

Global Initiative for Asthma (GINA)



Methodology GINA Report 2021

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 meets twice yearly in conjunction with the American Thoracic Society (ATS) and European Respiratory Society (ERS) international conferences, to review asthma-related scientific literature. Statements of interest for Committee members are found on the GINA website www.ginasthma.org.

PROCESSES FOR UPDATES AND REVISIONS OF THE GINA REPORT

GINA processes for the review of evidence and development of recommendations for GINA reports, including handling of conflict of interest, were reviewed by the Science Committee and approved by the Board in September 2018, and are described below.

Literature search

For each meeting of the GINA Science Committee, a rolling PubMed search is performed covering approximately 18 months, using filters established by the Committee: 1) asthma, all fields, all ages, only items with abstracts, clinical trial, human; and 2) asthma and meta-analysis, all fields, all ages, only items with abstracts, human. The 'clinical trial' publication type includes not only conventional randomized controlled trials, but also pragmatic, real-life and observational studies. The respiratory community is also invited to submit to the Program Director any other peer-reviewed publications that they believe should be considered, providing an abstract and the full paper are 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.

Screening and review

After initial screening of articles identified by a cumulative search of the literature by the Editorial Assistant and Chair of the Science Committee, each publication identified by the above search is reviewed for relevance and quality by members of the Science Committee. Each publication is allocated to at least two Committee member reviewers, neither of whom may be an author (or co-author) or declare a conflict of interest in relation to the publication. All members receive a copy of all of the abstracts and non-conflicted members have the opportunity to provide comments during the pre-meeting review period. Members evaluate the abstract and, by their judgment, the full publication, and answer written questions about whether the scientific data impact on GINA recommendations, and if so, what specific changes should be made. 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

During Committee meetings, each publication that is assessed by at least one member to potentially impact on the GINA report is discussed. This process comprises three parts: (1) evaluation of the relevance and quality of the publication; (2) a decision about inclusion of the publication in the report; and (3) (if relevant) discussion about related changes to the report. First, the Committee considers the relevance of the study 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 among members of the Committee. During this discussion, an author may be requested to

provide clarification or respond to questions relating to the study, but they may not take part in the second phase, during which the Committee decides whether the publication should be included in the GINA report. These decisions to modify the report or its references are made by consensus by Committee members present. 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. If the committee resolves to include the publication in the report, the author is permitted to take part in the third phase that involves 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 time 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.

In 2009, after carrying out two sample reviews using the GRADE system,¹ GINA decided not to adopt this methodology for its general processes because of the major resource challenges that it would present. This decision also reflected that, 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. The Science Committee includes systematic reviews conducted with GRADE methodology as part of its normal review process, once such reviews are published.

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, which was developed by the National Heart Lung and Blood Institute. From 2019, GINA has also described the values and preferences that were taken into account in making major new recommendations.

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.

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. Regulatory approvals of maintenance and reliever therapy (MART) also vary between countries.

For new therapies, the GINA Science Committee makes recommendations after approval for asthma by at least one major regulatory agency (e.g. European Medicines Agency, Food and Drug Administration). The reason is that regulators often receive substantially more safety data on new medications than are available to GINA through the peer-reviewed literature. However, decisions by GINA to make or not make a recommendation about any therapy, or in any particular subpopulation, are based on the best available peer-reviewed evidence and not on labeling directives from regulators.

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 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.

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.

LITERATURE REVIEWED FOR GINA 2021 UPDATE

The GINA report has been updated in 2021 following the routine twice-yearly review of the literature by the GINA Science Committee. The literature searches for 'clinical trial' publication types (see above) and meta-analyses identified a total of 2,986 publications, of which 2,219 were screened out for duplicates, relevance and/or quality. The remaining 767 publications (616 'clinical trials' and 151 'meta-analyses') were reviewed by at least two members of the Science Committee; a total of 84 were subsequently discussed at meetings of the Science Committee, which were held virtually rather than face to face because of the COVID-19 pandemic. A list of key changes in GINA 2021 can be found starting on p.15 of the report, and a tracked changes copy of the report is archived on the GINA website at www.ginasthma.org/archived-reports/.

FUTURE CHALLENGES

In spite of laudable efforts to improve asthma care over the past 20 years, many patients globally have not benefited from advances in asthma treatment and often lack even the rudiments of care. Many of the world's population live in areas with inadequate medical facilities and meager financial resources. The GINA Board of Directors recognizes that 'fixed' international guidelines and 'rigid' scientific protocols will not work in many locations. Thus, the recommendations found in this report must be adapted to fit local practices and the availability of health care resources.

At the most fundamental level, patients in many areas may not have access even to low dose inhaled corticosteroids, which are the cornerstone of care for asthma patients of all severity. More broadly, medications remain the major contributor to the overall costs of asthma management, so the access to and pricing of high quality asthma medications continues to be an issue of urgent need and a growing area of research interest.² With budesonide-formoterol now on the World Health Organization (WHO) essential medicines list, the changes to treatment of mild asthma first included in the 2019 report may provide a feasible solution to reduce the risk of severe exacerbations with very low dose treatment.³

A challenge for the GINA Board of Directors for the next several years is to continue working with primary health care providers, public health officials and patient support organizations to design, implement, and evaluate asthma care programs to meet local needs in various countries. The Board continues to examine barriers to implementation of asthma management recommendations, especially in primary care settings and in developing countries, and to

examine new and innovative approaches that will ensure the delivery of the best possible asthma care. GINA is a partner organization in a program launched in March 2006 by WHO, the Global Alliance against Chronic Respiratory Diseases (GARD). Through the work of the GINA Board of Directors, and in cooperation with GARD, substantial progress toward better care for all patients with asthma should be achieved in the next decade.

REFERENCES

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2. Asher I, Bissell K, Chiang CY, et al. Calling time on asthma deaths in tropical regions-how much longer must people wait for essential medicines? *Lancet Respir Med* 2019;7:13-5.
3. Chiang CY, Ait-Khaled N, Bissell K, Enarson DA. Management of asthma in resource-limited settings: role of low-cost corticosteroid/beta-agonist combination inhaler. *Int J Tuberc Lung Dis* 2015;19:129-36.