

ORIGINAL ARTICLE

Airway Diseases

National clinical practice guidelines for allergen immunotherapy: An international assessment applying AGREE-II

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Edited by: Thomas Bieber

Abstract

Background: Since 1988, numerous allergen immunotherapy guidelines (AIT-GLs) have been developed by national and international organizations to guide physicians in AIT. Even so, AIT is still severely underused.

Abbreviations: AAAAI, American Academy of Allergy, Asthma and Immunology; ACAAI, American College of Allergy, Asthma and Immunology; AGREE II, Appraisal of Guidelines for Research & Evaluation II; AIT, allergen immunotherapy; AIT-GL, allergen immunotherapy guideline; ARIA, Allergic Rhinitis and its impact on Asthma; EAACI, European Academy of Allergy and Clinical Immunology; FDA, United States Food and Drug Administration; GINA, Global Initiative on Asthma; GRADE, Grading of Recommendations, Assessment, Development and Evaluations; HDM, house dust mite; NICE, National Institute for Health and Care Excellence; RCT, randomized controlled trial; SCIT, subcutaneous immunotherapy; SIGN, Scottish Intercollegiate Guidelines Network (www.sign.ac.uk/); SLIT, sublingual immunotherapy; WAO, World Allergy Organization; WHO, World Health Organization.

Objective: To evaluate AIT-GLs with AGREE-II, developed in 2010 by McMaster University methodologists to comprehensively evaluate GL quality.

Methods: Allergist, from different continents, knowledgeable in AIT and AGREE-II trained were selected into the project team. The project received methodologists' guidance. AIT-GLs in any language were sought from 1980 to 2016; AIT-GLs were AGREE II-evaluated by at least 2 team members, independently; discrepancies were resolved in a second round, by team discussion or methodologists' consulting.

Results: We found 31 AIT-GLs (15 post-2010), ranging from local consensus reports to international position papers (EAACI, AAAAI-ACAAI, WAO). Pre-2010 GLs scored 1.6-4.6 (23%-67%) and post-2010 GLs scored 2.1-6 (30%-86%), on a 7-point Likert scale. The highest scores went to: German-Austrian-Swiss (6.0), Mexican (5.1), and the AAAAI/ACAAI AIT-GL (4.7). These were also the only 3 GLs that received "yes" of both evaluators to the item: "I would recommend this GL for use." The domains of "Stakeholder involvement" and "Rigor of Development" only scored 3/7, and "Applicability" scored the lowest. Strikingly, newer GLs only scored clearly better in "Editorial independence" and "Global evaluation."

Conclusions: In AIT-GLs, there is still a lot of room for improvement, especially in domains crucial for the dissemination. For some GLs, the "Scientific rigor" domain flawed. When resources are limited, transculturizing a high-quality GL might be preferable over developing a GL from zero. Our study and AGREE-II could help to select the best candidate.

Clinical Implications: We here evaluate allergen immunotherapy guideline (AIT-GL) quality. Only high-quality AIT-GLs should be consulted for AIT management decisions. In low-resource settings, transculturization of these is preferred over developing low-quality guidelines.

KEYWORDS

AGREE II instrument, allergen immunotherapy, allergic rhinitis, subcutaneous immunotherapy, sublingual immunotherapy

1 | INTRODUCTION

Allergen immunotherapy (AIT), as a causal treatment for IgE-mediated allergic diseases, such as rhinoconjunctivitis, allergic asthma, venom allergy, and in some regions atopic dermatitis, has a history of more than a century. In the course of its developing process, details on AIT practice have evolved differently in various parts of the globe, with a striking difference in the practice of AIT, especially subcutaneous AIT (SCIT), between the American and European continent,^{1,2} both with their supporting evidence. With the growing number of physicians administering AIT, subcutaneous and lately also sublingually (SLIT), several national and regional allergy societies have tried to give some guidance on the practice of AIT since the 1980s.³ Depending on the local regulatory situation and extract availability, in some regions the American school and in others the European school of the practice of AIT have been found to be more suitable. However, in general, AIT is still severely underused. In 2009, the first World Allergy Organization (WAO) consensus was

published on SLIT,⁴ but no such global consensus document for SCIT exists till now. Several AIT guidelines exist at national level; however, some have a more solid evidence-base than others.

With the ever-growing number of guidelines in any medical field being developed over the past decades, in 2010 methodologists from the McMaster University in Hamilton (Ontario, Canada) developed AGREE II (Appraisal of Guidelines for Research & Evaluation II^{5,6}) a comprehensive tool to evaluate guideline quality, in the broadest sense of the word. The primary goal of a guideline is improving the quality of care in a certain area. As such, the quality of a guideline should be evaluated at population level, rather than at the individual physician's level. Consequently, a guideline should be considered of high quality if it gives adequate evidence-based guidance on how to manage a particular medical condition, but also if it has an adequate strategy of how to be disseminated and applied. The AGREE II guidelines' appraisal tool encompasses all this and evaluates guidelines in 6 domains: (1) Scope and purpose; (2) Stakeholder involvement; (3) Rigor of development; (4) Clarity of presentation, (5)

Applicability, and (6) Editorial Independence. At the end, the AGREE II tool asks the reviewer to rate the overall quality of the guideline and to state whether the guideline would be recommendable for local use. The first guideline in the allergy world adhering to the AGREE II principals and following the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system for evidence evaluation was the Allergic Rhinitis and its impact on Asthma (ARIA) 2010 update, which includes a complete evaluation at that time-point of the evidence on AIT for allergic rhinitis and for asthma.⁷

In this article, we aim to evaluate guidelines specifically focused on allergen immunotherapy (AIT-GLs) with AGREE-II, to distinguish between AIT-GLs with a higher and a lower AGREE II quality score. This leads us to suggest which AIT-GLs might be best to adhere to, or might be most suitable for local adaptation in countries where no high-quality, evidence-based AIT guidelines exist. Finally, our study also shows in which domains existing AIT guidelines still flaw and could be improved in the future.

