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

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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.
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, 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. 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, 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), 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.\textsuperscript{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 fall 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\textsuperscript{7,8} and the Global Initiative on Asthma (GINA)\textsuperscript{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: [alerg* 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
| Specific guidelines on allergen immunotherapy | Year | Evidence model | No of RCTs SCIT/SLIT | No of meta-analyses |
|---------------------------------------------|------|----------------|----------------------|-------------------|
| EAACI 1988 Workshop report3                 | 1988 | None           | 8/0                  | 0                 |
| WHO consensus10                             | 1989 | None           | ±8/0                 | 0                 |
| EAACI Position Paper199311                  | 1993 | None           | 28/6                 | 0                 |
| Australasian guidelines on SCIT for asthma12| 1997 | None           | 5/0                  | 2                 |
| WHO Position Paper 199813                   | 1998 | None           | 11/0                 | 0                 |
| EAACI Local Immunotherapy14                 | 1998 | None           | x/4                  | 0                 |
| AAAAI/ACAAI 1st paper15                     | 2003 | Shekelle16     | 36/7                 | 4                 |
| Serbian guidelines17                        | 2005 | None           | 12/28                | 3                 |
| European Guidelines SCIT18                  | 2006 | None           | 8/x                  | 0                 |
| EAACI noninjection IT19                     | 2006 | None           | x/15                 | 0                 |
| Canadian guidelines20                       | 2006 | None           | 4/10                 | 0                 |
| AAAAI/ACAAI Practice parameters21           | 2007 | Shekelle16     | 62/14                | 4                 |
| WAO SLIT Position Paper4                    | 2009 | None           | 16/72                | 7                 |
| Indian Guidelines on AIT22                  | 2009 | None           | 20/9                 | 5                 |
| Chec guidelines23                           | 2009 | None           | 14/3                 | 2                 |
| Brazilian GLs24                            | 2001 | None           | 1/0                  | 0                 |
| Argentinian guidelines25                    | 2010 | None38         | No review            | 0                 |
| AAAAI/ACAAI Practice parameters26           | 2011 | Shekelle16     | 65/9                 | 7                 |
| British guidelines27                        | 2011 | SIGN           | 15/25                | 6                 |
| Mexican guidelines28                        | 2011 | GRADE          | 55/18                | 5                 |
| Chinese expert consensus on AIT for AR29    | 2011 | Consensus      | ?                    | ?                 |
| Finnish update on current care guidelines: AIT30 | 2012 | Article in Finnish. Data from abstract. |  |
| Lithuanian guidelines on AIT31              | 2012 | Guiding review article | 2/0 | 0 |
| Guiding principles of SCIT for AR in Japan32 | 2013 | Modified Shekelle | 12/x | 1 |
| Russian GL(personal file shared by colleagues)2013 | 2013 | SIGN | No references in the file | ? |
| Polish position paper on SLIT33,34          | 2014 | None           | x/17                 | 7                 |
| SLIT Spanish guideline35                    | 2014 | Oxford Center for Evidence Based Medicine | x/33 | 9 |
| Spanish allergists' consensus on IT in polysensitized patients36 | 2014 | Consensus with Delphi method | 0/0; review and opinion articles | 0 |
| WAO SLIT position paper update 201337       | 2014 | None           | x/26                 | 10                |
| German speaking countries guideline38       | 2014 | Modified Shekelle | 22/143 | 4 |
| Guiding principles of SLIT for AR in Japan39 | 2016 | Modified Shekelle | x/15 | 10 |

AAAAI, American Academy of Allergy, Asthma and Immunology; AC, allergic conjunctivitis; ACAAI, 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.

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

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

*Available 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/

*Table of evidence and recommendation taken from other GLs based on Shekelle.16

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

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**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]

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**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.43

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, allergic asthma, and for allergy prevention, 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.

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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.

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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, Antolin-Amérgio 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.