

Presentation of new GINA guidelines for paediatrics

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Summary

The Global Initiative on Asthma (GINA) has provided guidelines for the management of children with asthma. For a step-wise approach to therapy, asthma is divided into four categories based on severity of symptoms: intermittent, mild persistent, moderate persistent, and severe persistent asthma. Long-term preventive therapy is distinguished from quick relief therapy in each group. Although these guidelines are clear and simple there have been few studies on asthma therapy for infants. Moreover, the existence of different wheezing phenotypes with varying pathogenic mechanisms hampers the interpretation of these studies. Transient wheezers have stopped wheezing by the age of 3 years and there is no relationship to atopy or a family history of asthma. In contrast, persistent wheezers continue to wheeze from the first year of life throughout school-age and have a high risk of atopy. Although they have normal lung function at birth, persistent wheezers develop significant decrements in lung function by the age of 6 years. Whether these impairments are amenable to prevention by early initiation of anti-inflammatory therapy remains to be seen. At present, there are no disease markers to identify the different wheezing phenotypes in infancy, although eosinophil counts and measurements of eosinophil cationic protein in serum may prove to be helpful in distinguishing these conditions.

Keywords: asthma, children, guidelines, wheeze, atopy, early life

GINA guidelines for paediatric asthma

The Global Initiative on Asthma (GINA) has edited a searchable, internet-accessed set of asthma guidelines. These describe the aims of asthma treatment for children under the age of 5 years as the following: to have minimal (ideally no) chronic symptoms, including nocturnal symptoms; to suffer minimal (infrequent) episodes; no need for emergency visits; minimal need for use of prn β_2 -agonists; no limitations on activities, including exercise; (near) normal lung function; and minimal (or no) adverse effects from medicine. For the purpose of a step-wise approach to the management of childhood asthma, severity has been defined into four categories: severe persistent, moderate persistent, mild persistent and intermittent asthma according to the frequency of daytime and nocturnal symptoms. Long-term preventive treatment is distinguished from quick relief therapy in each category (Table 1). Patients should start treatment at the step most appropriate to the initial severity

of their condition and their treatment should be reviewed every 3–6 months. If control is sustained for at least 3 months, a gradual stepwise reduction in treatment is proposed. If, however, control is not achieved, the patient medication technique, compliance and environmental control with avoidance of allergen exposure and other trigger factors should be reviewed. Then an increase in medication may be considered. All therapy should include patient/parent education.

Although these guidelines appear clear and simple, the authors of the GINA guidelines recognize that very few studies on asthma therapy for infants have been performed. Moreover, the interpretation of these studies is hampered by the fact that probably different wheezing phenotypes with varying underlying pathogenic mechanisms exist.

Wheezing phenotypes in children

Wheezing is very common among children. In their longitudinal study in Tuscon, Arizona, Martinez *et al.* [1] showed

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Table 1. GINA guidelines on treatments for infants and young children (5 years or younger)

	Long-term preventive	Quick relief
Step 1: intermittent	None needed	<i>Inhaled short-acting bronchodilator</i> Inhaled β_2 -agonist or ipratropium bromide, or β_2 -agonist as needed for symptoms, but not more than 3 times a week. Intensity of treatment will depend on severity of attack.
Step 2: mild persistent	<i>Daily medication</i> Either inhaled corticosteroid (200–400 μ g) or cromoglycate (use MDI with a spacer and face mask or use a nebulizer)	<i>Inhaled short-acting bronchodilator</i> Inhaled β_2 -agonist or ipratropium bromide, or β_2 -agonist tablets or syrup as needed for symptoms, not to exceed 3–4 times in one day.
Step 3: moderate persistent	<i>Daily medication</i> Inhaled corticosteroid – MDI with spacer and face mask 400–800 μ g daily or nebulized budesonide < 1 mg b.i.d.	<i>Inhaled short-acting bronchodilator</i> Inhaled β_2 -agonist or ipratropium bromide, or β_2 -agonist tablets or syrup as needed for symptoms, not to exceed 3–4 times in one day.
Step 4: severe persistent	<i>Daily medication</i> Inhaled corticosteroid-MDI with spacer and face mask > 1 mg b.i.d. or nebulized budesonide > 1 mg b.i.d. If needed, add oral steroids, lowest possible dose on an alternate day, early morning schedule.	<i>Inhaled short-acting bronchodilator</i> Inhaled β_2 -agonist or ipratropium bromide, or β_2 -agonist tablets or syrup as needed for symptoms, not to exceed 3–4 times in one day.

