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A potential new therapy for cold urticaria and chronic idiopathic urticaria

To the Editor:

The report by Boyce¹ provides important information for understanding the pathophysiology of idiopathic acquired cold urticaria and possibly chronic idiopathic urticaria (CIU). A patient with idiopathic acquired cold urticaria was treated with omalizumab and had complete remission of cold urticaria symptoms. When she stopped the treatment, her symptoms returned, and when she resumed the treatment, the symptoms resolved. This remarkable response suggests a pivotal role of IgE in idiopathic cold urticaria, although it is unclear how IgE is involved in the mechanism of this condition. Proposals have included the presence of an IgE autoantibody² to a cold-dependent skin antigen resulting in cold-induced urticaria. However, to date, no putative skin antigen has been reported. It is my opinion that idiopathic acquired cold urticaria is caused by a variety of antigenic stimuli (eg, EBV²) that induce cold-sensitive immune complexes of IgG and/or IgM anti-IgE autoantibodies.^{2,3} Gruber et al³ established that idiopathic cold urticaria sera can contain IgG and IgM anti-IgE autoantibodies. These autoantibodies behaved like immune complexes and were capable of inducing histamine release *in vitro* and could passively transfer cold urticaria activity to human skin after cold challenge. By definition, idiopathic forms of acquired cold urticaria do not exhibit detectable cryoproteins. Nevertheless, it is my personal belief that IgG and IgM anti-IgE autoantibodies in idiopathic forms are probably immune complex cryoproteins, but their concentrations are low so they are not routinely detected. Removal and/or reduction of IgE in this patient could have interfered or competed with binding of IgE to circulating IgG/IgM anti-IgE autoantibodies, thereby preventing cold urticaria.

Nature can tell us a lot about disease if we are observant. For example, secondary forms of cold urticaria may be caused by cryoproteins (ie, IgG⁴ cryoglobulins and IgG-IgM² mixed immune complexes) that have the capacity to passively transfer cold urticaria activity to human skin after cold challenge. Some of these cryoproteins were able to activate complement,^{4,5} suggesting a role of anaphylatoxin-induced histamine release. It would not be surprising if studies in the future determine that these cold urticaria-associated cryoproteins are also immune complexes with anti-IgE functionality.

The observations for cold urticaria are remarkably similar to our current understanding of CIU with IgG

anti-IgE and/or anti-IgFcεRI autoantibodies.⁶ These autoantibodies are IgG₁ and IgG₃ and are capable of complement activation. The take home message may be that studies on cold urticaria can improve our understanding of the pathophysiology of CIU. Consequently, one might speculate that omalizumab may be beneficial in treatment of CIU, especially the subpopulation with circulating anti-IgE and/or anti-IgFcεRI autoantibodies.

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Reply

To the Editor:

I thank Dr Wanderer¹ for his thoughtful comments on the case report in question.² The dramatic improvement experienced by the patient referenced in the report suggests a role for IgE and FcεRI in her particular case. As noted, previous studies of small numbers of patients have yielded conflicting data on the roles of cryoproteins of the IgG and IgM classes in the pathogenesis of cold urticaria. In some of these instances, IgE or FcεRI may prove to be the target of cold-reactive antibodies of other isotypes. However, some reports indicate a direct role for IgE.^{3,4} The heterogeneous nature of these findings suggests that it is unlikely that a single antibody-based mechanism accounts for the vast majority of cases of cold urticaria, chronic idiopathic urticaria, or both. Nevertheless, carefully conducted controlled studies of sufficient sample size using anti-IgE may permit elucidation of mechanisms that are respectively FcεRI-dependent, complement-dependent, and dependent on other pathways leading to the final common endpoint of urticaria.

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Indoor allergen assessments: A call for universal standards

To the Editor:

Although fungi are common causes of well described illnesses, as reported in the position paper authored by Bush et al¹ on behalf of the Academy, various professionals and the legal system have promoted mold as a cause of nonspecific ailments in the general population. This has resulted in disagreement and debate among members of the medical community and other professionals, as reflected by the number of letters to the editor, published in the September issue of the Journal, rebutting the position of the Academy regarding the topic.

The high prevalence of allergies in developed countries contributes to the increased public concern about indoor air quality (IAQ). However, the general fear of mold exposure has resulted in an increase in demand for mold assessments, whereas more common and clinically relevant indoor allergens are not typically monitored during IAQ assessments. In addition, although a number of professional organizations provide training and certification for mold inspection and IAQ assessments, expertise and training to monitor and measure other indoor allergens are insufficient. Likewise, certification is not available.

Reference techniques to measure indoor allergens are ELISAs, initially developed at the University of Virginia,² which have been used in many research studies. Although allergen testing has been limited to research settings in the past, the number of commercial laboratories that now offer such testing is increasing in anticipation of an increase in public demand. However, few protocols are recommended for sampling and analysis, and accreditation/quality assurance programs are lacking.

An experimental proficiency program identified a large analytical variation in the measurement of indoor allergens.³ Therefore, standard laboratory operating procedures for sample preparation and analysis and laboratory quality assurance/accreditation programs are necessary. Several groups and organizations also are currently developing equipment for sample collection and producing antibodies to various indoor allergens and antigens and using them

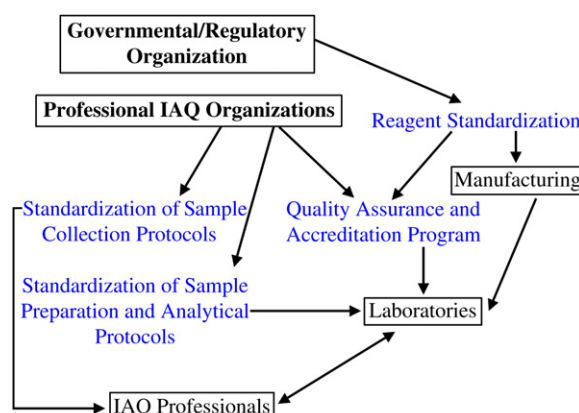


FIG 1. A governmental/regulatory organization should implement rules for reagent standardization and manufacturing. IAQ organizations should provide directives for sample collection and analysis, as well as the certification and supervision of IAQ professionals in the area of indoor allergens.

to develop assays for research and commercial testing purposes, including the manufacture of kits for home use.

To overcome properly the current caveats in the area of allergen testing, a governmental or not-for-profit regulatory organization should establish a program to assure consistency in the manufacturing of the reagents used in allergen analysis. This organization should also collaborate with professional IAQ organizations to implement accreditation/quality assurance programs for laboratories that perform allergen testing. The professional IAQ organizations should supervise the laboratory accreditation/assurance programs and develop standard protocols for sampling and analysis. The importance of indoor allergens should be emphasized in the various training programs currently administered by professional organizations to certify individuals in the area of IAQ (Fig 1).

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Editor's note: There is no accompanying reply to this correspondence.

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