Guidelines on allergic rhinitis or asthma, which mention AIT, but apart from it analyze many other treatment options, were not included in this analysis, as their scope goes beyond the sole evaluation of AIT. As such, the ARIA^{7,8} and the Global Initiative on Asthma (GINA)⁹ guidelines are not included in the here presented evaluation.

2 | METHODS

The project team consisted of allergists from different continents, knowledgeable in AIT. Moreover, several of them had already worked with AGREE II in the evaluation of other guidelines. All team members were trained in AGREE II during the starting phase of the project, with the guidance of methodologists.

MEDLINE and Embase were searched from January 1980 until October 2016 using logical combinations of the following terms: [allerg* AND immunotherapy OR desensitization] AND [guideline OR practice parameter OR position paper OR statement OR consensus]. As the team consisted of allergists from various parts of the world, language was not a restriction. When needed, GLs were translated into English. The collection of AIT-GLs was cross-checked and completed against those identified in an active search by team members contacting local and regional AIT experts to also identify those papers published in gray literature. In online-discussion rounds, the investigators selected the GL papers from among the found articles. Each selected publication was scored on 23 items, divided into the 6 domains of AGREE II, related to GL content, presentation, involved authors, declaration of conflict of interest, among others. In a first round, each AIT-GL was AGREE-II-evaluated by 2 independent reviewers, scoring each item on an ordinal Likert-type scale from 1 to 7, and sustaining the given score with a detailed explanation, for example, where the item could be found in the GL or what was missing; discrepancies were resolved in a second round in which mutual evaluations and their reasoning were sent back to both reviewers. After that, unresolved issues were decided in a third round by team discussion or methodologists' consulting. After

receiving feedback from US AIT experts regarding the medium scores of some of their AIT guidelines, the project team decided to conduct a final valuation, with the same team members evaluating all 3 versions (2003, 2007, and 2011) of the AAAAI/ACAAI guidelines (American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology). Six team members re-assessed them: 2 team members reviewed domains 1-2 of all 3 AAAAI/ACAAI guidelines, 2 team members reviewed domains 3-4 of all 3 AAAAI/ACAAI guidelines, and 2 team members reviewed domains 4-6. Special care was taken to strictly adhere to the methodologists' recommendations and to score in the same trend as other AIT-GLs had been scored.

Total scores were calculated per guideline, taking the mean of the 6 scores per domain. Moreover, for each domain the median score (intergroup quartiles) from all GLs was calculated, grouping GLs from before the publication date of AGREE II (2010) and GLs published from 2010 onward. The differences between both groups of GLs (pre-2010 and 2010-onward) were analyzed with the Wilcoxon rank sum test (Mann-Whitney U test): As AGREE II evaluates each item on an ordinal scale (from 1, worst, to 7, best score), we used a nonparametric test considering $P < .05$ a statistically significant difference.

3 | RESULTS

We found 31 publications of AIT-GLs, see Table 1. Fifteen of them were guidelines published from 2010 onward.

The papers covered the range from local consensus reports to position papers issued by regional and global allergy organizations, such as the European Academy of Allergy and Clinical Immunology (EAACI), the joint council of the American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI), and the World Allergy Organization (WAO). Some smaller consensus documents, written in the local language, were translated into English before evaluation. The total scores of the pre-2010 GLs ranged from 1.6 to 5.2 and of the 2010-onward GLs from 2.1 to 6 (ordinal scoring from 1-7), see Figure 1. The best evaluations went to the German AIT-GL (6.0) followed by the Mexican AIT-GL (5.1) and the latest versions of the AAAAI/ACAAI guidelines (4.6-4.7). These were also the only 3 GLs that received an affirmative answer from both evaluators to the last item: "I would recommend this GL for use."

In Figure 2, the median evaluations per domain are depicted, comparing the pooled domain scores from the older and the newer AIT-GLs. Differences in domain scores between the newer and pre-2010 GLs ranking were detected for *Scope and purpose* ($P < .05$), *Rigor of development* ($P < .05$), *Editorial independence* ($P < .01$) and *Global evaluation* ($P < .001$). In general, the domains of *Stakeholder involvement* and *Rigor of development* scored low, and *Applicability* very low in all GLs. The AIT-GLs that best scored per domain were as follows: (1) *Scope and purpose* (German GL 2015), (2) *Stakeholder involvement* (German GL 2015), (3) *Scientific*

TABLE 1 Guidelines and consensus papers included in this review

Specific guidelines on allergen immunotherapy				
	Year	Evidence model	No of RCTs SCIT/SLIT ^a	No of meta-analyses ^b
EAACI 1988 Workshop report ³	1988	None	8/0	0
WHO consensus ¹⁰	1989	None	±8/0	0
EAACI Position Paper 1993 ¹¹	1993	None	28/6	0
Australasian guidelines on SCIT for asthma ¹²	1997	None	5/0	2
WHO Position Paper 1998 ¹³	1998	None	11/0	0
EAACI Local Immunotherapy ¹⁴	1998	None	x/4	0
AAAAI/ACAAI 1 st paper ¹⁵	2003	Shekelle ¹⁶	36/7	4
Serbian guidelines ¹⁷	2005	None	12/28	3
European Guidelines SCIT ¹⁸	2006	None	8/x	0
EAACI noninjection IT ¹⁹	2006	None	x/15	0
Canadian guidelines ²⁰	2006	None	4/10	0
AAAAI/ACAAI Practice parameters ²¹	2007	Shekelle ¹⁶	62/14	4
WAO SLIT Position Paper ⁴	2009	None	16/72	7
Indian Guidelines on AIT ²²	2009	None	20/9	5
Chec guidelines ²³	2009	None	14/3	2
Brazilian GLs ²⁴	2001	None	1/0	0
Argentinean guidelines ²⁵	2010	None ^d	No review	0
AAAAI/ACAAI Practice parameters ²⁶	2011	Shekelle ¹⁶	65/9	7
British guidelines ²⁷	2011	SIGN	15/25	6
Mexican guidelines ²⁸	2011	GRADE	55/18	5
Chinese expert consensus on AIT for AR ²⁹	2011	Consensus	?	?
Finnish update on current care guidelines: AIT ³⁰	2012	Article in Finnish. Data from abstract.		
Lithuanian guidelines on AIT ³¹	2012	Guiding review article	2/0	0
Guiding principles of SCIT for AR in Japan ³²	2013	Modified Shekelle	12/x	1
Russian GL(personal file shared by colleagues)	2013	SIGN	No references in the file	?
Polish position paper on SLIT ^{33,34}	2014	None	x/17	7
SLIT Spanish guideline ³⁵	2014	Oxford Center for Evidence Based Medicine	x/33	9
Spanish allergists' consensus on IT in polysensitized patients ³⁶	2014	Consensus with Delphi method	0/0; review and opinion articles	0
WAO SLIT position paper update 2013 ³⁷	2014	None	x/26	10
German speaking countries guideline ³⁸	2014	Modified Shekelle	22/14 ^c	4
Guiding principles of SLIT for AR in Japan ³⁹	2016	Modified Shekelle	x/15	10

