

Revisiting Desensitization and Allergen Immunotherapy Concepts for the International Classification of Diseases (ICD)-11



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Allergy and hypersensitivity intervention management procedures, such as desensitization and/or tolerance induction and immunotherapy, have not been pondered up to now in the content of International Classification of Diseases (ICD) context because the focus has been on prioritizing the condition

implementations. Tremendous efforts have been devoted to implementing allergic and hypersensitivity conditions in the forthcoming ICD-11. However, we consider that it is crucial now to have nomenclature and classification universally accepted for these procedures to be able to provide scientifically consistent

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proposals into the new ICD-11 platform for the best practice parameters of our specialty. With the aim of promoting a harmonized comprehension and aligning it with the ICD-11 revision, we have reviewed the definitions and concepts currently used for desensitization and/or tolerance induction and immunotherapy. We strongly believe that this review is a key instrument to support the allergy specialty identity into the ICD-11 framework and serves as a platform to perform positive quality improvement in clinical practice. © 2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;4:643-9)

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REASONS FOR REVISITING OLD CONCEPTS

Rationale for revisiting desensitization and immunotherapy concepts in the International Classification of Diseases

Concepts in medicine and our understanding of the immune system have evolved over the last decade having implications in both research and clinical practice. This development has led to a growing number of products commercially available for diagnosis purposes as well as progresses in interventional management and/or prevention procedures, such as allergen immunotherapy (AIT) and immune modulation drugs, with an increasing number of new products registered.

Medical and scientific literature has been using the terms “desensitization” and “immunotherapy” in many contexts. Conceptually, immunotherapy may encompass prophylactic and therapeutic approaches. It may involve the administration of antibodies, antibody fragments, peptides of antigens, polypeptide allergens, immunosuppressants, immunomodulators, nucleic acids, small molecules, and even immune system cells, and can be used to treat cancers, autoimmune diseases, organ transplantation, heart failure, and allergic conditions.¹ Because concepts are changing, it is an ideal time to review semantics and the classification paradigms to adopt a clear, intuitive, product-based nomenclature and reach a harmonized point of view.

The International Classification of Diseases (ICD), supported by the World Health Organization (WHO), is the most accepted and widely used classification and/or coding system worldwide, utilized in both research and clinical practice.^{2,3} It supports mapping plans for health management and prevention strategies, allocation of resources, and generation of epidemiological data. Because the ICD codes permit the tracking of many diagnoses and support the medical decision making, implementation of new concepts in the ICD framework can consequently have economic impacts.

Misconceptions and underrepresentation of common allergy interventional management and/or prevention procedures in health care coding systems can contribute to a lack of recognition of their importance for health care planning, allocation of resources, and reimbursement, and inhibit quality clinical research from being performed.

With the aim of promoting a harmonized comprehension and aligning it with the ongoing ICD-11 revision, we review the definitions and concepts currently used for allergy desensitization and/or tolerance induction and AIT.

The action-plan background to increase the visibility of allergic and hypersensitivity conditions in the ICD-11

Efforts to update allergy and hypersensitivity conditions in the ICD-11 revision started in 2013 after anaphylaxis and many other allergic diseases were found to be misclassified or underclassified in both ICD-10 and ICD-11 β -draft frameworks.^{4,5} The strategy used was mainly sustained by a tripartite action plan to (i) provide scientific and technical evidence for the need for changes, (ii) update the allergy codes in ICD-11 β -draft in collaboration with the WHO representatives in charge of the revision, and (iii) construct an appropriate high-level classification structure for allergy and hypersensitivity conditions. The actions taken have followed the WHO timeline and the recommendations of providing a scientific basis to ensure quality, comparability, and consistency.

Our actions represent the collaboration of the major allergy and/or immunology professionals academies, composed of the European Academy of Allergy and Clinical Immunology; the World Allergy Organization; the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; the Asian Pacific Association of Allergy, Asthma and Clinical Immunology; and the Latin-American Society of Allergy, Asthma and Immunology; and all the steps have been published.^{3,5-7} The main outcome of this process was the construction of the “Allergy and hypersensitivity conditions” parent chapter in the ICD-11 guided by the WHO ICD-11 revision representatives, with whom we have been keeping bilateral discussions.