that about 50% of children have had symptoms of wheeze during the first 6 years of life (Fig. 1). More importantly, they showed there are different patterns of wheezing. Firstly, there are children who wheeze during the first 2 years of life and stop by the time they reach 3 years of age (transient wheezers). Secondly, there are children who do not wheeze during the first 3 years of life but have developed asthma by the age of 6 years (late onset wheezers) and, finally, there are those who start wheezing at birth and continue wheezing for the next 6 years (persistent wheezers) (Fig. 1).

Martinez *et al.* [1] have shown that the risk factors and characteristics of these different wheezing phenotypes are different. Children with transient benign wheezing who lose their symptoms around their third birthday, have impaired lung function before wheezing occurs but have no atopy or family history of asthma. This group has a good prognosis. In the other two groups of late onset and persistent wheezers, there is a familial background of asthma, there are more boys than girls, and they are associated with atopic sensitization. Interestingly, both groups have normal lung function at birth but the persistent wheezers develop significant decrements in lung function by the age of 6 years. Whether it is possible to detect these children in the first years of life and prevent the lung function impairments by early initiation of anti-inflammatory therapy remains to be seen. The identification of disease

markers unambiguously related to wheezing phenotype is still lacking, though recent studies indicate that eosinophil counts during attacks of infant wheezing [2] or eosinophil cationic protein (ECP) measurements in serum [3] may provide some help in distinguishing both conditions in the future.

Asthma, atopy and viral infection

Part of the cross-sectional International Study of Asthma and Allergies in Childhood (ISAAC) involved assessing the risk of asthma and the frequency of fever episodes in infancy determined by parental questionnaires. School age children with asthma were divided into those who were atopic (using skin tests or RAST measurements) and those who were non-atopic. In addition, they were divided into those with and without bronchial hyperresponsiveness (BHR) to a hypertonic saline challenge. Figure 2 shows that the risk for asthma (the odds ratio) increases with an increasing number of fever episodes in the first year of life. The risk is markedly increased for those with non-atopic asthma compared with those who have atopic asthma. Similarly, the risk is higher for those with asthma without BHR. This suggests that there is a phenotype that is associated with viral infections, which may be called wheezy bronchitis, and which is quite different from atopic asthma.

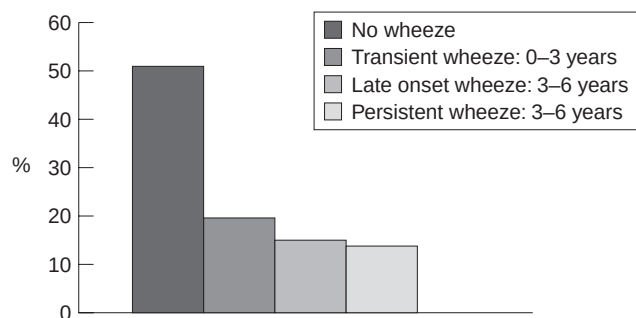


Fig. 1. Wheeze in the first 6 years of life. Reproduced with permission from ref [1].

Interestingly, Russell and Helms [4] showed that there has been a consistent increase in the prevalence of wheeze and atopy from 1964 to 1994. In contrast, there has been little change in the prevalence of wheezy bronchitis (i.e. in children who wheeze only with an upper respiratory tract infection). This again points towards a different mechanism and may prove important when attempting to identify subgroups of wheezing infants amenable to early anti-inflammatory therapy.