AAAAI, American Academy of Allergy, Asthma and Immunology; AC, allergic conjunctivitis; ACAA, American College of Allergy, Asthma and Immunology; AIT, allergen specific immunotherapy; AR, allergic rhinitis; EAACI, European Academy of Allergy and Clinical Immunology; FDA, United States Food and Drug Administration; GL, guideline; GRADE, Grading of Recommendations Assessment, Development and Evaluation (<http://www.gradeworkinggroup.org/>); HDM, house dust mite; IT, immunotherapy; NICE, National institute for Health and Care excellence, RCT, randomized controlled trial; SCIT, subcutaneous immunotherapy; SIGN, Scottish Intercollegiate Guidelines Network (www.sign.ac.uk/); SLIT, sublingual immunotherapy; WAO, World Allergy Organization; WHO, World Health Organization.

^aNumber of randomized controlled trials on AIT that were reviewed for the guideline subcutaneous AIT/sublingual AIT.

^bNumber of systematic reviews and/or meta-analysis on allergen immunotherapy cited in the guideline.

^cAvailable in tables on the website of the German Society (Deutsche Gesellschaft für Allergologie und klinische Immunologie), linked to the guidelines: <http://www.dgaki.de/Leitlinien/s2k-Leitlinie-sit/>

^dTable of evidence and recommendation taken from other GLs based on Shekelle.¹⁶

rigor (Mexican GL 2011), (4) *Clarity in presentation* (Mexican GL 2011), (5) *Applicability* (German GL 2015), (6) *Editorial independence* (Japanese GL 2016).

Some specific comments of the reviewers on the guidelines can be found in Table S1 (see the online supporting information tab for this article).

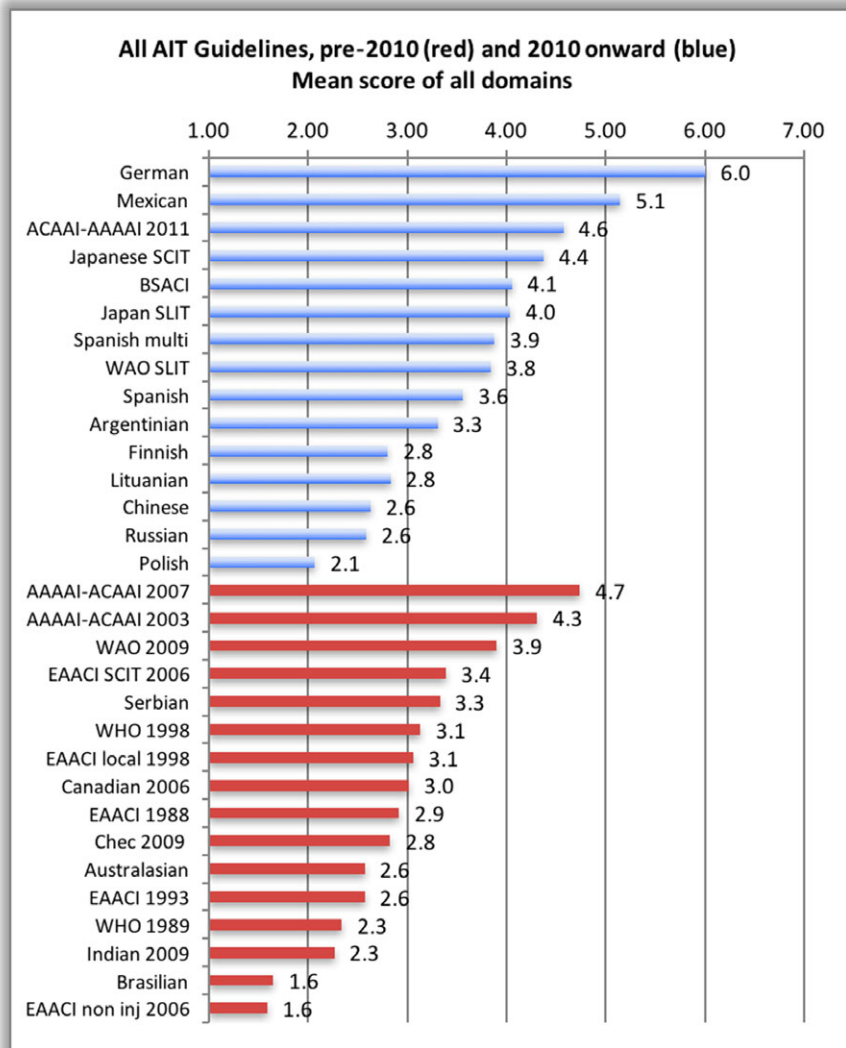


FIGURE 1 Mean total score of the 6 domains per guideline (each domain scored on a 1- to 7-point Likert scale), grouped in guidelines pre-2010 and guidelines from 2010 onward [Colour figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

The guidelines-quality assessment tool AGREE II was published in 2010, and the first guideline in the field of allergic diseases published shortly thereafter was the ARIA 2010 revision. When assessed using the AGREE II method, ARIA 2010 was found to rank high for all items, which did not hold true for several other guidelines on allergic rhinitis.⁴⁰ The here presented quality evaluation according to AGREE II for AIT-GLs from before and after this publication shows that in general, AIT-GL quality has improved since 2010. Echoing the universal development of GL making, from consensus documents in the 1970-1980s, through pure evidence-based-medicine in the 1990s, to the more comprehensive GRADE approach from the past decade. In GRADE, a balance is sought between the 4 pillars on which recommendations and suggestions for medical treatment are based (evidence, patient preference, cost, and safety). AIT-GLs have had a similar evolution since the first document in 1988.³

Even so, certain domains are still sensitive to improvement. This holds especially true for the domains (2) *Stakeholder involvement*, (3) *Rigor of Development*, and (5) *Applicability*.