Allergy and hypersensitivity intervention management procedures, such as desensitization and/or tolerance induction and immunotherapy, have not been pondered up to now in the ICD context because we have been prioritizing the implementations of allergic and hypersensitivity condition codes. However, we consider that it is crucial now to have nomenclature and classification universally accepted for these procedures to be able to provide scientific consistent proposals into the ICD-11 platform.⁸

Current status of the allergy management procedures in the ICD-11 β -draft

Considering the intensive preparation of the ICD-11 and the fact that the revision process is constantly updated, we decided to search for essential allergy interventional management and/or prevention procedures in daily clinical practice named desensitization and AIT in the ICD-11 β phase system.⁸ This process supports the submission of new proposals into the ICD-11 framework and tracks changes in favor of our specialty. For that, we first prepared a list of the main allergy and hypersensitivity management procedures currently in use in clinical practice, initially validated by the first and last authors and then reviewed by the co-authors. The search procedure had an online basis considering the ICD-11 β phase foundation platform (August 2015 version). We did not include for this search allergy diagnostic procedures because they are covered by a different project.⁹ We decided to search the general terms “desensitization” and “immunotherapy” because more specific terms such as “allergen immunotherapy” or “specific immunotherapy” were not available in the current ICD-11 β phase system.

When searching for the term “desensitization” in the ICD-11 β phase foundation, the system addresses 2 conditions:

ICD-11 Beta Draft (Foundation)	
Search DESENSITIZATION [Advanced Search]	Foundation Linearizations Contributions Info
"Factors influencing health status and contact with health services" chapter	Conditions associated with interventions
	Care involving use of rehabilitation procedures
	Desensitization to allergens Parent(s): Conditions associated with non surgical interventions not involving intervention devices Synonyms: desensitization to allergens, desensitization Etiology Type: Allergic state (disorder)
	Need for certain specified prophylactic measures
	Prophylactic immunotherapy Parent(s): need for certain specified prophylactic measures Narrower Terms: administration of immunoglobulin *, administration; prophylactic, immune sera (immunoglobulin) prophylactic; administration of gamma globulin prophylactic; administration of immune sera (immunoglobulin)
	Other prophylactic chemotherapy
ICD-11 Beta Draft (Foundation)	
Search IMMUNOTHERAPY [Advanced Search]	Foundation Linearizations Contributions Info
"Factors influencing health status and contact with health services" chapter	Conditions associated with non surgical interventions
	Need for certain specified prophylactic measures
	Prophylactic immunotherapy Parent(s): need for certain specified prophylactic measures Narrower Terms: administration of immunoglobulin *, administration; prophylactic, immune sera (immunoglobulin) prophylactic; administration of gamma globulin prophylactic; administration of immune sera (immunoglobulin)
	Conditions associated with non surgical interventions not involving intervention devices
	Chemotherapy other than for neoplasm
"Diseases of the nervous system" chapter	Paraneoplastic and autoimmune disorders of the nervous system
	Autoimmune encephalopathy Synonyms: Hashimoto's encephalopathy, steroid-responsive-encephalopathy-associated with autoimmune thyroiditis, immunotherapy responsive encephalopathy , autoimmune dementia

FIGURE 1. Searching "desensitization" and "immunotherapy" in the ICD-11 β -draft foundation (August 2015 version).

"desensitization to allergens" and "need for certain specified prophylactic measures," both classified under the "Factors influencing health status and contact with health services" chapter. However, as shown in Figure 1, "desensitization to allergens" is placed as a synonym of desensitization generically and "prophylactic immunotherapy" receives as narrow terms "administration of immunoglobulin, immune sera (immunoglobulin) prophylactic, administration of gamma globulin prophylactic, and administration of immune sera

(immunoglobulin)." On the other hand, the search for the term "immunotherapy" resulted in the following conditions: "prophylactic immunotherapy," "immunotherapy responsive encephalopathy," and as a narrow term of "chemotherapy other than neoplasm."

The results of this search lead us to 2 main conclusions: (i) the modern concepts used by the allergy community for these allergy interventional management and/or prevention procedures that are included in regular continuous medical educational programs in

TABLE I. Allergy and hypersensitivity intervention management procedures for the ICD-11 “Conditions associated with interventions” chapter**Allergic and hypersensitivity conditions associated with interventions: desensitization and/or immunotherapy**

