Global Initiative for Asthma (GINA) Methodology 2022

GINA SCIENCE COMMITTEE

The GINA Science Committee was established in 2002 to review published research on asthma management and prevention, to evaluate the impact of this research on recommendations in GINA documents, and to provide yearly updates to these documents. The members are recognized leaders in asthma research and clinical practice with the scientific expertise to contribute to the task of the Committee. They are invited to serve for a limited period and in a voluntary capacity. The Committee is broadly representative of adult and pediatric disciplines as well as from diverse geographic regions. The Science Committee normally meets twice yearly in conjunction with the American Thoracic Society (ATS) and European Respiratory Society (ERS) international conferences, to review asthma-related scientific literature. During COVID-19, meetings of the Science Committee were held online each month. Statements of interest for Committee members are found on the GINA website www.ginasthma.org.

PROCESSES FOR UPDATES AND REVISIONS OF THE GINA REPORT

Literature search

A PubMed search is performed twice a year, each covering the previous 18 months, using filters established by the Science Committee. The search terms include asthma, all ages, only items with abstracts, clinical trial or meta-analysis or systematic review, and human. The search is not limited to specific PICOT questions (Population, Intervention, Comparison, Outcomes, Time). The 'clinical trial' publication type includes not only conventional randomized controlled trials, but also pragmatic, real-life and observational studies. Systematic reviews include, but are not limited to, those conducted using GRADE methodology[2] including, where relevant, guidelines documents published by other international organizations. The respiratory community is also invited to submit any other fully published peer-reviewed publications that they believe should be considered, providing the full paper is submitted in (or translated into) English; however, because of the comprehensive process for literature review, such *ad hoc* submissions have rarely resulted in substantial changes to the report.

Systematic reviews

Unique among evidence-based recommendations in asthma, and most other therapeutic areas, GINA conducts an ongoing twice-yearly update of the evidence base for its recommendations. GINA does not carry out or commission its own GRADE-based reviews, because of the current cost of such reviews, the large number of PICOT questions that would be necessary for a comprehensive practical report of this scope, and because it would limit the responsiveness of the GINA report to emerging evidence and new developments in asthma management. However, the Science Committee includes relevant systematic reviews conducted with GRADE methodology as part of its normal review process, once such reviews are published. GINA recommendations are constantly being reviewed and considered for update as new evidence (including GRADE-based systematic reviews on specific topics) is identified and indicates the need.

Literature screening and review

Each article identified by the literature search, after removal of duplicates and those already reviewed, is pre-screened in Covidence for relevance and major quality issues by the Editorial Assistant (a medical librarian) and by at least two non-conflicted members of the Science Committee. Each publication selected from screening is allocated to be reviewed for quality and for relevance to the GINA strategy by at least two members of the Science Committee, neither of whom may be an author (or co-author) or declare a conflict of interest in relation to the publication. Articles that have been accepted for publication and are online in advance of print are eligible for full text review provided the approved/corrected copy-edited proof is available.

All members receive a copy of all of the abstracts and full text publication, and non-conflicted members have the opportunity to provide comments during the pre-meeting review period. Members evaluate the abstract and the full text publication, and answer written questions in a review template about whether the scientific data impact on GINA recommendations, and if so, what specific changes should be made. In 2020, the CASP checklist was provided in the review template to assist in evaluation of systematic reviews. A list of all publications reviewed by the Committee is posted on the GINA website (www.ginasthma.org).

Discussion and decisions during Science Committee meetings

Each publication that is assessed by at least one reviewer to potentially impact on the GINA report is discussed in a Science Committee meeting (virtual or face-to-face). This process comprises three parts, as follows:

1. Quality and relevance of original research and systematic review publications. First, the Committee considers the relevance of the publication to the GINA report, the quality of the study, the reliability of the findings and the interpretation of the results, based on the responses from reviewers and discussion by members of the Committee. For systematic reviews, GRADE assessments, if available, are taken into account. However, for any systematic review, GINA members also independently consider the clinical relevance of the question addressed by the review, and the scientific and clinical validity of the included populations and study design. During this discussion, an author (or member with a conflict) may be requested to provide clarification or respond to questions relating to the study, but they may not otherwise take part in this discussion about the quality and relevance of the publication.