Domain 3 directly relates to the methodological evaluation of the evidence that sustains a guideline. Although AIT-GLs have progressively become more and more evidence-based, most of them still lack a structured way of doing so. Many of the AIT-GLs reviewed here, lack one or several of the following elements: (i) a strictly planned, and well-documented literature search; (ii) critical appraisal of the literature, with inclusion and exclusion criteria for articles, bias evaluation and when possible conducting meta-analyses; (iii) a structure to synthesize the evidence, giving the correct weight to each evidence element; (iv) a clear, unbiased and comprehensive schedule to go from the pooled evidence to a certain level of recommendation, in which also safety, patient-related issues, and costs are considered. Many AIT-GLs did have an explicit link between the supporting evidence and the level of recommendation, using the Shekelle system from 1999.¹⁶ However, in Shekelle one randomized controlled trial is enough to reach a level A of recommendation, without analyzing further trial design details and possible bias elements, nor other issues apart from mere evidence. In today's world, this has become deficient. In this sense, the GRADE methodology for developing guidelines seems more adequate. However, only 2

guidelines (the German³⁸ and the Mexican²⁸) made an attempt to follow this GRADE approach and consequently scored higher in domain 3. Many other guidelines still followed the Shekelle system, thus obtaining a suboptimal score for domain 3. Therefore, there has only been a slight improvement in this domain, comparing older vs newer AIT-GLs ($P < .05$).

Concerning the low scoring domains 2 and 5, these are closely linked to dissemination and implementation of a GL. Domain 5 (applicability) seems the most interesting domain, as here the pre-2010 AIT-GLs scored better than the newer ones. A possible explanation for this finding might be that older GLs were more focused on informing clinical assistants on how to treat allergic diseases, while

newer GLs might be focusing more on improving knowledge, reducing the focus on dissemination.

It is generally accepted that AIT is still underused,⁴¹ with many candidate patients not even aware of this management option. In AIT-GL developing, we have not been aware of how important it is to include all stakeholders from the beginning of the process. To enhance GL acceptability among a broad range of physicians, including primary healthcare deliverers and representatives of all groups involved in the management of allergic diseases, they should be invited to participate from initial stages onward. For the correct implementation of AIT, nonexpert input is crucial in the section on patient selection and criteria for patient referral and the section on

Scores per domain: AIT Guidelines pre-2010 vs. 2010 onward

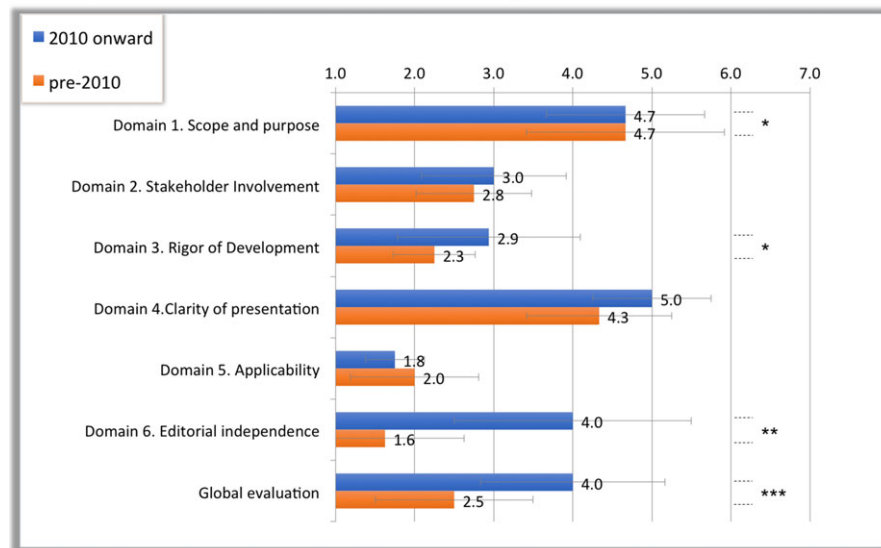


FIGURE 2 Median score of all guidelines per domain with interquartile ranges (each domain scored on a 1- to 7-point Likert scale), grouped in guidelines pre-2010 and guidelines from 2010 onward. Differences between guideline groups per domain calculated with Wilcoxon rank sum test (Mann-Whitney U test): * $P < .05$; ** $P < .01$; *** $P \leq .001$ [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Suggestions per domain on how to enhance guidelines' quality. For more detailed suggestions, see the AGREE II handbook

Domain	Suggestions
Domain 1. Scope and purpose	State in the first section of the document the detailed scope of the GL (which patients, which disease, which interventions) and the purpose of the GL.
Domain 2. Stakeholder involvement	Into the guideline development group one should invite experts, related expert groups (eg, ENT, pulmonologists), primary care physicians, patients, and others that might be involved in GL implementation (eg, representatives of governmental/administrative bodies, pharmaceutical industry) and methodologists. Involve them early-on in the process. A core group of only a few that prepares the initial lay-out and drafts might be a solution, to avoid slowing the process when the GDG becomes too big. But an initial, mid-, and final face-to-face meeting with the whole group is recommendable.
Domain 3. Rigor of Development	For original GLs: structured literature search, selection and analysis of articles, fusion of evidence and how recommendations are developed based on evidence, safety, cost, patient preference. (eg, GRADE approach, SIGN) For transculturized GLs: see ADAPTE approach, all evidence comes from the selected "mother" GL(s).
Domain 4. Clarity of presentation	Bullet-point presentation at the beginning/end of the document on the recommendations and suggestions, so they can easily be found by readers without going through the whole document.
Domain 5. Applicability	Discuss with the whole GDG barriers and obstacles for GL implementation, and how to solve them. Facilitate GL implementation with user-friendly (downloadable) application sheets, in which recommended steps are plotted. (eg, US AIT practice parameters' sheets).
Domain 6. Editorial independence	Apply a method (and describe in the GL) to reduce bias from GDG members with conflicts of interest and from the financing body.