Groups of allergic and hypersensitivity conditions (ICD-11 β phase foundation, August 2015 version)	Allergic and hypersensitivity conditions subtitles*	Definitions of allergy interventional management and/or prevention procedures
Allergic or hypersensitivity disorders involving the respiratory tract	• Allergic rhinitis (AR)* • AR due to allergens • Local AR • Allergic aspergillus rhinosinusitis • Allergic bronchopulmonary aspergillosis • Allergic asthma (AA)*	Allergen immunotherapy (AIT) is the stimulation of the immune system with the administration of gradually increasing doses of the substance and/or allergen to which the patient is allergic. Indicated for the treatment of moderate-to-severe intermittent or persistent symptoms of AR, especially in those who do not respond well to pharmacotherapy. Allergen extracts are available for grass, tree, and weed pollens; mold; house dust mite, cockroach, and animal dander. Several double-blind, placebo-controlled trials and meta-analysis have confirmed that AIT is of value in patients with AR and patients with AA associated or not with AR.
Allergic or hypersensitivity disorders involving the eye	• Allergic conjunctivitis (AC)* • Vernal keratoconjunctivitis (VKC) • Atopic keratoconjunctivitis	AIT is effective in reducing total and individual ocular symptom scores in participants with allergic rhinoconjunctivitis and AC. AIT results in a significant reduction of symptoms score and medication use in suitably selected cases of VKC.
Allergic or hypersensitivity disorders involving skin and mucous membranes	• Allergic contact urticaria • Oral allergy syndrome • Acute urticaria due to IgE-mediated allergy • Atopic eczema (AD)*	There is still controversy about the potential role of AIT as a therapeutic intervention for patients with AD and aeroallergen sensitivity. Case reports and smaller cohort and randomized controlled studies showed some positive effects of AIT on skin conditions. AIT seems to have positive response in cases of oral allergy syndrome and other skin IgE-mediated allergies, but still lacks strong evidence.
Drug hypersensitivity	• Exanthematic drug eruption* • Drug-induced urticaria, angioedema and anaphylaxis* • Samter syndrome*	Drug hypersensitivity desensitization or drug-tolerance induction is known as a procedure used to induce temporary state of tolerance to a compound responsible for an allergic and/or hypersensitivity reaction. It is done by the administration of increasing doses of the causative medication over a short period of time (from several hours to few days), until the total cumulative therapeutic dose is achieved and well tolerated.
Food hypersensitivity	• Food-induced urticaria, angioedema, anaphylaxis* • IgE-mediated food-induced gastrointestinal hypersensitivity* • Oral allergy syndrome*	Specific oral tolerance induction consists of administering increasing doses of the offending food to the patient, aiming to reach clinical tolerance. Various procedures concerning up-dosing, maintenance dose, and in- or outpatient protocols have been proposed. Food immunotherapy can induce desensitization that would require continuous exposure. Whether food immunotherapy can induce long-term tolerance in which therapy can be discontinued indefinitely is unknown.
Hymenoptera and other insects hypersensitivity or allergy	• Anaphylaxis due to insect venom* • Cutaneous reactions to hymenoptera venom • Large local reaction to hymenoptera venom*	Hymenoptera venom immunotherapy (VIT) is indicated both in children and adults with a history of large local reaction or severe systemic reactions including respiratory and cardiovascular symptoms and documented sensitization to the respective insect with either skin tests and/or specific serum IgE tests.

*Target for AIT and/or desensitization.

allergy meetings and congresses are not universally recognized or are not all accepted as having the current same meanings used in the clinical practice of the allergists; (ii) the terms as they currently appear in the ICD-11 β -draft (August 2015 version) do not have the same meanings as they do in the clinical practice of allergists; (iii) the concepts of “desensitization” and “immunotherapy”

should have a broad view to allow different specialties to accept the definitions and to understand the differences.

The outcomes of this search process allowed us to support the need of reviewing the desensitization and/or tolerance induction and immunotherapy concepts, updated by current knowledge,^{1,10-36} and to make proposals for some changes.

TABLE II. Global view of concepts and applicability of allergy and hypersensitivity intervention management procedures

Allergy and hypersensitivity intervention management procedures	Current definitions	Applicability of immunotherapy and desensitization procedures
Immunotherapy	• Treatment for disease by inducing or suppressing immune response • Therapy designated to produce immunity to a micro-organism or a transplanted organ or to induce resistance and/or tolerance by the immune system • Any approach or manipulating a patient's immune system to treat or cure a disease • General term encompassing active and passive immunization • Allergen immunotherapy is the class of therapies that aims to induce immune tolerance to allergens	Allergen immunotherapy: • Allergic rhinitis • Allergic asthma • Allergic conjunctivitis • Allergic rhinoconjunctivitis • Atopic eczema • Immune-mediated food allergy • IgE-mediated hymenoptera venom large-local reaction and/or anaphylaxis Other immunotherapies: • For infectious diseases: Immunization (vaccines) Use of anti-infective agents (antibiotics, antifungal, and antiparasitic agents) • For autoimmune diseases, organ transplantation: Use of immunosuppressor agents Biological and monoclonal agents • For cancers: Use of chemotherapy agents Nonallergen immunotherapy Monoclonal and biological agents • For primary immunodeficiencies: Immunization (vaccines) Use of anti-infective agents (antibiotics, antifungal, and antiparasitic agents) Monoclonal and biological agents Immunoglobulins • For allergic and hypersensitivity diseases: Biological and monoclonal agents Use of immunosuppressor agents Use of pro/pre/symbiotics
Desensitization	Desensitization is a method, procedure, or approach used to induce temporary state of tolerance to a compound responsible for an allergic and/or hypersensitivity reaction	• Drug hypersensitivity: Allergic drug hypersensitivity Nonallergic hypersensitivity

