts and methodologies. *Transl Med UniSa* 2012; 4:27–33.

34. Pahr S, Constantin C, Mari A, *et al.* Molecular characterization of wheat allergens specifically recognized by patients suffering from wheat-induced respiratory allergy. *Clin Exp Allergy* 2012; 42:597–609.

Excellent study describing the molecular characterization, recombinant expression, and purification of five wheat allergens. These allergens seem to be useful for development of serological tests, which allow the discrimination of different clinical manifestations of wheat allergy (respiratory vs. food allergy).

35. Olivieri M, Biscardo CA, Palazzo P, *et al.* Wheat IgE profiling and wheat IgE levels in bakers with allergic occupational phenotypes. *Occup Environ Med* 2013; 70:617–622.

Interesting study showing the usefulness of CRD of wheat allergy for identifying different clinical phenotypes of occupational allergy to wheat.

36. Green BJ, Cummings KJ, Rittenour WR, *et al.* Occupational sensitization to soy allergens in workers at a processing facility. *Clin Exp Allergy* 2011; 41:1022–1030.

37. Bernstein DI, Biagini RE, Karnani R, *et al.* In vivo sensitization to purified *Hevea brasiliensis* proteins in healthcare workers sensitized to natural rubber latex. *J Allergy Clin Immunol* 2003; 111:610–616.

38. Ebo DG, Hagendorens MM, De Knop KJ, *et al.* Component-resolved diagnosis from latex allergy by microarray. *Clin Exp Allergy* 2010; 40:348–358.

39. Schuler S, Ferrari G, Schmid-Grendelmeier P, Harr T. Microarray-based component-resolved diagnosis of latex allergy: isolated IgE-mediated sensitization to latex profilin Hev b8 may act as confounder. *Clin Transl Allergy* 2013; 3:11.

Study demonstrating the applicability of microarray-based CRD to discriminate between relevant latex allergy and latex sensitization.

40. Caballero ML, Ordaz E, Bermejo M, *et al.* Characterization of occupational sensitization by multiallergen immunoblotting in workers exposed to laboratory animals. *Ann Allergy Asthma Immunol* 2012; 108:178–181.

Usefulness of multiallergen immunoblotting in the molecular diagnosis of laboratory animal allergy, providing the sensitization profile for each allergic worker.