the applicability of the GL. Paying special attention to improving these domains in future AIT-GLs would be highly desirable, see Table 2. In the previously mentioned AGREE II evaluation of allergic rhinitis GLs, the same domains 2 and 5 were found to rank low.⁴⁰

After analyzing all results, it amazed the investigators to see how little difference there is between older and the newer AIT-GLs in the global mean guideline AGREE-II-quality-scoring. Taking a closer look, we realized that this could partly be due to the fact that within each group of newer vs older AIT-GLs, some GLs are of higher and others are of much lower quality (see Figure 1) resembling more consensus documents and thus reducing the mean scoring of the whole guidelines' group. Therefore, in a post hoc analysis, we selected from the 2010-onward GLs only those with a mean score above 40%. Recalculating statistics based on this group of 9 AIT-GLs all domains showed statistically significant improvement vs the older GLs.

Under low-resource conditions (both economically and intellectually, because of time restraint of local experts), it can be very difficult to develop a GL from zero, based on all published literature. In such situations, the ADAPTE tool can be very useful, allowing high-quality existing GLs to be adapted to local reality.⁴² In ADAPTE, the literature search is thus for GLs published specifically in the field of interest, which subsequently are analyzed with AGREE II to select the ones with best-quality, most suitable for adaptation. As such, a locally adjusted high-quality GL can be developed without too much investment in the collection and evaluation of evidence. This might leave some resources for inviting more stakeholders and thus enhancing applicability.

The last domain, 6, on editorial independence, though much improved in the newer GLs, still only scores 4/7 points, as often conflict of interests and financing bodies are declared, without describing a method to avoid that these interfere with the GL content.

In this discussion, a word must be said about the tool we used, AGREE II, as well. Although it analyzes guidelines through a structured item list, with clear explanations in a manual on how to apply them,⁴³ finally it is based on the reviewer's criterion of scoring, a subjective measure. We came across this issue, as most GLs were revised in groups of 2 and on some items discrepancies arose, that in 3 cases continued even after the second round of discussion and re-revision of both reviewers. In these cases, we asked orientation of the methodologists. At that point, it became clear that some items could be sensitive to personal interpretation and thus not be uniformly scored by all reviewers. Here, the group decided to interpret as unanimously as possible and analyze all GLs with the same criterion.

Resuming, Table 2 shows per domain suggestions of the reviewers for developers of future AIT-GLs that might enhance the overall quality and thus implementation. These are only suggestions, as till now no AIT guideline has been subject to validation in the real world, nor can we assure that the best guidelines as described by AGREE II are more able to be used more often and at their best in the real life. But till now, it is the best tool we have.

During the past months, several systematic reviews have been published by a Task Force of the European Academy of Allergy and Clinical Immunology (EAACI) on AIT for allergic rhinitis,⁴⁴ allergic asthma,⁴⁵ and for allergy prevention,⁴⁶ to name some. Authors

anticipate these are the preparatory documents for a set of guidelines from the EAACI on the different aspects of AIT. This kind of preparation seems adequate for the development of a high-quality guideline. The final EAACI guideline documents shall have to be awaited to evaluate them with AGREE II and to confirm or reject this suspicion.

5 | CONCLUSIONS

In AIT-GLs, there is still a lot of room for improvement, especially in 2 domains, crucial in dissemination (stakeholder involvement and applicability). For some, the "Scientific rigor" domain flawed. In situations with limited resources, local adjustment ("transculturizing"), a high-quality AIT-GL might be appropriate and preferable over the development of a low-quality one. The AGREE II instrument could help to pick quality candidate AIT-GLs for such a procedure.

ACKNOWLEDGMENTS

We would like to thank M. Brouwers, MD, PhD, from the McMaster University (Ontario, Canada) for her expert advice concerning several issues related to AGREE-II. We would like to thank some of our colleagues for sending us their national guidelines, especially Prof. Dr. Violeta Kvedariene (Lithuania), Lucasz Skolimowski and Prof. Dr. Piotr Kuna (Poland), Dr. Petr Panzner (Czech Republic), and Prof Dr Vesna Tomic—Spiric (Serbia).

CONFLICTS OF INTEREST

DLL has received honoraria (speaker, advisory board), grants, or travel grants from AstraZeneca, Boehringer Ingelheim, MSD, Novartis, Grunenthal, Meda, Sanofi, UCB, pfizer, TEVA, GSK, Amstrong, Siegfried, DBV technologies.

DAA has received honoraria (speaker, advisory board, grants, or travel grants) from ALK-Abelló, Allergy Therapeutics, AstraZeneca, Diater Laboratorios, Ferrer, GlaxoSmithKline, Leti, MEDA, Merck, Merck-Serono Fundación 2000, Novartis, Pfizer, Sandoz, Stallergenes). AN has received honoraria (speaker, advisory board), grants, or travel grants from MEDA, ALK-Abello, ThermoFisher, Novartis, Allergy Therapeutics, Emerade, Shire and was recipient for Multinational, Multicenter Study provided by Novartis. BW has received honoraria (speaker, advisory board) from ALK-Abelló, Stallergenes, Novartis, Dr. Pflieger, Astellas, Shire, Celgene, HAL Allergy and was recipient of a research grant from Novartis. DI declares having received honoraria for lectureship from ALK, Astra, Chiesi, Novartis, and Stallergenes, and for participation in advisory boards from Alk-Abelló, Astra, Novartis, Sanofi, and Stallergenes. He has also received research support from Merck and ThermoFisher Diagnostics. DI reports personal fees from ASTRA-ZENACA, personal fees from SANOFI, personal fees from NOVARTIS, personal fees from GSK, personal fees from STALLERGENES, personal fees from ALK, personal fees from CHIESI, grants from MERCK, grants from THERMOFISHER DIAGNOSTICS, outside the submitted work. OP reports

grants and personal fees from ALK-Abelló, Allergopharma, Stallergenes Greer, HAL Allergy Holding B.V./HAL Allergie GmbH, Bencard Allergie GmbH/Allergy Therapeutics, Lofarma, Biotech Tools S.A., Laboratorios LETI/LETI Pharma and from Anergis S.A.; OP reports grants from Biomay, Nuvo, Circassia and personal fees from Novartis Pharma, MEDA Pharma, Sanofi US Services, Mobile Chamber Experts (a GA2LEN Partner) and Pohl-Boskamp, outside the submitted work.