REVISITING DESENSITIZATION AND IMMUNOTHERAPY CONCEPTS FOR THE ICD-11

Desensitization and/or tolerance induction and allergy immunotherapy for allergists

In general medicine, desensitization and/or tolerance induction is a method used to reduce or eliminate an organism's reaction to a substance or stimulus (eg, use of antibiotics or antiparasitic agents). For allergists, desensitization and/or tolerance induction is a method, procedure, or approach used to induce the temporary state of tolerance to a compound responsible for an allergic hypersensitivity reaction. It covers respiratory, ocular, and cutaneous allergic conditions, venom, drug, and food allergies (Table I). However, considering the overly general term “immunotherapy” per se, it covers a myriad of pharmacological and/or biological compounds targeted to a broader range of conditions (Table II) and is not limited to the context of allergy. This huge umbrella concept covering many classes of pharmacological and biological formulations for treatment or prophylaxis of several conditions should be addressed so as to highlight the differences to allergic diseases.

From the point of view of the allergy specialty,¹ we consider the need of a unidirectional definition based on the fact that all

AITs are desensitization procedures. However, the desensitization and/or tolerance induction procedures can be used with allergens (procedure named allergen immunotherapy) or other products not made of allergens, procedure named allergy immunotherapy (eg, the anti-IgE omalizumab). It can address both true allergic hypersensitivity conditions, such as IgE-mediated food-induced anaphylaxis, and non-immune-mediated hypersensitivity conditions (eg, some drug hypersensitivity conditions). In this way, the concepts concerning “desensitization” and “tolerance induction” should be reviewed because these terms have been in use in similar contexts and raise the question about which situations these terms would fit better. Conceptually, “desensitization” has a degree of mechanistic meaning and should be used in cases where the sensitization has been proved, and the treatment is used to manage immune-mediated allergic hypersensitivity reactions.

On the other hand, the term “tolerance induction” can capture all hypersensitivity conditions, both immune and non-immune-mediated conditions. Immunologists however would use “tolerance induction” when regulatory T cells are induced, and in the case of allergy, the immune system has lost its capacity

to “ignore” allergens such as pollens and cat, but is still able to fight bacterial pathogens. We are aware of these differences, but to avoid conceptual misunderstandings between nonallergists and nonphysicians in the ICD context, we always decided to link the terms *desensitization* and *tolerance induction* across the current paper.

AIT was introduced by Leonard Noon 103 years ago and is the only potential disease-modifying treatment for allergic subjects.^{10,37} Significant progress has been made in terms of proving its efficacy and safety, standardizing the production of natural allergens and modifying them to elicit better therapies. Immunotherapy for treating allergy (now named allergy immunotherapy) has received various terms, such as allergen-specific immunotherapy, specific immunotherapy, AIT, desensitization, allergen shots, and allergy immunotherapy. Because there is a need for uniformity in naming, and because immunotherapy can include both allergen-specific and nonspecific approaches, the academies have proposed using the term “allergen immunotherapy,” universally used to refer to the class of therapies that aim to induce tolerance to allergens.¹ AIT has been indicated for many allergic conditions so far (Table I), and allergen extracts are commercially available for house dust mite, mold, furry animals, cockroach, and grass, tree, and weed pollens. Although AIT has been performed mainly in IgE-mediated respiratory allergies, increasing lines of evidence have shown its efficacy in other allergic and/or hypersensitivity diseases, such as in atopic eczema.^{23,24} The terms “subcutaneous immunotherapy” and “sublingual immunotherapy” are often used to describe the route of AIT administration and are well accepted in clinical practice. Several other administration routes for AIT are in use or in development: oral, nasal, epicutaneous, intradermal, bronchial, and intralymphatic.

Allergy and hypersensitivity intervention management procedures for the ICD-11 “Conditions associated with interventions” chapter

With the aim of actively supporting changes in favor of our specialty, we intended to use the results of the above search to base new proposals to be submitted into the ICD-11 platform.⁹ For this purpose, we first constructed the structures with all key words and definitions able to fit the ICD content model (Tables I and II). Each of the key words has been submitted into the ICD-11 β -draft platform following the WHO guidance, after exposed to colleagues (co-authors) discussion, and supported by contemporary guidelines in the field. For the first time, the term AIT has been implemented into the ICD framework (ICD-11 β -draft September version) as a result of the allergy academies collaboration efforts. However, because the ICD-11 revision process is not completely set, we will undergo field trial validation and the WHO approval.

More than proving that the allergy and hypersensitivity intervention management procedures review presented here is a key instrument to support the allergy specialty identity into the ICD-11 revision, we strongly believe that this allergy and hypersensitivity intervention management procedures review is an opportunity to aggregate data to perform positive quality improvement in clinical practice. Whether or not all countries will move to the ICD-11 after general assembly in 2018 should not hamper the dissemination of this document, as it supports our specialty worldwide.

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