Discussion following Bousquet and Von Mutius

Holgate: Firstly, we want to debate the issue of the importance of guidelines in informing practice and, in particular, the way they are currently being used by different people and different countries. Secondly, in relation to the paediatric guidelines and the adult guidelines, how we might try to open these up a bit more to create an opportunity for diversity in treating patients as individuals.

Calhoun: Professor Bousquet, you indicated that it would be best if we used evidence-based guidelines and I think most of us would agree with that. But evidence-based guidelines require validation which takes time and new

medications and new therapeutic strategies are continually evolving. From a philosophical standpoint, how do you pull that together with the evidence necessarily trailing the state of the art by 3–5 years? Also, evidence-based medicine in children is even more difficult than in adults because comprehensive paediatric studies are extraordinarily difficult to perform.

Bousquet: I think that evidence-based medicine is probably the new paradigm in medicine and has not yet been widely accepted. There has been a second study in rhinitis comparing histamine (H)-1 blockers and topical corticosteroids and again there has been much debate on this. Evidence-based medicine is only one aspect. We are taking a gradual approach and investigating pieces of the guidelines, i.e. the effects of allergen avoidance, then education, then treatment and so on. In the future, we should be able to say that for a particular group of patients we need this approach and that approach is better than no intervention at all. This is what we have done in rhinitis. We have tried to see whether a stepwise approach in the treatment of hayfever was better than just giving drugs to the patient.

Holgate: Effectiveness studies are really needed now rather than efficacy studies, which is what we base many of our treatment paradigms on. There are very few effectiveness studies in the real world because often a drug gets introduced in one area, with a repertoire of clinical trial data, and then gets used in whole different population.

Von Mutius: I think there are problems with the meta-analysis approach. I have just reviewed a meta-analysis on a drug for use in children of different age groups. Interestingly, recent cohort studies were judged by the investigators as adequate in terms of statistics but older placebo-controlled studies that followed up children for a year were excluded as not being sufficient in their statistics. I think this approach dismisses extremely valuable information. Also, in children, it is difficult to identify distinct groups of patients to study because of these different phenotypes and the lack of markers to identify them.

Bousquet: I agree about the need for effectiveness studies.

Björkstén: I have a general comment about the guidelines. They do not consider the patient's point of view. What are the patients' concerns and how do we cope with getting a partnership rather than compliance? Also, the health economics and quality of life need to be included in the guidelines. I think it is a serious omission to produce guidelines based only on the medical paradigm rather than broadening the concept and actually going outside the medical community.

Bousquet: I cannot agree more.

Holgate: In the UK, guidelines are being used by health authorities to stop prescribing of certain drugs, particularly the antileukotrienes. The excuse is they are not in the guidelines.

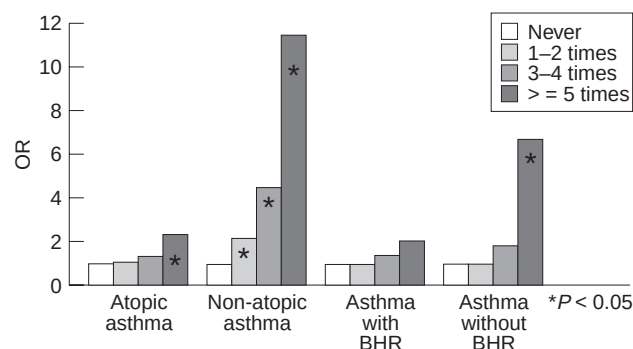


Fig. 2. Risk of asthma increases with an increasing number of fever episodes in the first year of life.

Bousquet: This is a bad use of guidelines. They should not be used as a stick because every patient is different.

Djukanovic: Are there attempts to come up with guidelines on the prevention of the development of asthma in children?