AUTHOR CONTRIBUTIONS

Larenas-Linnemann DES conceptualized the project, coordinated all steps, AGREE II-evaluated AIT guidelines, correspondence with co-authors, and wrote the draft article. Pfaar O, Antolín-Amérigo D, Parisi C, Nakonechna A, Davila I, Gómez M, Levin M participated in go-to-meeting discussions to polish the project, AGREE II-evaluated AIT guidelines, discussed outcomes/interpretation, and corrected the article. Wedi B, Luna-Pech JA, Ortega Martell JA Klimek L, Rosario N participated in last 1-2 go-to-meeting discussions to discuss results, AGREE II-evaluated AIT guidelines, discussed outcomes/interpretation, and corrected the article. Muraro AM, Agache I, Bousquet J gave background guidance on the project, discussed project, discussed outcomes/interpretation, and corrected the article. Sheikh A, Methodologist, counseled us in project and implementation phases and reviewed the manuscript.

PROTECTION OF HUMAN SUBJECTS AND ANIMALS IN RESEARCH

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this investigation.

PATIENTS' DATA PROTECTION

The authors declare that no patient data appear in this article.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Larenas-Linnemann DES, Antolín-Américo D, Parisi C, et al. National clinical practice guidelines for allergen immunotherapy: An international assessment applying AGREE-II. *Allergy*. 2018;73:664–672. <https://doi.org/10.1111/all.13316>

ONLINE REPOSITORY

Table 2: Specific comments of reviewers on the AIT-GLs

Guideline	Reviewer's Comments
1. EAACI 1988	Amazingly well elaborated, for being a GL from 30 years back, it was a pleasure to read. Surely improvement is possible: • GDG is composed of EAACI members only. • The text is neatly divided into very small paragraphs, with headings and each one recommends certain action. However, there is no structured way questions are posed and recommendations are made: no link between evidence-recommendation • No comments on applicability, facilitators/barriers in implementation are made. • No COIs
2. WHO consensus 1989	This consensus only mentions it is intended to be a review of the status of AIT, its scientific basis, and the clinical evidence of its efficacy. It is the report of a Working Group which met in Geneva on 25-28 October 1988. As such, this document works more as a systematic review of the then-current concepts than a clinical GL. Although it includes useful information, it lacks an evidence-based approach or strategy in making its recommendations, and its bibliographic support is not evidence-weighted. The fact that this is a 1989 consensus with no upgrade published in the last 27 years implies that, although it could be a valuable tool for the clinic (it includes and discusses relevant clinical and therapeutic aspects of AIT), it hardly could be considered adequate for today's standards, as many very important concepts in quality of extracts, AIT modalities and clinical indications have been added in recent years. Plus, this consensus lacks of essential components like cost study, diversity of specialities involved, barriers, conflict of interest, update plan, and the absence of a strategy for the use of weighted evidence as the base of their recommendations.
3. EAACI 1993	This GL seems to be more an expert point of view than an evidence-based GL. Nevertheless, it should be considered that it was written more than 20 years ago and the bibliography is very complete. In its time it was useful from a clinical point of view
4. Australasian GL 1997	• This position statement is an overview and focusing only on AIT by asthma, does not cover all aspects. • This position statement is unacceptable to be a GL because of having a lot of limitations, as: describing methods for study selection, methods of assessing studies, alternative option of therapies, applicability of patient populations, the absence of external reviewers and audit as well as advice and/or tools on how the recommendations can be put into practice and many other issues
5. WHO position Paper 1998	The main strength of this guide is the expert opinion, but from my point of view, it presents significant methodological deficits, e.g., no structured evidence evaluation linked to recommendations, no comments on the applicability, facilitators/barriers in implementation etc. No COIs
6. EAACI Local Immunotherapy 1998	GL inadequate in describing the composition of panel, methods for study selection, methods of assessing studies, alternative therapies, applicability of patient populations and many other shortfalls.
7. AAAAI/ACAAI 2003	Reviewer 1 (R1). Very detailed and practical GL for clinicians However, some important AGREE II criteria are missing: ✓ no participation of patient organizations, patient views/preferences