2. Decision about inclusion of the evidence. During this phase, the Committee decides whether the publication or its findings affect GINA recommendations or statements and should be included in the GINA report. These decisions to modify the report or its references are made by consensus by Committee members present and, again, any member with a conflict of interest is excluded from these decisions. If the chair is an author on a publication being reviewed, an alternative chair is appointed to lead the discussion in part 1 and the decision in part 2 for that publication.

3. Discussion about related changes to the GINA report. If the committee resolves to include the publication or its findings in the report, an author or conflicted member, if present, is permitted to take part in the subsequent discussions about and decisions on changes to the report, including the positioning of the study findings in the report and the way that they would be integrated with existing (or other new) components of the GINA management strategy. These discussions may take place immediately, or over the course of the year as new evidence emerges or as other changes to the report are agreed and implemented. The above conflict of interest considerations also apply to members of the GINA Board who ex-officio attend GINA Science Committee meetings.

As with all previous GINA reports, levels of evidence are assigned to management recommendations where appropriate. A description of the current criteria is found in Table A (p.4), which was developed by the National Heart Lung and Blood Institute. From 2019, GINA has included in Evidence Level A strong observational evidence that provides a consistent pattern of findings in the population for which the recommendation is made and has also described the values and preferences that were taken into account in making major new recommendations. The table was updated in 2021 to avoid ambiguity about the positioning of observational data and systematic reviews.

New therapies and indications

The GINA report is a global strategy document. Since regulatory approvals differ from country to country, and manufacturers do not necessarily make regulatory submissions in all countries, some GINA recommendations are likely to be off-label in some countries. This is a particular issue for pediatrics, where across different

diseases, many treatment recommendations for pre-school children and for children aged 6–11 years are off-label.

For new therapies, GINA's aim is to provide clinicians with evidence-based guidance about new therapies and their positioning in the overall asthma treatment strategy as soon as possible, as the gap between regulatory approval and the periodic update of many national guidelines is otherwise filled only by advertising or educational material produced by the manufacturer or distributor. For new therapies, the GINA Science Committee generally makes recommendations after approval for asthma by at least one major regulatory agency (e.g. European Medicines Agency or Food and Drug Administration), since regulators often receive substantially more safety and/or efficacy data on new medications than are available to GINA through peer-reviewed literature. However, decisions by GINA to make or not make a recommendation about any therapy, or about its use in any particular population, are based on the best available peer-reviewed evidence and not on labeling directives from regulators.

Table A. Description of levels of evidence used in this report

Evidence level	Sources of evidence	Definition
A	Randomized controlled trials (RCTs), systematic reviews, observational evidence. Rich body of data.	Evidence is from endpoints of well designed RCTs, systematic reviews of relevant studies or observational studies that provide a consistent pattern of findings in the population for which the recommendation is made. Category A requires substantial numbers of studies involving substantial numbers of participants.
B	Randomized controlled trials and systematic reviews. Limited body of data.	Evidence is from endpoints of intervention studies that include only a limited number of patients, post hoc or subgroup analysis of RCTs or systematic reviews of such RCTs. In general, Category B pertains when few randomized trials exist, they are small in size, they were undertaken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent.
C	Nonrandomized trials or observational studies.	Evidence is from non-randomized trials or observational studies.
D	Panel consensus judgment.	This category is used only in cases where the provision of some guidance was deemed valuable but the clinical literature addressing the subject was insufficient to justify placement in one of the other categories. The Panel Consensus is based on clinical experience or knowledge that does not meet the above listed criteria.

For existing therapies with evidence for new regimens or in different populations than are covered by existing regulatory labels, the Science Committee and Board agreed in May 2018, in the context of new evidence for use of long-term low dose macrolides in moderate-severe asthma, that the Committee may, where relevant, consider making recommendations that are not necessarily covered by regulatory indications in any country at the time, provided the Committee is satisfied with the available evidence around safety and efficacy/effectiveness. The same approach was again taken in 2019 with recommendations for mild asthma about treatment with as-needed inhaled corticosteroid (ICS)-formoterol and taking ICS whenever SABA is taken rather than regularly.

Since the GINA report represents a global strategy, the report does not refer to recommendations being 'off-label'. However, readers are advised that when assessing and treating patients, they should use their own professional judgment and should also take into account local and national guidelines and eligibility criteria, as well as licensed drug doses.

External review

Prior to publication each year, the GINA report undergoes extensive external review by patient advocates and by asthma care experts from primary and specialist care in multiple countries. There is also continuous external review throughout the year in the form of feedback from end-users and stakeholders through the contact form on the GINA website.