Von Mutius: My view is that we don't know how to prevent asthma and that is primary prevention. We had a lot of discussion at the World Asthma meeting in Barcelona with a heterogeneous group around the table. The conclusion was that we don't know whether primary prevention works. Secondary prevention, where you would try to prevent the lung function decrements, needs to be studied much more rigorously. But what selection criteria should we use? Also, we need to follow people for a long time because we can only judge the outcome after 5–6 years. You must also have sufficient numbers of subjects.

Djukanovic: Currently there are no studies to address this?

Von Mutius: No. The question is, if you start at the first year of life, can you prevent a decrement in lung function like the Tuscon data suggests? Interestingly, the US didn't have inhaled steroids at the time that study was done. So this seems to be the natural course of the disease. Could you have prevented it if you had administered inhaled steroids?

Holgate: A study from Aberdeen will be published shortly in the *BMJ* where they found that the introduction of inhaled steroids from 18 months had no effect on the natural course in quite a large population of babies.

Kroegel: In Germany, as in England, general practitioners are not allowed to go over their budget. The economic view is a very important view and must be integrated into the guidelines.

Holgate: Certainly in Britain, we are told we must always put the patient first. But in fact that is not the way it is running at the moment; it is financially driven.

Chung: I think I heard Jean Bousquet say that guidelines do not improve asthma. You suggested that you couldn't shift patients from step 4 to step 3, or from step 3 to step 2.

Bousquet: What I said is that, overall, guidelines have improved patients. However, they probably didn't touch the most severe ones. There are more severe asthmatic patients than 10 years ago. Secondly, those who have implemented the guidelines have reduced mortality and hospitalizations. However, there is still a fraction of patients who are the most difficult to treat and are still very severe, and whatever we do we don't improve them.

Chung: I completely agree with you. What do you think is the problem there?

Bousquet: Well, I think it is a different disease.

Holgate: It is a fact that there are components of asthma that we know very little about. For example, its early life origin

and its implication for the future. Also, no one really understands why some people have severe persistent difficult asthma or what we should do.

Chung: Professor Bousquet, could you elaborate further on how you think meta-analysis should be analysed. You mentioned it should be analysed by a team of experts.

Bousquet: Because the guidelines on allergen avoidance from the meta-analysis caused such a debate, I think that the guideline should have been published without recommendations. There should have been a second paper accompanying the guidelines written by a panel of 5 or 6 experts who make recommendations based on what is relevant.

Holgate: Meta-analysis is a difficult business because the analyses are as good as the trials that make them up.

Chung: Do you think the whole area of evidence-based medicine in asthma is a problem?

Bousquet: Meta-analysis and evidence-based medicine both have a specific meaning and in 3 or 4 years they will be regarded as essential.

Holgate: My view is that the more we pool everything together, the more likely we are to do our patients a disservice by not treating their disease in relation to their individual circumstances.

Von Mutius: Meta-analysis is an interesting research tool, but it is sold as the evidence on which we need to base our decisions. We need to communicate that this is only one way at looking at studies and that it is not going to tell us the truth. We need objective data, but we also need an experienced doctor to treat the patients.

Fahy: We have talked about how there is a lack of evidence to help us formulate some parts of the guidelines. There are also times when guidelines are created and evidence is ignored. For example, in thrombolytic therapy of ischaemic heart disease the guidelines were at least 8 years behind the data. The people who make up guidelines have a tremendous responsibility and need to have adequate resources to create guidelines and be allowed to gather data in a systematic unbiased way. Should we have professional data gatherers? Should GINA have a resource that is funded that creates a database of ongoing trials and has a dispassionate person advising the experts.

Bousquet: We have tried to do it not only from a small committee but also the guidelines went to a much broader committee of around 50 people throughout the world who reviewed the guidelines and gave their comments. Of course, this is not efficient. The guidelines should be implemented and tested. We have done the best we could, but it is not the best that could be.

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