	✓ funding, COIs ✓ Literature search strategy (in-/exclusion criteria) ✓ Method of consensus/bias? For formulation of the recommendations ✓ How many reviewers/members agreed? How many participated? Voting results? Acceptance rates? ✓ update procedure ✓ Implementation strategy ✓ Resource implications ✓ Monitoring/auditing criteria The GL represented a first manual of use of immunotherapy for the US doctors. The statements clearly specify the course of action, but nowadays many of them could be outdated. It is well structured but I would have included probably more figures or algorithms in case of adverse events or other recommendations as synoptic tables. Reviewer 2 (R2). This GL is adequately evidence-based. Includes and discusses relevant clinical and therapeutic aspects of AIT using an evidence-based mechanism. The strategies in evaluating the body of evidence were poorly described. Recommendations were made using the body of evidence by informal consensus. External reviewers did participate, but their impact on the final statements are not clearly established. Participation in the decision's spectre of use of AIT of other personal apart of the allergist is not considered. No GL update plan provided.
8. Serbian GL 2005	This GL provides a large amount of information, but the main problem is that lacks of an evidence-based approach or strategy in making its recommendations, and its bibliographic support has been used more as if were a systematic review instead as a support of an evidence-based clinical GL. Another important weakness is that this document dates back to 2005, with no upgrade published, as far as I can ascertain. Could be undoubtedly a valuable tool for the clinic, as it includes and discusses relevant clinical and therapeutic aspects of AIT, in both conventional and special clinical scenarios, but it hardly can be considered adequate because lacks of essential components like cost study, diversity of specialties involved, barriers, conflict of interest, a clear update plan, and, more importantly, the absence of a strategy for the use of weighted evidence as the base of their recommendations.
9. European SCIT GL 2006	Quite some methodological flaws for being a GL, however, I particularly like the practical part on how to set-up a clinic, how to refer and cooperate with family doctors and first level health care system are of great value.
10. European non-injection IT 2006	Poorly structured GL. Apparently, no schematic system was used, no model to searching for levels of evidence or grades of recommendation was specified, and evidence degree is referred quite informally. Has much more the structure of a systematic review article than a clinical structured GL. No authors are indexed; neither objectives nor methods are described. Looks more like a sub-chapter in a compilation of review paper or part of a supplement.
11. Canadian GL 2006	GL inadequate in describing methods for study selection, methods of assessing studies, alternative therapies, applicability of patient populations and many other shortfalls.
12. AAAAI/ACAAI 2007	The GL has been updated and improved from the first version of 2003. It includes a greater body of evidence, which has been researched within those years. Immunotherapy and proceedings have evolved and provides a chart on allergen cross-reactivity to be considered by physicians dealing with Immunotherapy.

	• This GL is adequately evidence-based. • Includes and discusses relevant clinical and therapeutic aspects of IT using an evidence-based mechanism. • The strategies in evaluating the body of evidence were poorly described. • Recommendations were made using the body of evidence by informal consensus. • External reviewers did participate, but their impact on the final statements are not clearly established. • No GL update plan clearly provided. • This 2007 update represents a clear improvement over the previous 2003 GL in terms of content (i.e. IT dose schemes) but I can not say the same regarding methodology, as it suffers almost the same limitations of its predecessor, hence the identical global score provided by this reviewer. It now includes a list of invited external reviewers and an expiry date of its statements, but lost the AAP endorsement.
13. WAO SLIT position paper 2009	The WAO GL is more a state of the art review on SLIT more than a “graded” evidence report on the published studies on SLIT. It is not explicitly stated whether there is going to be an update and when it shall be published. Notwithstanding, it constitute a very good review of the current worldwide status of SLIT
14. Indian AIT GL 2009	Very descriptive, but without clear methodology
15. Chec AIT GL 2009	This GL is indeed a national consensus which provides a quite valuable amount of information, but its main problem relates to the lack of an evidence-based approach or strategy for making its recommendations, and the bibliographic support has been used with no link for the reader to know what body of evidence support which paragraph. This is a first update published 4 years after the first paper, but as far as we can ascertain, no other efforts have been made to make additional updates. Could be a valuable tool for the clinic, as it includes and discusses relevant clinical and therapeutic aspects of IT, in both conventional and special clinical scenarios, but it hardly can be considered definitive because lacks of essential components like barriers, conflict of interest, costs, a clear update plan, and, more importantly, the absence of a strategy for the use of weighted evidence as the base of their recommendations.
16. Brazilian AIT consensus 2001	This document is in my opinion a general overview of the immunotherapy procedure but it remains elusive whether it is addressed to specialists, general practitioners, etc. Although contraindications are named, there is no paragraph about special situations or the types of initiation schedules.
17. Argentinian GL 2010	R1. This GL is more a review of the literature and an expert consensus. A methodological review of the evidence is lacking. R2. Although it is a good review of what was known about Immunotherapy 6 years back, there is no systematic assessment of the evidence. Also, colleagues do not review how to implement the GL, nor were any first contact specialists and doctors involved in their development.
18. AAAAI/ACAAI 2011	R1. There’s been a throughout update of the GL since the first version of 2003, due to the continuous improvement of knowledge and the application of methodology procedures which warrant the reproducibility and reliability of the GL. Notwithstanding, it is intended for the use within a reality that may not be suitable for every country. Its implementation in other regions may be considered with caution and taking into account the particularities. R2. This GL is adequately evidence-based. It includes and discusses relevant clinical and therapeutic aspects of IT using an evidence-based mechanism. However:

	✓ The strategies in evaluating the body of evidence were poorly described. ✓ Recommendations were made using the body of evidence by informal consensus. ✓ External reviewers did participate, but their impact on the final statements are not clearly established. ✓ No GL update plan clearly provided. This 2011 update represents a clear improvement of the previous 2003 & 2007 GLs in terms of content, and now, for example, grants more importance to nurses and other medical extensors in the processing and evaluation of IT aspects. However, it suffers many of the same important methodological limitations of its 2 predecessors, hence the only marginal improvement in the global score provided by this reviewer. Reviewer 3. This GL is focused on the US practitioner; however, statements and recommendations are somehow equivalent everywhere. If having external reviewers (just one: Dr. Larenas) could be generalizable. There is no methodological precision in the development of the update, the time of searching for evidence, selection process of articles. Analysis of cost effectiveness is lacking. Also, how the declared conflicts of interest potential influences in the content of GL are addressed should be explained.
19. British GL on AIT in AR 2011	R1. This is rather a review article, but not a GL; there are no clear recommendations (besides one vague algorithm), no description of the development process, the methods (representative GL authors? Evidence-based? Evidence strategy? Method of consensus?), the acceptance (accepted by the society?) The GL is only for UK with its specific local issues regarding AIT. R2. This GL is designed for the UK. It covers different issues, from the setting and equipment an AIT Unit should include, to the types of AIT along with their costs in 2011. It is somehow outdated, due to novel schemes (which are not covered at all) and galenic formulations of AIT.
20. Mexican GL on AIT2011	R1. The strength of the GL is on methodological issues. It has a deficit in the domain applicability. It presents some small differences between the content of the text and the summary box, but these do not represent substantive changes in the information. Finally, it is a GL which takes into account the country context where it is developed, so some points cannot be generalized in other geographical areas. Otherwise, I think it is a recommendable GL. R2. This GL has been elaborated following most AGREE-II recommendations and it is a high quality GL.
21. Chinese consensus on AIT 2011	R1. This GL is more an expert consensus than a methodological review of the evidence. Difficulty in translation. This consensus is unacceptable to be a GL as several important issues are missing, such as: describing methods for study selection, assessment of studies, alternative option of therapies, applicability of patient populations, the absence of external reviewers and other shortfalls. R2. Too descriptive without clear methodology
22. Finnish AIT GLs 2012	R1. This GL's authors researched evidence-based, but the strategies in evaluating evidence and systematic method were not described. Despite it includes clinical efficacy aspects of AIT by using a research evidence mechanism, it hardly can be considered adequate for using as GL, because lacks of very important issues, as: overall objectives, inclusion/exclusion of evidence, methods of formulation of recommendations, cost study, diversity of specialities involved, external reviewers, barriers, facilitators, conflict of interest, update

	plan, applicability tools. R2. It is a 2nd update on AIT recommendations, with very concise and precise recommendations. However, being such a short document fundamental issues are missing. Evidence is stated, but not sustained by literature.
23. Lithuanian AIT GLs 2012	R1. This is a transculturization of the WAO and EAACI GLs on AIT, but not done in the formal way. As such, it appears a Consensus document, based on some of the evidence from the WAO-EAACI documents. Key recommendations are not easy to find. The domains of applicability and editorial independence score 1, as they are not addressed. R2. General: This seems to be more a „practice oriented review“ / Position Paper (PP) than a GL. Hence, relevant criteria of AGREE II are not met! Moreover, I see problems in using the (Google-)translated text as a basis for this review as it only roughly outlines content and is imprecise in some details. To me this approach is insufficient!
24. Japanese SCIT for AR GL 2013	R1. The strength of the GL is on methodological issues. But It has a deficit in the domain applicability and unclear information on the editorial independence domain. Otherwise, I think it is a recommended guide. R2. Methodologically strong, but poor stakeholder involvement, no external reviewers and no discussion on applicability issues.
25. Russian AIT GL 2013	R1. This GL is adequately evidence-based, but the strategies in evaluating evidence and consensus was not formal. Although it includes and discusses relevant clinical and therapeutic aspects of IT using an evidence-based mechanism, it hardly can be considered adequate because lacks of essential components like overall objectives, cost study, diversity of specialities involved, barriers, facilitators, conflict of interest, update plan, applicability tools, and inclusion/exclusion of evidence. There was some discrepancy over the other reviewer's opinion on several items. This could be partially explained by the fact she is apparently a native Russian speaker, and I accept that the automatic translation that I used could have led me to misunderstand some aspects of the author's statements and induce an information bias. In conclusion, a poor GL, my last statement is that could not be recommended as an international standard GL, in favour of other more strongly evidence-supported GLs. R2. This GL is more a review of the literature and an expert consensus more than a methodological review of the evidence. Alternative therapies, applicability of patient populations, evidence, reviewing and other issues have to be considered. Measuring the application of GL recommendations can facilitate their ongoing use. This requires clearly defined criteria that are derived from the key recommendations in the GL, particularly clinical or health outcome measures. A clear statement about the procedure for updating the GL should be provided. It cannot be considered a suitable for use as a mother GL.
26. Polish AIT GL 2014	R1. This document is more an expert review than a GL. No systematic review has been performed and the search strategy is not reproducible. Funding and conflicts of interest are not specified. There are more conclusions than recommendations and these are incomplete and not clearly highlighted. R2. This reads as a current review rather than “guiding” for the physician. Recommendations cannot be identified easily.
27. Spanish GL on SLIT 2014	R1. While it is an interesting guide with many practical aspects, it was done without taking into account the AGREE II criteria It has a deficit in the domain applicability, Stakeholder involvement and editorial independence.

	R2. This is a very specific GL focused on SLIT only. Authors are representative of allergists only. The health issues (beneficial and harmful) associated with SLIT are adequately described. Although objectives and research strategy are well clarified, the absence of a list of clinical questions or summary of recommendations is notable, as well as a more meticulous consensus technique (only informal consensus was used). Level of evidence is adequately noted in its different paragraphs, and some concepts and data from reference meta analyses are disclosed in algorithms. The criteria for selecting the evidence appear to have been subjective. Not using neither methodology experts in the core group, nor external reviewers are very important omissions. The overall consensus with the other reviewer was good, as there were coincidence in most of the evaluation criteria and opinions, with only a couple of exceptions.
28. Spanish consensus on polysensitized 2014	R1. The present document is a consensus, not a GL. Method is fair, in order to have expert opinion in a topic where evidence is scarce. Recommendations are limited to consensus' agreement but not evidence-based in almost all of them. Impact of present recommendations should be measured in the target population; then check its generalization. Useful to stimulate searching for this data in other regions / populations Can not suggest specific modifications in order to revert it as a recommended GL
29. WAO SLIT update 2014	R1. This GL is an update of a previous GL but the degree of agreement with AGREE-II recommendations is low (although is higher in some parts of it) R2. This Position Paper on SLIT is extensively elaborated and reviews all relevant literature for this treatment option. However, it lacks relevant features of a GL which are standardized in AGREE II
30. German 2016	R1. Excellent methodology and presentation. Mechanism of action very well described. Tables not so visual effective.
31. Japanese SLIT	Are guiding principles a GL? This publication represents rather a very concise and well structured evidence-based literature review that addresses 17 well defined clinical questions. GL for Japan only; • Made by Japanese oto(rhino)laryngologists only • Special attention to Japanese pts., cedar pollen, HDM • No clear conclusions, recommendations or treatment algorithm • Looking at the drawn conclusions in the abstract, the only clear recommendation is that SLIT should be continued for 3 years or longer and what is critical for safe performance. Does not consider single SLIT treatments (SLIT ≠ SLIT)